Volume 4, Issue 2

MOFFITT MOMENTUM®

PORTRAITS OF HOPE, INNOVATION AND TRIUMPH

ADAPTIVE THERAPY
Mathematics lights the way

GLOBAL COLLABORATION
Large numbers give valid results

THE HUMAN MICROBIOME
Epidemiology And Surgery Intersect

Alan F. List, MD
President & CEO
Moffitt Cancer Center

MOFFITT MOMENTUM®
VOLUME 4. ISSUE 2

Dear Friends,

Recently we were excited to learn that the U.S. Food and Drug Administration announced approval of Yescarta, Kite Pharma's Chimeric Antigen Receptor (CAR) T-cell Therapy for adults with diffuse large B-cell lymphoma. The previous issue of Momentum included a feature story on how CAR T helped a patient with B-cell lymphoma who benefitted by participating in a clinical trial of CAR T here at Moffitt. Our own Dr. Frederick Locke was the co-principal investigator of the national multi-center trial leading to Yescarta's approval. Moffitt is proud to be leading the way in the development of this particular new immunotherapy and so much more.

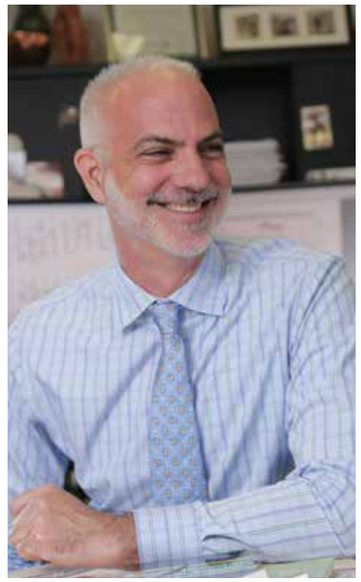
Sometimes a therapy can be deceptively simple, such as adaptive therapy, which uses existing treatments. The complexity comes into play when determining how to keep resistant cancer cells in check by giving just enough chemo to stop their growth, then repeatedly resuming or changing treatment. This requires the dexterity of our Integrated Mathematical Oncology faculty members Dr. Robert Gatenby and Dr. Alexander Anderson.

Other times, our patients require the soothing services of our interfaith, board-certified chaplains who work quietly behind the scenes, tending to matters of the spirit and soul.

And what would we do without our Board members like Valerie Goddard, who generously give their time and share their community knowledge and business expertise to help make Moffitt Cancer Center a better place?

Research areas described in this issue include collaborating on a global scale to find answers that will help lead to cancer cures and also that will help to eliminate cancer health disparities. And we are learning more about how the intestinal microbiome (the collection of microbes that includes bacteria, viruses and fungi) can affect our immune system and response to cancer treatment.

We hope you enjoy reading these stories, which share our growing global scientific research initiatives, innovative new treatments and more.



ADAPTING *for* SURVIVAL

Moffitt Researchers Study Cancer Therapy that Evolves as Patients Respond

By Ann Miller Baker

Alexander Anderson, PhD (left) and Robert Gatenby, MD

Photography: Jeremy Peplow

IMAGINE YOU ARE A CANCER PATIENT, ENDURING THE NEGATIVE SIDE EFFECTS OF YOUR CHEMOTHERAPY BECAUSE YOU ARE SEEING POSITIVE RESULTS.

YOUR ONCOLOGIST SAYS THE CHEMO HAS CONTAINED YOUR CANCER'S PROGRESSION – IT'S NOT GETTING WORSE. BUT IT'S DOUBTFUL THE DRUG CAN CURE YOU.

WOULD YOU WANT TO CONTINUE THE CHEMO IN SLIM HOPES OF OBLITERATING THE CANCER? OR WOULD YOU STOP?

