Welcome!

NOT LONG AGO, THE FIELD of cancer immunology and immunotherapy (ie: harnessing the patient’s own immune system to fight cancer) was considered the “road to nowhere.” As an earlier member of a generation of “dreamers” and “truly believers” in this field, I was thrilled to learn this fall, that the Nobel Foundation in Stockholm presented the 2018 Nobel Prize in Physiology or Medicine to two cancer immunotherapy pioneers, James P. Allison and Tasuku Honjo, “for their discovery of cancer therapy by inhibition of negative immune regulation.”

The rise to prominence for the rapidly expanding scientific field is also gratifying news for the members of the George Washington University (GW) Cancer Center, as cancer immunology and immunotherapy research is a cornerstone of our basic science efforts – along with cancer biology (genetics, genomics, and epigenetics), microbial oncology, and cancer engineering. Together with our community outreach and engagement initiatives, cancer control, prevention and policy efforts and education, we are committed to rapidly move these areas of discovery to benefit the community we serve in Washington, D.C., and the surrounding counties.

At the GW Cancer Center, we have many investigative teams pursuing immunological research to refine and develop this new generation of cancer therapies. By tapping into the body’s immune system to fight disease, we are “re:discovering” that the cure is inside us. Although cancer immunotherapy has been around for several decades, and after many failures, basic and translational investigations have begun to yield revolutionary results.

Featured in this edition of re:discover is work by Catherine Bollard, MD, who has developed a new immunotherapy called TAA-T, which is a multi-antigen specific T-cell product that appears to be superior in many ways and with less toxicity that the recently FDA-approved CAR T-cell therapy. Another team of GW Cancer Center investigators, led by Rohan Fernandes, PhD, is integrating nanotechnology with the immune response to achieve greater therapeutic results. They have re:discovered a use for nanoparticles found in a pigment once commonly used by the world’s great artists. Those tiny particles are super-heated to destroy previously inaccessible tumor tissue in the brain. And a third research team, led by Katherine Chiappinelli, PhD, is pouring through the body’s “junk DNA” to define the mechanisms controlling the immune signaling in cancer cells. By understanding how to increase the immune signaling coming from tumors, we can increase the number of immune cells in the tumors and make immunotherapies even more effective.

This basic and translational science research is a key facet of our comprehensive approach to cancer care. Projects such as these help to inform our clinical research enterprise, and those programs help to advance cancer care at every level. Reading these and other stories in the pages of re:discover, I hope you’ll agree that the new generation of scientific “dreamers” and innovators we have brought together under the umbrella of GW Cancer Center are well-poised to transform cancer care and, hopefully one of them will receive a phone call from Stockholm one cold morning in October.

EDUARDO SOTOMAYOR, MD
Director, George Washington University Cancer Center
GW CANCER CENTER LEADERSHIP

EDUARDO M. SOTOMAYOR, MD
Director, GW Cancer Center, Director of the Division of Hematology and Oncology, and Professor of Medicine

LORIEN ABROMS, SCD
Intern Associate Center Director for Population Sciences and Policy, GW Cancer Center, and Associate Professor of Prevention and Community Health

MICHAEL K. BENEDICT, PharmD
Associate Center Director for Administration and Finance

CATHERINE BOLLARD, MD
Associate Center Director for Translational Research and Innovation, GW Cancer Center, and Professor of Pediatrics and of Microbiology, Immunology, and Tropical Medicine

MANDI PRATT-CHAPMAN, MA
Associate Center Director for Community Outreach and Health Equity

CATHARINE BOLLARD, MD
Associate Center Director for Translational Research and Innovation, GW Cancer Center, and Professor of Pediatrics and of Microbiology, Immunology, and Tropical Medicine

MARTI PRATT-CHAPMAN, MA
Associate Center Director for Community Outreach and Health Equity

EDWARD SETO, PhD
Associate Center Director for Basic Science, GW Cancer Center, King Faisal Professor of Cancer Biology, and Professor of Biochemistry and Molecular Medicine

THE GEORGE WASHINGTON UNIVERSITY CANCER CENTER

MISSION: To drive transformational research, personalized therapy, family-centered care, and cancer policy in the Nation’s Capital.

VISION: To create a cancer-free world through groundbreaking research, innovative education and equitable care for all.

For more information about GW Cancer Center visit gwcancercenter.com
LESS THAN 3 PERCENT OF the DNA in our genome encodes proteins. Recent work has shown that a significant part of the genome, initially considered “junk DNA,” does not code for proteins, but still has important biological functions, especially in cancer initiation and progression. A two-year, $300,000 grant from the G. Harold and Leila Y. Mathers Foundation will help fund research led by Katherine Chiappinelli, PhD, assistant professor of microbiology, immunology, and tropical medicine at SMHS, to define epigenetic determinants of repetitive element “junk DNA” control during tumor progression and lay the groundwork for understanding interactions between these elements and the host immune system.

The research project, titled “Epigenetic Modification and Expression of Retroelements in Cancer Development,” includes a subcontract with Kathleen Helen Burns, MD, PhD, at Johns Hopkins Medicine, an expert in the field of repetitive elements in cancer. Repetitive elements are very different in cancer cells than they are in normal cells, but the medical community does not yet know which elements are affected and how they are altered as the cancer progresses. Outcomes of the project will include a more complete understanding of cancer progression and the identification of novel cancer therapeutic targets and/or biomarkers.

Chiappinelli and her colleagues will work to produce a comprehensive map of repetitive element regulation and expression during the progression of common tumors, including lung and ovarian cancer.

A Vision for Public Health

LORIEN ABROMS, SCD, ASSOCIATE PROFESSOR of prevention and community health at the Milken Institute School of Public Health at GW, has been named interim associate center director for population sciences and policy at the GW Cancer Center.