TWO ICONOCLASTIC THINKERS at Moffitt Cancer Center argue that a break in treatment may be the key to living longer. Their approach, a containment strategy called adaptive therapy, is based on a mix of tumor biology and evolution with a hefty dose of high-powered mathematics. It seeks to turn now-lethal cancers into chronic disorders a patient could live with for years. And their theory is now yielding living proof: preliminary findings from Moffitt patients in adaptive therapy's first clinical trial.

TOXIC CHASE FOR A CURE

Robert Gatenby, MD, says the current maximum tolerated dose approach to cancer treatment is "probably the worst way you could give cancer therapy." He's watched it from the frontlines of patient care as a radiation oncologist and chair of Moffitt's Diagnostic Imaging and Interventional Radiology Department. Too often, he's witnessed cancer come roaring back after seemingly being beaten into submission.

Make no mistake: he's all for using standard therapy when it clearly can cure a patient's cancer. The trouble is - there are many situations where we now know cures are unlikely. A case in point is metastatic breast cancer. Not so long ago, many of these patients underwent grueling stem cell transplants, their hopes of a cure mostly in vain.

"There's always been this sense that if we just kill a few more cells, if we could use nine chemo drugs instead of three - we could get the cancer," he says. "But all you do is increase the toxicity for the patient. You don't increase the probability of a cure."

In fact, from his vantage point as a researcher and co-chair of Moffitt's Cancer Biology and Evolution Program, Dr. Gatenby says we're probably making matters worse.

"There's always been this sense that if we just kill a few more cells, if we could use nine chemo drugs instead of three - we could get the cancer."

NOT ALL CANCER CELLS ARE CREATED EQUAL

You might think a tumor is one homogenous mass of deranged cells, identically bent on growing out of control.

Not so. The cells within a tumor are diverse and continually evolving in response to their environment.

Some cancer cells gobble up resources to quickly multiply in place, a trait that makes them susceptible to chemotherapy drugs. Other cells are chemo-resistant. They don't exhibit the fast replication skills targeted by the drugs. Instead, they wait for opportunities and resources to migrate throughout the body, setting up new tumor outposts. Killing off the susceptible cells frees up resources for resistant cells to thrive and spread, in a well-documented phenomenon of evolutionary biology called competitive resistance.

Rather than trying to kill as many cancer cells as possible with as much chemo as a patient can endure, Dr. Gatenby theorizes, we should focus on keeping the resistant cancer cell population in check. Give just enough chemo to stop the cancer's growth – and stop treatment until the cancer's progression resumes. Then resume chemo or change treatment. And repeat.

But what treatment should come next? When? And how do you convince a patient to stop a drug that's working?

That's where Moffitt's math wizards come in.

WHY STOP WHAT'S WORKING?

Alexander "Sandy" Anderson, PhD, is well aware of the counterintuitive choice being suggested and has a ready argument. "Suppose I could give you five years of controlled treatment with a good quality of life," he says in his native Scots brogue, "or I can give you one year of excruciating, high-dose therapy to which you become resistant. Then I have to switch you to another chemo drug. Or, even worse, there may be no other drug." Leave it to the mathematician to lay out the logic for this choice.

Dr. Anderson is a relative rarity; a mathematical biologist. He spent a dozen years at the University of Dundee in Scotland developing mathematical models for many different aspects of tumor progression and treatment before Dr. Gatenby enticed him to move his team to Moffitt in 2008 and establish the nation's first Integrated Mathematical Oncology (IMO) Department. Moffitt's IMO now counts seven independent faculty members with their own labs, post-docs, PhD students and interns – all with Dr. Anderson as their chair. They can often be found in the IMO's collaboratorium, an informal gathering space replete with blackboards ideal for brainstorming. It's a cross between classroom and coffee house with chalk scrawls straight out of "Good Will Hunting."

Photography: Jeremy Peplow

Photography: Jeremy Peplow

These intimidating equations have a lot in common with the math that helps meteorologists predict the path of hurricanes. As Floridians, we spend summers monitoring TV weather, hoping not to be in a developing storm's narrowing cone of uncertainty. Each colorful strand of those "spaghetti plots" is the graph of an equation; a mathematical model that predicts the storm's trajectory based on various pertinent weather data run through a computer simulation. With every hour, as additional updated weather data are added to the various models, the spaghetti strands converge to predict a fairly precise point of landfall.

Like hurricanes, tumors are complex, ever-changing systems shaped by a variety of forces. Equations scrawled on the IMO's blackboards are meant to replicate the spaghetti plot of a cancer's growth and predict its future development. These equations don't simply make correlations based on a tumor's growth to date. They take into account what we understand about cancer biology – the mechanisms behind why certain types of cancer respond to one drug and not another, how the relative oxygen level in tumor cells can aid or hinder cancer growth and myriad other details.

Unlike hurricanes shaped by weather forces beyond our control, a tumor's development is also impacted by any of the multitude of treatments that physicians can choose to prescribe. Each one of them can be plugged into these equations to predict its potential effect on the patient's cancer.

"We can simulate hundreds of thousands of different treatments, different sequences, different combinations - you name it," Dr Anderson explains." And it's all done in the computer, without ever actually treating the patient."

But it's what happens once a treatment is chosen and administered that truly sets adaptive therapy apart.

ADAPTING TREATMENT TO KEEP UP WITH A PATIENT'S RESPONSE

To understand what's different about the adaptive therapy approach to treatment, it helps to understand how standard therapies work today. Whether it's standard chemotherapy or precision medicine tied to a type of genetic mutation, treatment

DR. ALEXANDER ANDERSON IS NAMED DISTINGUISHED ENDOWED CHAIR

As this issue of Moffitt Momentum goes to press, Moffitt Cancer Center is pleased to announce that Dr. Alexander "Sandy" Anderson has been named the **Richard O. Jacobson Distinguished Endowed Chair** in the Department of Integrated Mathematical Oncology. The chair is made possible by a gift from the Richard O. Jacobson Foundation.

This generous gift will accelerate Dr. Alexander's work which is focused on integrating mathematical and computational modeling approaches with experimental and clinical data to better understand cancer growth and development and translate this understanding into novel therapies, ultimately benefitting patients with cancer.

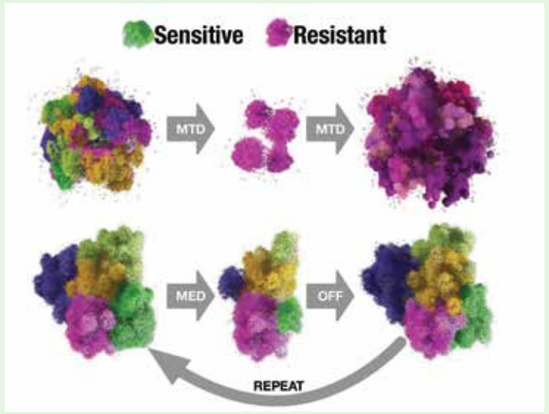
"It's like developing a personal spaghetti plot of a patient's cancer over time.

Instead of ignoring the patient's response to the treatment, you use that information to make a decision about how you should treat them next."

is administered according to a protocol. A strictly detailed plan for the course of treatment, protocols are evidence based – meaning, it's the product of past experiences of a multitude of patients with a similar diagnosis. Treatments follow a fixed schedule.

BUT EACH PATIENT – AND EACH TUMOR – IS UNIQUE.

Adaptive therapy creates a unique treatment strategy guided by the individual patient's experience. Updated information about the patient's treatment response – and how their tumor cells are evolving to survive and thrive - is constantly being fed back through its mathematical models.



This slide illustrates the key difference between Maximum Tolerated Dose treatment (upper panel, where treatment is given at maximum strength leading quickly to the dominance of resistant cells in the tumor) and Maximum Effective Dose treatment (lower panel, where treatment is given to control growth leaving behind both sensitive and resistant cells that regrow when treatment stops) in treating a heterogeneous tumor that contains both sensitive (green) and resistant cells (pink).