In this role, Abroms collaborates with faculty across GW to create a vision for the public health programs within the GW Cancer Center. She develops and manages initiatives to foster university-wide cancer research collaborations among population sciences and policy researchers. Abroms is a behavioral scientist with expertise in applying communication technology to design scalable programs aimed at tobacco cessation. Her responsibilities also include identifying and nurturing the development of program areas in cancer population sciences and policy, such as screening, environmental carcinogens, health care disparities, cancer epidemiology, and virus-related cancers such as HIV and HPV.
SHARAD GOYAL, MD, professor of radiology at the George Washington University (GW) School of Medicine and Health Sciences, was recently selected as a member of the NRG Oncology Developmental Therapeutics Radiation Therapy Subcommittee, where he will spend the next two years collaborating with fellow committee members and the National Institutes of Health to bring new drugs to clinical trials.

“I think this is a great opportunity to give GW a place at the table with respect to working in a cooperative group,” said Goyal. “It raises the profile of not only radiation oncology, but also GW and the GW Cancer Center.”

NRG Oncology is one of three major cooperative groups that run clinical trials across the United States. There are subcommittees that cover each type of cancer that NRG Oncology works on. The Developmental Therapeutics Radiation Therapy Subcommittee helps to determine what molecular pathways or drug combinations may be more interesting or feasible in treatments. It also determines what types of tumors may benefit from those drug combinations with radiation therapy.
Robert Siegel, MD ’77, described a new treatment developed for patients suffering from oropharyngeal cancer during the American Society of Clinical Oncology’s (ASCO) Annual Meeting, held in Chicago.

Oropharyngeal cancer involves the base of the tongue, floor of the mouth, and tonsils, said Siegel. It’s not the most common cancer, but is also not a rare one, he noted. “Historically, patients who develop this cancer have smoked heavily and consumed large amounts of alcohol,” he said. However, now most oropharyngeal tumors are a consequence of human papillomavirus (HPV) infection; patients with HPV often have no history of heavy smoking or alcohol abuse. HPV tumors are more responsive to both chemotherapy and radiation, he added.

The current standard treatment includes a combination of high-dose radiation plus chemotherapy. Siegel noted that the treatment is “80 to 90 percent successful.” However, the radiation leaves patients suffering from myriad side effects.

Short-term effects include damage to the back of the throat that makes eating painful, and often creates the need for gastrostomy tubes to maintain adequate nutrition. In the long term, radiation knocks out the salivary glands, leaving patients with chronic dry mouth, which can lead to increased gum and dental disease. The radiation can also alter a patient’s sense of taste and cause chronic swallowing problems.

The investigational treatment eliminates the need for radiation in most patients. Instead, said Siegel, patients receive three doses of standard chemotherapy followed by surgery.

“We found that the primary cancer and involved lymph nodes shrunk dramatically with chemotherapy,” he said. After chemotherapy treatment, the cancer was removed through a new technique — TORS (transoral robotic surgery). Siegel credited Nader Sadeghi, MD, a former faculty member, for bringing the technique to GW. Currently that technology is used by GW School of Medicine and Health Sciences head and neck surgeons Arjun Joshi, MD, associate professor of surgery; Punam Thakkar, MD, assistant professor of surgery; and Joseph Goodman, MD, assistant professor of surgery.

Siegel added that throughout the study, patients were referred to standard radiation therapy if the new treatment wasn’t working. “We were doing something unique, and we wanted to make it as safe as possible for the patients,” he said.

Sixteen of the 20 patients in the study never needed radiation, and 18 of 20 patients remain in remission. “We saw at least equal effectiveness in the treatment, but were cutting way back on the side effects,” Siegel said.

Siegel would like to add two more steps in a follow-up study: using next-generation sequencing of the tumor to identify which patients are at high risk for relapse, and incorporating additional drugs, such as immunotherapy drugs, to see if they would make the treatment even more effective.
ALEXANDROS TZATSOS, MD, PHD, assistant professor of anatomy and cell biology at the George Washington University (GW) School of Medicine and Health Sciences and a researcher at the GW Cancer Center, has uncovered a connection between a specific gene, KDM6A, and the most aggressive form of pancreatic cancer.

Tzatsos’ study, published in Cancer Cell, found that a loss of KDM6A, an X chromosome-encoded histone demethylase, induces a histologically distinct subtype of pancreatic cancer known as “squamous-like.” The gene, connected to pancreatic cancer uncovered

Tzatsos and his team found, is also frequently mutated or deleted in squamous-like pancreatic cancer and acts as a tumor suppressor. He further determined that bromodomain and extra-terminal inhibitors, a class of small molecules now in clinical trials for treating several malignancies, could offer a potential treatment by restoring cell identity and sensitizing tumors to current therapies.

Pancreatic cancer accounts for 3 percent of cancers in the United States, and 7 percent of all cancer deaths. The squamous-like subtype of this cancer offers the worst prognosis and accounts for 20–30 percent of pancreatic cancer cases.

THE GEORGE WASHINGTON UNIVERSITY HOSPITAL, along with the GW Cancer Center, recently earned a Screening Center of Excellence designation from the Lung Cancer Alliance (LCA) for its ongoing commitment to responsible lung cancer screening. GW Hospital is one of only two hospitals in the region to hold this distinction.

“GW Hospital and the GW Cancer Center are committed to bringing lifesaving cancer research, screenings, and treatment to [the] community,” said Kimberly Russo, MBA, MS, chief executive officer and managing director at GW Hospital, adding that low-dose CT screening for lung cancer – carried out safely, efficiently, and equitably – saves tens of thousands of lives a year. “We are proud to receive this recognition that reflects this ongoing and focused dedication to reducing cancer deaths across our region.”

GW Hospital has been performing low-dose CT screenings for lung cancer for four years. In that time, the hospital has performed more than 800 screenings and identified 320 at-risk individuals. The scan itself takes only 60 seconds to complete and is covered by Medicare and most insurance plans.