It's like developing a personal spaghetti plot of a patient's cancer over time, says Dr. Gatenby. "Instead of ignoring the patient's response to the treatment, you use that information to make a decision about how you should treat them next."

He says that allows for a personalized long-term strategy. "There are often many drugs to treat a given type of cancer," he explains. "If you can use those intelligently, maximizing the time to progression with each of them, you could imagine stringing together treatment strategies. The models also allow you to think through the sequence of drugs that you're going to give, so that one follows the other in a way that makes sense, as opposed to a sort of 'whack a mole' approach."

"It's a continuous process. And the strategy is constantly building on what was done before."

It sounds perfectly logical. In a landmark paper in the prestigious journal Cancer Research in June of 2009, Dr. Gatenby's team demonstrated adaptive therapy's effectiveness on an ovarian cancer tumor cell line growing in immune-deficient mice. And the team's work made the cover of Cancer Research this May with a study that used computer models to predict that small changes of the pH within mouse prostate tumors could tip the balance between chemo-sensitive and resistant cells. By adding sodium bicarbonate to the drinking water of mice to change the pH of their prostate tumors' environment, they found that susceptible cells within the tumors developed a survival advantage over the invasive tumor cells. As a result, the mice had smaller tumors that were confined to the prostate - and fewer invasive metastatic tumors.

But the true test is applying adaptive therapy in humans. A select group of Moffitt prostate cancer patients are now blazing that trail.

A FORTUITOUS FIND

Robert Butler is something of an adventurer. Along with wife Caroline, he was a well-traveled engineer with postings in Qatar, Holland, Oman, Syria, Nigeria and lastly, Houston, before retiring in Tampa to be close to his sons. All those travels didn't lend easily to developing an annual routine with a physician. Mr. Butler's prostate cancer diagnosis was, as he puts it in his clipped British accent, "purely fortuitous." He simply needed a prescription refill when he visited his family practitioner ten years ago and happened to ask if, at age 64, he might need any type of health screenings.

The news was not good. His PSA level was 76; normal range is below 4. A biopsy revealed aggressive cancer throughout the prostate, making surgery impractical. Though scans found no evidence elsewhere in his body, his doctor cautioned that didn't mean the cancer hadn't spread. It just wasn't detectable.

Mr. Butler went through radiation, chemo, immunotherapy, you name it. His cancer still progressed to late stage four. Then in 2015, his Moffitt oncologist, Jingsong Zhang, MD, put Mr. Butler on abiraterone (Zytiga), a relatively new type of chemo that blocks production of the testosterone crucial to prostate cancer

Photography: Ray Reyes

growth. If taken regularly, previous studies had shown it might give Mr. Butler a year without cancer progression.

But Dr. Zhang had a different option in mind. Intrigued by evolutional biology in cancer treatment since his graduate student days in a research lab, Dr. Zhang had been showing up at the IMO's math meetings for years. He suggested prostate cancer would be a perfect model to test the adaptive therapy approach. With a Moffitt Foundation grant for a pilot study, he collaborated with Drs. Gatenby and Anderson to construct adaptive therapy's first clinical trial in 2014. He thought this trial might be a good fit for Butler.

To the engineer in Mr. Butler, Dr. Zhang's description of adaptive therapy "seemed a very reasonable thing to do. You don't give the cancer cells too much of a chance to look at this stuff and martial their defenses against it if you just take it in short sharp bursts and then you stop," he surmised. "Taking it regularly every month as has happened hitherto must give the cancer cells more of a chance to see what they're up against and adapt accordingly."

Mr. Butler has been on and off the drug for two years now. He stops when monthly PSA levels drop to 4 or below, and starts

Moffitt genitourinary oncologist Jingsong Zhang, MD (left), is intrigued by evolutional biology and is conducting a clinical trial of adaptive therapy.