“Early detection of lung cancer in high-risk individuals is vital to effective treatment,” said Keith Mortman, MD, associate professor of surgery at the GW School of Medicine and Health Sciences and chief of the Division of Thoracic Surgery at GW Hospital. “By finding lung cancer early, we are able to work closely with our patients and multidisciplinary teams to create a care plan that will yield the best possible outcomes.”

Individuals may be at high risk if they meet the following criteria: they are between 55 and 77 years old; have smoked a pack of cigarettes or more every day for at least 30 years; and are a current smoker, or quit smoking less than 15 years ago. It is recommended that those people have a baseline CT scan with annual follow-up scans. To schedule an appointment, call 1-855-495-8647 (1-855-GWLUNGS).
GW-SPARC Fuels Passion for Research

BY KATHERINE DVORAK

LEXIS DESHAZOR-BURNETT, A RISING JUNIOR at North Carolina A&T State University, credits the George Washington University (GW) Summer Program Advancing Research on Cancer (GW-SPARC) with opening her eyes to the myriad research paths she could follow.

Becoming a doctor was always her goal, she said, but once arriving at college, Deshazor-Burnett discovered a new passion: research. Through GW-SPARC, she spent the summer in the lab of Alexandros Tzatsos, MD, PhD, assistant professor of anatomy and cell biology at the GW School of Medicine and Health Sciences (SMHS) and researcher at the GW Cancer Center. She assisted with using CRISPR, a revolutionary gene editing tool, to knockout KDM6A, a histone demethylase, in pancreatic cancer cell lines.

“I’m thinking about what I want to do, and it was great to see a lot of different types of people [at SMHS] with a lot of different careers,” she said. “It gave me a broader idea of what I could do after undergrad, and how I can satisfy each facet of what I want to do in my career.”

New to GW this year, the program is open to undergraduate school students from groups underrepresented in biomedical science and provides participants with a hands-on approach to cancer research. Students worked in laboratories focused on cancer immunology and immunotherapy; cancer biology, namely targeted therapies and epigenetics; and cancer engineering and technology.

The goals of GW-SPARC, according to Alison Hall, PhD, associate dean for research workforce development and professor of neurology at SMHS, who serves as co-director of the program, are to expand opportunities for potential researchers and enhance diversity in the biomedical research community.

“GW-SPARC not only exposes participants to cutting-edge research and contemporary cancer research techniques, but also fosters their understanding of health disparities and the impact of cancer in different communities,” said Hall.

Students attended workshops on topics including sample size and experimental design, applying to graduate and medical school, and how to make a research poster. They also sat in on seminars from GW.
Cancer Center researchers, such as Katherine Chiappinelli, PhD, assistant professor of microbiology, immunology, and tropical medicine at SMHS; Norman Lee, PhD, professor of pharmacology and physiology at SMHS; and Edward Seto, PhD, associate center director for basic sciences at the GW Cancer Center, King Fahd Professor of Cancer Biology, and professor of biochemistry and molecular medicine at SMHS, who is also a co-director of GW-SPARC.

Ann Obi, a rising junior at Prairie View A&M University, worked in Chiappinelli’s lab over the summer. She first was drawn to medicine after visiting family in Nigeria during a summer break in high school and realizing the lack of health care services available there.

Obi said working in Chiappinelli’s lab was an exceptional experience. “Everyone is nice and understanding. I don’t have a strong research background, so they really made an effort to make sure I understood what was going on. Dr. Chiappinelli was very open to answering all my questions,” she said. “I learned a lot.”

In addition to their time in the lab, cohort members also were required to create a poster on their research and presented their findings to faculty and staff on the last day of the program.

Obi confidently presented her research to the crowd gathered in the Science and Engineering Hall that day, answering questions with a confident smile.

Before the presentation began, Hall and Seto said a few words to the students and attendees.

“This past week I had a chance to talk to the students, and I asked them what they liked about the program, and a lot of them told me ... they were surprised that the faculty here, despite their busy schedules, were willing to sit down with them to talk with them and talk about their passion and how they got into science,” Seto remarked. “To the students, I want to say this is a mutual feeling. As a faculty member, I’ve learned a lot from you and benefited from the enthusiasm you’ve brought to this program.”

The GW Hospital Women’s Board provided partial support for this initiative.

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**A PASSION FOR RESEARCH**

Becoming a doctor was always Lexis Deshazor-Burnett’s goal, but once at college, she developed a passion for research. The George Washington University Summer Program Advancing Research on Cancer and her work in the lab of Alexandros Tzatsos, MD, PhD, opened her eyes to the myriad research paths she could follow.
THE FUTURE OF CANCER RESEARCH, in the opinion of Katherine Chiappinelli, PhD, of the George Washington University School of Medicine and Health Sciences (SMHS), revolves around combining immunotherapy with other treatments. Pairing immunology with epigenetics, the study of changes in organisms caused by modifications to gene expression, she seeks to better understand the mechanisms behind epigenetic control of immune signaling in cancer cells.

“The body’s own immune system is our most potent weapon against cancer cells,” says Chiappinelli, assistant professor of microbiology, immunology, and tropical medicine at SMHS.

Although immunotherapy alone can work to fight cancer, Chiappinelli notes, it is most successful in patients who already have immune cells in their tumors. “Those patients in general respond to immune therapy, but there’s another set of patients [whose] tumor cells are growing very fast and there are few or no immune cells in the tumor to fight it,” she says. “These patients don’t do well with drugs that release the brakes on the host immune system. That’s a big problem in the field.”

And it’s a problem her lab is tackling head-on.

During a postdoctoral fellowship with Stephen Baylin, MD, at Johns Hopkins University, Chiappinelli found that a drug that activates tumor suppressor genes also has a strong immune effect.

“When we treated cancer cells with this drug, they had more immune signaling coming from the tumors and more immune cells in the tumors. But we didn’t know why,” she says.