"You don't give the cancer cells too much of a chance to look at this stuff and martial their defenses against it if you just take it in short sharp bursts and then you stop..."

again when they top 15. In between, he may be off the drug for months at a time with the only discernable difference, he says, "in my wallet." Without insurance, the drug costs $9,000 a month. Dr. Zhang refers to it as "financial toxicity," another reason some patients can't take the continuous therapy that is the standard of care. Any opportunity to reduce the amount of drug needed provides an added benefit.

In the nearly two years since the trial began, Dr. Zhang says, the adaptive therapy approach has matched or exceeded the benchmark established for standard, continuous drug therapy. Eleven study patients have survived without progression for more than a year so far – on half the amount of drug.

Dr. Zhang is cautiously optimistic about preliminary findings from such a small group: "what we can say right now is that adaptive therapy is feasible for this patient population." But he says this study provides the groundwork for further trials and, perhaps, more confident statements about adaptive therapy in the future. Dr. Zhang notes Moffitt has "the right people and the resources to do this."

In fact, five more adaptive therapy clinical trials are currently in the works for melanoma, ovarian, thyroid, breast and lung cancer. And a clinical trial of adaptive therapy as a first-line treatment for prostate cancer patients is awaiting final approval.

A SPAGHETTI PLOT APP

Not every cancer care practitioner has access to an IMO Department of mathematicians to run individual simulations on each patient. Nor will they need it, if Dr. Anderson has his way.

He's developing an adaptive therapy app to run on a clinician's smart device. For efficiency's sake, Dr. Anderson foresees an app linked to electronic health records that could automatically pull all of a patient's pertinent information and "load it into a model that would run, make predictions and then deliver visually to the clinician - these are your options. It will even give a statistical likelihood of this being the best drug versus that."

The plan is to initially demonstrate its usefulness among Moffitt patients and clinicians. That will require physicians to buy in to adaptive therapy for their patients. Dr. Gatenby says the concept is already gaining momentum. Clinicians and researchers worldwide clamor to gain access to Dr. Anderson's annual week-long IMO workshop for hands-on experience with mathematical modeling for cancer treatment. And as clinical trials of adaptive therapy continue, Dr. Gatenby hopes findings will sway more supporters.

"The good preliminary results from our first clinical trial have motivated other clinicians to get involved," he notes. "We actually think we could turn prostate cancer into a chronic disease. I think that it's a reasonable expectation."

"I think we've broken the logjam in terms loosening the strategy for therapy – this sort of grip of the high-dose density that has held oncology for 50-60 years. We can at least say we've shaken that up enough that people are willing to try other things."

One can only wonder – and hope for - what they'll come up with next.

Photography: Rachel Lawrence

Spiritual Salve

MOFFITT CHAPLAINCY CARE HONORED FOR EXPANDING REACH

By Cathy Clark and Ann Miller Baker

Photography: Rachel Lawrence

The son hadn't even made it back to his home in north Florida when the call came through on his cell phone. It was Moffitt Cancer Center, where he'd just been visiting his dad. Things had taken a turn for the worse.

With the phone held to his ear for one final father and son talk, the patient took his last breath.

The fact that this emotional call even took place owes to the help of Moffitt's Chaplaincy Care team. Manager Rev. Valerie Storms helped to track down the son and prepare him for the situation he was about to face. Not every interaction with the Chaplaincy Care team is as dramatic or poignant. But Storms says each interaction is vitally important.

For patients with cancer, physical pain is often accompanied by spiritual distress. Moffitt Chaplaincy Care can provide a salve for these spiritual wounds. Its five full-time board-certified chaplains (BCC), bolstered by another five as-needed chaplains and local clergy, all hold credentials in their own faith traditions. But like the health care professionals they work alongside, the chaplains have trained in their own specialty: listening skills and the ability to connect with patients on spiritual issues that accompany a cancer diagnosis. Interfaith in approach, Moffitt chaplains offer patients, family members and Moffitt team members opportunities to reflect on their spiritual concerns and to garner strength from their beliefs.