It turned out the answer was in our genomes. “Only about 2-3 percent of [human] DNA codes for proteins. However, about half of our DNA is repetitive sequences, and we don’t really know what they do,” she says. Originally, that was characterized as junk DNA, but it’s not junk, according to Chiappinelli. Those sequences include endogenous retroviruses, or dead viruses in our genetic code. Our cells turn off these viruses on purpose. But epigenetic drugs turn them back on.

We don’t get viral particles that can infect the cell when the retroviruses get a green light, Chiappinelli explains, but the viral RNA is transcribed, and that sets off an alert in
“The alert makes tumor cells think they are infected with a virus, and they die or send out signals to host immune cells to come and kill them,” Chiappinelli says. “So the big effect in human cancer cells and in mouse models of cancer is that you get more immune cells coming in to kill the tumor and a good anti-tumor effect, especially when you combine that with immune therapies.”

Chiappinelli’s interest in medical research dates back to high school AP biology. It was a hands-on class full of lab work that showed her how pursuing science could mean doing something different every day and enjoying the excitement of not knowing what would happen next.

“That can be frustrating sometimes,” she says about the unknowns of scientific research, “but I think it also makes for a really interesting career.”

She notes that she gravitated toward epigenetics, a new field during her time in graduate school, because not much was known about it then, and researchers still have much to learn.

“I think, for a young person, there’s the opportunity to make important discoveries. It’s a field where there’s still a lot of progress to be made, in terms of both basic science discoveries and impact on patient care,” she adds.

Now a clinical trial Chiappinelli was involved in during her postdoctoral work at Johns Hopkins is underway, combining epigenetics with immune therapy. But even with the discoveries she’s helped make, Chiappinelli has more questions to answer: Which sequences do this? What things are being secreted to bring in the host immune cells? What are the best combinations to fully eradicate tumors?

That’s what Chiappinelli says she likes most about her work, day in and day out: “There’s always something new to discover.”
Alumni Gift Supports Immunologic and Epigenetic Research

ESTABLISHING THE MARLENE AND MICHAEL Berman Endowed Fund for Ovarian Cancer Research was both personal and professional for Michael Berman, MD ’67, RESD ’69, a specialist in gynecologic oncology at the University of California, Irvine, Medical Center.

On a warm September day in 2017, Berman toured the George Washington University (GW) Cancer Center as part of Reunion Weekend at the GW School of Medicine and Health Sciences (SMHS); it was on that tour that he met Katherine Chiappinelli, PhD, assistant professor of microbiology, immunology, and tropical medicine at SMHS, and spoke with her about her research on immunology and epigenetics.

Berman, always interested in discoveries that could benefit the patient population he has been serving for nearly 50 years, was intrigued; not long after talking with the young researcher, he wrote a $100,000 check to help with the growth of the Chiappinelli Lab.

“We’re on the threshold for major advances in immunology and immunological treatments of cancers, and Dr. Chiappinelli’s research is the kind that will lead to positive developments in the care of patients with ovarian cancer,” he says.

That was the professional reason for Berman’s generous donation. His personal reason hit closer to home; Berman’s wife, Marlene, who passed away in 2014, had breast cancer. Later, all four of his daughters tested positive for the BRCA gene, which places them at a higher risk for developing breast or ovarian cancers.

“It’s a strange set of events, when you think about it,” Berman says. “I’m an oncologist with all four daughters at risk for cancer. But I think we’re not too far away from some major breakthroughs that may help patients suffering from this devastating disease.” He adds that the donation was also made to show his appreciation for his alma mater, to which he feels greatly indebted.

“GW has permitted me and many others to have an impact on the lives of the people who trust us to make correct decisions and do the right things for them,” he says. “It’s that indebtedness that made me want to give back.”
Counting on Clinical Trials

BY KATHERINE DVORAK
INNUMERABLE QUESTIONS AND CONCERNS LOOM after a cancer diagnosis. Among them: Should I participate in a clinical trial, or should I stick with the standard of care? Cancer treatment success rates continue to rise. The National Cancer Institute predicts that by 2024, almost 19 million people will live well beyond their diagnosis. Clinical trials play an important role in such progress.

“[They] are the mechanism by which we make progress in the treatment of cancer,” says Robert Siegel, MD ’77, associate center director for education, training, and network development at the George Washington University (GW) Cancer Center and professor of medicine at the GW School of Medicine and Health Sciences (SMHS).

Treatments and techniques from clinical trials may be more effective than the current standard of care, or they may be equally effective but have fewer side effects, he explains.

Finding the right fit
Not every patient who signs up to be a part of a clinical trial will be accepted. Trials have certain criteria that a patient must meet to be included, measures that vary from trial to trial.

A patient signing up to take part in a trial must first undergo a screening procedure, which can include blood tests, physical examinations, a CAT scan, an electrocardiogram (EKG) test, and other tests and procedures required for the study.

If patients have, say, an abnormal EKG, or if their medical record shows a history of cardiovascular disease, they may be excluded from a trial. In addition, a person who is confined to a bed may not be considered for participation.

Patients should be guided by their physician when considering participating in a trial, Siegel says. Physicians can identify the right clinical trials for their patients and determine whether they’re good candidates for participation.
Before a patient is accepted for clinical trial, he or she must review and sign an informed consent form. The form includes in-depth details on the trial, such as participation requirements, possible side effects of the treatment, and possible benefits.

Once the form is signed and the patient meets all the eligibility criteria, therapy begins.

**Participation expectations**

Clinical trial volunteers will have to meet certain obligations during the course of the trial. Some of the obligations may depend on what stage of development the drug is in.

“There will be questions that need to be answered about how the drug behaves in the patient, what sort of side effects it has, and how quickly those [side effects] occur and disappear,” explains Richard Lush, PhD, director of the Clinical Trials Office at the GW Cancer Center. “When those questions need to be answered earlier in the development, the patient might be asked to come back into the clinic for additional visits so that the patient can be checked and have laboratory tests done to make sure [he or she is] OK.”

In later development stages, visits may ease up because doctors have a better understanding of what to expect from the drug.

However, generally there is a limit to the number of visits a patient needs to make. “We realize that people have lives they want to live even while on a study,” Lush says.

He adds that patients are encouraged to talk with the doctor and study team at any time if they have questions, or if they are experiencing a new symptom or side effect.

**Betting on benefits, but considering the risks**

The benefits of a clinical trial can differ, as can any associated risks.

The major benefit from a Phase I trial can be, simply, a new option when other treatments have been exhausted. Drugs administered during such trials could prolong a participant’s life or better their quality of life, says Imad Tabbara, MD, director of the GW Medical Faculty Associates Blood and Bone Marrow Transplant Program and professor of medicine at SMHS. For Phase III trials, benefits could include a drug with improved efficacy, treatment that is less toxic than the alternatives, a medication that’s easier to administer, or a medication that causes milder or fewer side effects.

However, no trial is risk-free.

“We have to be frank and tell [patients] we don’t know everything about this medication, that’s why we’re doing this [closely regulated] clinical trial,” Tabbara explains. “Sometimes unexpected things happen.”

He adds that if a patient experiences unexpected outcomes, the trial will be halted for further investigation into the problem. If a trial is halted, patients experiencing positive outcomes from the medication may be allowed to continue to receive treatment, but that’s at the discretion of the FDA, Tabbara says.

**Post-trial**

A trial that gets through to Phase III often results in the treatment earning FDA approval and becoming a new option of care for patients across the United States.

The decision to participate in a trial, and whether it is the best option for an individual’s wants, needs, and health, is completely in the patient’s hands.

But one thing is true: When patients participate and treatments are found to be effective, the impact reverberates far beyond the clinic’s walls.

“For the benefit of all current and future patients with cancer, we need patients to volunteer in trials so that we can advance the drugs that will improve the lives of patients,” Lush says.
The Phases

Imad Tabbara, MD, director of the GW Medical Faculty Associates Blood and Bone Marrow Transplant Program, and Richard Lush, PhD, director of the Clinical Trials Office at the GW Cancer Center, offer their expertise and advice for understanding the steps of the clinical trial process.

**Phase I:** The first phase of a clinical trial allows researchers to determine the efficacy of a new treatment. Phase I trials also help determine the right dose of the drug, demonstrate whether it has adverse side effects, and reveal any toxicity it might have.

The patients, says Tabbara, “have received regular treatment, or standard treatment as we call it, and they didn’t respond to it, or they responded and then the cancer progressed. Those are usually the best candidates," he explains.

**Phase II:** These trials are the second phase of drug development. A trial reaches Phase II once researchers have determined the effectiveness of the treatment. This second step establishes the response of individual agents when treating specific cancer types.

These trials are often randomized, meaning trial participants receive either the new drug or a standard drug already in use. This enables researchers to compare the efficacy of the new drug to other treatments.

**Phase III:** Larger randomized studies are engineered during a Phase III trial, which frequently is conducted by more than one institution.

Phase III trials are conducted if the treatment demonstrated sufficient activity in early stages of development. These trials are the last stage of testing prior to submitting the drug for FDA approval.

**Questions to Consider**

From a patient perspective, before joining a clinical trial, the most important thing is to get all the facts, speak with physicians, and ask, “is this what’s best for me?”

Valuable questions to consider include:

> What are the potential side effects, and can they be managed easily?
> What kinds of results have been established with this new treatment, for instance from Phase I or Phase II trials?
> How much of a commitment will participating involve?
> Have there been any unexpected reactions in patients already participating?
UNDER ATTACK

A scanning electron micrograph of T-cells (blue) attacking a lymphoma cancer cell (pink). Chimeric antigen receptor (CAR) T-cell therapy takes T-cells from a patient’s bloodstream and reprograms them to recognize a specific protein found on lymphoma cells. The T-cells are reintroduced in the patient where they find and attack the lymphoma cells.
As little as two decades ago early adopters of immunotherapy, looking to harness the body’s immune system to fight disease, toiled in the shadow of the holy trinity of cancer therapy — surgery, chemotherapy, and radiation therapy. Now, the immunological approach to cancer treatment has undergone a research renaissance. Times certainly have changed.

Following news of remarkable recoveries, this once-overlooked avenue to a cure for cancer has captured the public’s imagination. Oncologists have embraced immunotherapy as an important advancement, and the focus now is on refining those therapies to increase the cure rate and ameliorate potential adverse side effects.

One of the most exciting developments on the immunological front is T-cell therapies for lymphoma. T-cells are a type of lymphocyte produced or processed by the thymus gland (the T comes from thymus) that actively participate in the immune response. Typically, the most widely reported among these new treatments is CD19 CAR T-cell therapy. Doctors attach chimeric antigen receptors (CAR) to T-cells and reintroduce them in the patient to seek out cancer cells and produce chemical compounds that destroy them.

A research team led by Catherine Bollard, MD, associate center director for translational research and innovation at the George Washington University (GW) Cancer Center, has developed a different therapeutic approach called TAA-T, which is a multi-antigen specific T-cell product that may be superior in many ways to the recently FDA-approved CD19 CAR T-cell therapy.

“If you’ve got a tumor cell, there are several ways to kill it,” says Bollard, who also serves as professor of pediatrics at the GW School of Medicine and Health Sciences (SMHS) and director of the Center for Cancer and Immunology Research at Children’s Research Institute, part of Children’s National Health System (Children’s National). The CD19 CAR T-cell technique, she explains, involves genetically engineering a T-cell — adding an artificial receptor — so that it recognizes and kills the tumor.
TAA-T requires no genetic engineering. Tumor-killing T-cells, present naturally in everyone, are harvested from the patient and fed with cytokines or other chemicals in the lab where technicians grow their numbers to millions. They are then re-infused into the patient. Bollard says the entire process used to take three to six months, which dimmed its luster. Now it can be completed in less than two weeks, “so it’s a much more nimble process,” she notes.

Genetic modification, on the other hand, is expensive and heavily regulated and thus a cumbersome process. TAA-T has none of these disadvantages. Moreover, CAR T is limited to recognizing proteins on the surface of the tumor cells, and that is very restricting, Bollard explains. “There are only a limited number of proteins on the surface of tumors (or ‘extracellular antigens’) you can target with CAR T,” she says, “whereas our TAA-T can target what is known as intracellular antigens – proteins within the tumor cells – and there are many more of these cancer-specific proteins that can be targeted. In addition, because CAR T targets only one antigen, the patient can develop a resistance to the therapy.”

The minimal toxicity of TAA-T is perhaps its most significant advantage. Patients undergoing CD19 CAR T-cell therapy sometimes experience cytokine release syndrome, or CRS, which is caused by a large, rapid release of cytokines and cellular by-products into the bloodstream when the cancer cells are destroyed. Symptoms can vary from the relatively mild – fever, nausea, headache, rash, rapid heartbeat, low blood pressure, and trouble breathing – to the more severe. According to Bollard, CD19 CAR T-cell therapy is associated with “appreciable toxicities including neurotoxicity and, in some cases, death.”

In Phase I clinical trials with Bollard’s TAA-T therapy, researchers are now seeing 75 percent efficacy, especially in acute myeloid leukemia, which the trials with CAR T have thus far been unable to achieve. “We’re just beginning to increase the number of patients [in the trials], both adult and pediatric,” says Bollard. “We were initially collaborating with [Johns] Hopkins because the program at GW wasn’t up and running, but with Kieron’s arrival at GW we are now ready to move this therapy forward at GW for the treatment of other forms of lymphoma and even multiple myeloma.”

Kieron is Kieron Dunleavy, MD, director of the lymphoma program and professor of medicine at SMHS. “We are excited for Kieron to lead the novel T-cell therapy studies at GW,” Bollard says. “We obviously see GW as a huge player in this because of Eduardo [Sotomayor, MD, director of the GW Cancer Center and professor of medicine at SMHS], Kieron, and Mitch [Smith, MD, PhD, associate center director for clinical investigations at GW Cancer Center], who are all internationally renowned lymphoma physicians.”

Chimeric Antigen Receptor (CAR) T-cell Therapy

THE CONCEPT OF ENGINEERING CHIMERIC antigen receptors dates back about 20 years, and it has been touted as a treatment for a range of cancers. Two CAR T-cell therapies were approved by the FDA in 2017, and since then the number of immunotherapy trials has grown.

Cytokine Release Syndrome, or CRS, occurs after CAR T-cell treatment. Symptoms such as fever, nausea, headache, or trouble breathing can range from mild to severe or even life-threatening. According to the National Cancer Institute, the more effective the CAR T-cell treatment is, the more likely a patient is to experience CRS because the therapy has destroyed so many cancer cells the body is littered with cellular debris. The rapid release of cytokines into the blood from the immunotherapy can send the immune system into a tailspin.
A research team led by Catherine Bollard, MD, has developed a therapeutic approach called TAA-T, which may be superior in many ways to the recently FDA-approved CD19 CAR T-cell therapy.

Dunleavy came to GW in May 2017 after nearly 15 years at the National Institutes of Health working on lymphoma therapies and trials. “My goal is to improve the cure rate for the most common form of lymphoma, called diffuse large B-cell lymphoma. There are lots of exciting therapies in development, and they are really changing the face of lymphoma,” he says.

Because all cancer tumors have proteins on their surface, Bollard’s lab “trains” the T-cells by loading “trainer cells,” called antigen-presenting cells, with pieces of the proteins (peptides) that are expressed by the tumor cell. Then the researchers mix these peptide-loaded training cells with T-cells from the patient or a healthy donor. The T-cells are stimulated by the tumor peptides to reproduce in the laboratory, growing to large enough numbers that they can then be infused back into the patient. “These [enhanced] T-cells,” explains Bollard, “will then kill the tumor target, get stimulated, and continue to replicate in the patient.”

“In some ways it’s like a cancer vaccine,” she explains, “but you’re doing the job of the vaccines in the lab.”

Adult trials began in the fall of 2016, and pediatric patients joined the study in April 2017. “We started with patients who had a bone marrow transplant,” says Bollard. “What we want to do with Kieron is to incorporate patients who are ineligible for transplants, or who weren’t going to have a transplant, and combine [TAA-T] with other immunotherapies — for instance, adding checkpoint inhibitors.”

Checkpoint inhibitors are molecules that block immune checkpoints, which are receptors or ligands that modulate the immune response. In many cancers, tumor cells express these checkpoints to “put the brakes on” the immune system. Blocking the immune checkpoint thus releases the brakes.

“Tumors are clever,” Bollard says with a wry grin, “and they try to resist attack from the immune system. We’ve always treated cancer with different drugs. My feeling now is we should treat cancer with different immune therapies. And as long as you don’t increase toxicity to crazy levels, it’s really enhancing the immune therapy to increase efficacy.”

Bollard opens her computer and pulls up a graphic that displays the huge number of immunotherapy projects going on around the world. It’s nearly as vast and dense as a chart of stars. For years, she explains, oncologists have thought of cancer as a disease that needed to be treated by drugs. “Those of us who were proponents of the immune system being our best defense against cancer were looked at with a pretty dim view,” she says.

“Whether or not these cells are the be-all and end-all, what this means is that the community is now understanding that the immune system is really our first line of defense against cancer,” says Bollard. “We should be harnessing it early in the disease process and not waiting until we’ve killed off the immune system with multiple lines of chemotherapy and/or radiation, and then trying to get the immune system to help us.”
Gazing at the iconic 19th-century Japanese woodcut known as "The Great Wave off Kanagawa," one would hardly suspect it contains a key to a medical breakthrough. Yet the pigment in the artwork has opened a new perspective in the treatment of juvenile cancer.

The artist, Hokusai, used Prussian blue pigment in his masterpiece. By combining the same deep blue nanoparticles with an immunotherapy class called checkpoint inhibitors, researchers have engineered a “nanoimmunotherapy” for treating neuroblastoma, a leading cause of cancer-related death among children. The nanoparticles are administered to neuroblastoma tumors, where they are activated with near infrared light. The light activation causes the nanoparticles to heat and destroy tumor tissue and elicit a robust anti-tumor response from the immune system. These anti-tumor effects are made more potent by the administration of the checkpoint inhibitor treatment.

Nanoimmunology, as the field is called, is really the synthesis of nanotechnology and immunotherapy—a marriage of engineering and medicine. Nano is the science of tiny, explains Rohan Fernandes, PhD, the leader of a team in the George Washington University (GW) Cancer Center, integrating nanoscience with the immune response. "Nanoimmunology takes these tiny particles that can interact with the immune system to elicit a robust response for any therapeutic purpose, whether it be infections or cancer," says Fernandes, who also serves as assistant professor of medicine at the GW School of Medicine and Health Sciences (SMHS).
How small are nanoparticles? The particles are measured in nanometers, a measure equal to a billionth of a meter. Nanotechnology is concerned with the use and control of structures that range from one to 100 nanometers in size.

Fernandes, 39, is an engineer by training who earned his PhD in bioengineering from the University of Maryland. After a fellowship at Johns Hopkins University, he came under the mentorship of Catherine Bollard, MD, associate center director for translational research and innovation at the GW Cancer Center, and professor of pediatrics and of microbiology, immunology, and tropical medicine at SMHS. Fernandes joined the GW Cancer Center in December 2017. “I thought my field [of nanotechnology] would be useful for immunology,” says Fernandes, adding that the science “is actually the dynamic interplay between the nano world and the immunotherapy world.”

Over his career, Fernandes saw a lot of neuroblastomas. As a grad student, he’d become familiar with the story of Alexandra “Alex” Scott, who, after being diagnosed with neuroblastoma, set up a front-yard lemonade stand to raise money for research. A year after Alex died in 2004, her parents started the Alex’s Lemonade Stand Foundation. “Alex’s courageous struggle was one of the motivations to undertake research that is more translational,” he explains. In January 2018, Fernandes and his team received more than $700,000 from the foundation for neuroblastoma research.

What are checkpoint inhibitors? They are molecules that block immune checkpoints, which are receptors or ligands that modulate the immune response. In many cancers, tumor cells express these checkpoints to “hide” from the immune system. Blocking the immune checkpoint “releases the brakes” on the immune system.

“We try to break up the tumor so that the tumor cells are killed by the nanoparticles, and in doing so we present the dying tumor cells to the immune system. Simultaneously, we take the brakes off the immune system, which recognizes the tumor cells, so the immune system can go after what we want.”

ROHAN FERNANDES, PhD

“A year after Alex died in 2004, her parents started the Alex’s Lemonade Stand Foundation.”

AN ENGINEER BY TRAINING
Rohan Fernandes, PhD is an engineer by training. He earned his PhD in bioengineering from the University of Maryland. After a fellowship at Johns Hopkins University, he came under the mentorship of Catherine Bollard, MD, associate center director for translational research and innovation at GW Cancer Center, and professor of pediatrics and of microbiology, immunology, and tropical medicine at SMHS. Fernandes joined the GW Cancer Center in December 2017.
A technique that uses temperature control to turn immunotherapy on or off in a tumor environment.

“When temperatures are at 60 degrees, the tumors are not immunogenic, meaning that the immune response cannot recognize the nanoparticles,” reports Juliana Caro-Mejia, a University of Maryland bioengineering PhD candidate. “With the heat varying in a window of 60 to 65 degrees, the tumor cells are expressing immunogenic markers. Finding this window was very exciting!”

The process has already been tested on mice. The results to date indicate that treatment can boost long-term survival rates by 50 percent in the treated animals. Testing on humans is not imminent, however. “The Food and Drug Administration is very stringent about allowing pediatric trials,” says Fernandes. His goal is to get into clinical trials within the decade.

At the Core

THE GEORGE WASHINGTON UNIVERSITY (GW) Cancer Center offers its investigators a wealth of state-of-the-art infrastructure for research and development, with additional resources available through a partnership with the Clinical and Translational Science Institute at Children's National (CTSI-CN). Much of the infrastructure to support GW research is organized in scientific cores offering a range of services, including the Nanofabrication and Imaging Center, the Research Pathology Laboratory, the Flow Cytometry Core Facility, the GW Biorepository, the Biostatistics Center, and the Cancer Informatics Core.

The Nanofabrication and Imaging Center includes a class 100 cleanroom equipped with a full spectrum of nanotechnology equipment, in addition to a microimaging suite with ultra-high-resolution lithography and scanning electron microscopy allowing visualization of structures at the atomic level.

A Research Pathology Core provides research services for both human and animal tissues, including tissue processing, embedding, sectioning, routine and specialized sample staining, frozen sections, and immunohistochemistry.

The Flow Cytometry Core Facility provides sophisticated cell sorting and cell analysis experiments, as well as services in data analysis, instrument training and cytometry education, and cytometry data.

The GW Biorepository is a comprehensive, state-of-the-art resource that features more than 100,000 biospecimens and clinical data related to HIV malignancies, neurology, and cancer cases.

The Biostatistics Center serves as the coordinating center for large scale, multi-center clinical trials and epidemiologic studies, offering statistical leadership for the design, execution, and analysis of multi-center clinical trials and epidemiologic investigations.

GW Cancer Center researchers also have access to GW’s Cancer Informatics Core pilot project, which provides collaborative informatics support for cancer research through guidance for software use and by acting as liaison for various next-generation sequencing data services.
**SUPPORT GROUPS**

The George Washington University Cancer Center, with support provided by the Dr. Cyrus and Myrtle Katzen Cancer Research Center (Katzen Center), offers a wide variety of holistic and wellness services for cancer patients and their families. These groups are free of charge and open to the community.

### THE GW MEDICAL FACULTY ASSOCIATES (GW MFA)

**2150 Pennsylvania Ave., NW**

Washington, D.C. 20037

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**ACTIVE TREATMENT**

(all cancers)

Open to patients currently in treatment. Registration required.

Second and Fourth Wednesday of each month, 12:30–1:30 p.m.

GW Cancer Center Board Room

MFA, first floor, 1-402

Facilitator: Lauren Broschak, LGSW

lbroschak@mfagwu.edu

202-677-6229

**ADVANCED BREAST CANCER GROUP**

Open to patients with stage IV breast cancer. Registration required.

Fourth Tuesday of each month, Noon–1 p.m.

GW Cancer Center Board Room

MFA, first floor, 1-402

Facilitator: Lauren Broschak, LGSW

lbroschak@mfagwu.edu

202-677-6229

**BRAIN TUMOR SUPPORT GROUP**

Open to brain tumor patients and survivors and caregivers.

Registration required.

First Tuesday of each month, 5–6:30 p.m.

GW Cancer Center Board Room

MFA, first floor, 1-402

Facilitator: Lauren Broschak, LGSW

lbroschak@mfagwu.edu

202-677-6229

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**GENTLE YOGA**

This group introduces patients and caregivers to the physical and emotional benefits of yoga.

Tuesdays, 4–5 p.m.

GW Marvin Center,

Fifth floor activities room

800 21st St., NW

Facilitator: Yael Flusberg

eruz@mfagwu.edu

202-677-6228

**HEAD AND NECK CANCER GROUP**

For head and neck cancer patients and survivors, and their caregivers. Registration required.

First Tuesday of each month, 12:30–1:30 p.m.

GW Cancer Center Board Room

MFA, first floor, 1-402

Facilitator: Alicia Gray, LGSW

algray@mfagwu.edu

202-677-6597

**KIDS’ CLUB**

For families with kids (ages 6–12) in which a parent or sibling is in treatment or is a survivor.

Fourth Wednesday of each month, 6–7:30 p.m.

Smith Center for Healing and the Arts

1632 U St., NW

Facilitators: Erin Price and Lauren Broschak, LGSW

202-483-8600

**MULTIPLE MYELOMA GROUP**

This group is open to multiple myeloma patients and survivors, and their caregivers. Registration required.

Third Tuesday of each month, 5:30–6:30 p.m.

GW Cancer Center Board Room

MFA, first floor, 1-402

Facilitator: Alicia Gray, LGSW

algray@mfagwu.edu

202-677-6597

**NUTRITION CLUB**

First Monday of each month, Noon–1 p.m.

GW Cancer Center Board Room

MFA, first floor, 1-402

Facilitator: Jennifer Leon

202-741-6489

**PROSTATE CANCER EDUCATIONAL GROUP**

The prostate cancer educational group is open to patients and survivors, and their caregivers. Registration required.

Second Tuesday of each month, 6–7 p.m.

GW Cancer Center Board Room

MFA, first floor, 1-402

Facilitator: Lauren Broschak, LGSW

lbroschak@mfagwu.edu

202-677-6229

**SURVIVORSHIP SERIES**

An educational series featuring a different speaker each month.

Second Thursday of each month, 11:45 a.m.–12:45 p.m.

GW Cancer Center Board Room

MFA, first floor, 1-402

Facilitator: Alicia Gray, LGSW

algray@mfagwu.edu

202-677-6597

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**EXECUTIVE COMMITTEE**

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**Robert E. Kelly, MD, CEO of the clinical enterprise, GW Medical Faculty Associates**

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**Helen Heslop, MD, PhD,** director, Center for Cell and Gene Therapy, Baylior University

**Marcy Waldinger, MS,** former chief administrative officer, University of Michigan
A TEAM Approach to Cancer Care

REPRESENTATIVES FROM 24 MULTIDISCIPLINARY HEALTH care teams nationwide joined the George Washington University (GW) Cancer Center for its inaugural TEAM (Together, Equitable, Accessible, Meaningful) Training program intended to help health care organizations implement quality improvements in patient-provider communication, cultural sensitivity, health literacy, and shared decision-making.

Leading experts discussed ways to support health equity, patient engagement, and culturally affirming cancer care. Keynote speaker Camara Jones, MD, MPH, PhD, past president of the American Public Health Association and senior fellow at the Satcher Health Leadership Institute, Morehouse School of Medicine, discussed the impact that social determinants of health and health equity can have on patient outcomes. Fellow speaker Tamika Felder, founder of Cervivor, a nonprofit cervical cancer awareness and support organization, stressed the need to support patient engagement in clinical care.

“When we were awarded funding from the Pfizer Foundation in 2016 to develop a project focused on reducing cancer disparities, we conducted extensive formative research with patients and providers to find out where the gaps [were] when it comes to patient-provider communication,” said Mandi Pratt-Chapman, MA, associate center director for patient-centered initiatives and health equity at the GW Cancer Center. “This training is the culmination of many months of learning for these teams, and we’re hopeful that the insights they gain will result in real positive changes as they return to their home institutions.”

Before arriving, participants completed an online course covering topics such as engaging patients and their loved ones in shared decision-making, increasing minority patient representation in cancer research, supporting patient self-advocacy, and enacting culture change to support the provision of culturally affirming care. The TEAM training is part of a multiphase project that includes development of patient resources.

“The GW Cancer Center is committed to advancing the health of all patients,” said Eduardo M. Sotomayor, MD, director of the GW Cancer Center. “Programs like TEAM represent a significant opportunity for institutions across the country to address inequities in health care that continue to challenge racial, ethnic, sexual, and gender minority cancer patients.”

To learn more, visit bit.ly/AboutTEAMProject.