Rev. Storms, an ordained Baptist minister and past president of the Association of Professional Chaplains, says an important facet of the chaplains' work is simply "being there." Often just getting something out in the open can help a patient and their loved ones to face a difficult diagnosis, for example, and then reach out for necessary assistance and resources. Chaplains are trained and experienced in being available to facilitate conversations. And while chaplains willingly contact a leader within the patient's faith upon request (including rabbis, priests, imams and other spiritual leaders), Rev. Storms says patients can find it helpful to speak with someone one step removed.

"Many times a patient prefers to talk to a hospital chaplain," Rev. Storms explains, "because, not being part of their spiritual community, they feel more anonymous and often will open up and share things they otherwise would keep to themselves."

The challenge is making sure patients and family members know that Moffitt's chaplains are here to help in ways that reach beyond organized religion.

Last year, the Chaplaincy Care Department partnered with Supportive Care Medicine on a project called "In The Spirit." Its aim was to improve delivery of spiritual care to inpatients referred to Supportive Care Services for palliative care at any stage of illness. Team members identified a spiritual care quality measure through collaboration with the Global Palliative Care Quality Alliance and initiated plan-do-check-act iterative cycles to monitor and improve outcomes. Revised electronic health record templates, standardized chaplaincy workflows and automatic referral processes were developed.

When filling out information upon admission, each patient is automatically asked if they have a faith connection and a note is made in the electronic health record. Patients are also informed that Moffitt chaplains make regular rounds through the units and can stop in to visit. Any patient being served in Supportive Care Services is automatically referred to Chaplaincy Care for a visit.

The "In The Spirit" initiative didn't take long to generate results. At baseline in February 2014, 60 percent of SCS inpatients referred to the chaplains were visited and received a spiritual assessment within 24 hours of the referral. By January 2016, compliance rates for completed spiritual assessment for SCS patients within 24 hours of referral climbed to 100 percent. The compliance rate consistently continues to be between 90 to 100 percent

Photography: Ray Reyes

Photography: Ray Reyes

L-R: Tony Winter, chaplain; Sandy Harbour, chaplain; Sean Powell, director, Case Management and Patient Family Services; Michael Miller, chaplain; Mareda Kennedy, chaplain; Valerie Storms, manager, Chaplaincy Care.

NUMBERS GARNER KUDOS

In late February, team members across the institution gathered at the 2017 Spirit of Moffitt Awards. Seven teams in various categories were recognized for efforts that improved processes or services, increased efficiencies or positively impacted the work environment at Moffitt.

But only one team would walk away with the highest honor, the Nick Porter Award. Named for our now-retired executive vice president of Institutional Advancement and Corporate Relations, the Nick Porter Award is given to the team that best exemplifies Moffitt's core values, persists despite obstacles and increases team member morale by acting as a role model to other departments.

Chaplaincy Care and Supportive Care's "In The Spirit" initiative was named 2017's Nick Porter Award recipient. But that honor is not the highest reward for their efforts. Rev. Storms says it can be found in the faces of the patients and families who find a path to some spiritual strength and comfort with help from Moffitt's chaplains.

"The scientists and medical doctors work miracles with modern science and the latest treatments," she says, "while the chaplains work quietly behind the scenes, tending to matters of the spirit and soul."

For the patients and families served, it seems they are equally sacred callings.

Photography: Rachel Lawrence

MOFFITT'S INTERFAITH CHAPEL

Moffitt's trained chaplains spend most of their time at bedsides, in waiting rooms or quiet spaces. But there is another spot always open for contemplation and prayer. Moffitt's Interfaith Chapel is located on the first floor of the hospital on the Magnolia Campus, near the Publix Pharmacy.

For more information, call 813-745-2856.

THE BEST OF

BOTH WORLDS

MOFFITT PHYSICIAN-SCIENTIST TRACKS ROOTS OF PROSTATE CANCER DISPARITIES THROUGH NATIVE GHANA

By Ann Miller Baker

Kosj Yamoah, MD, PhD, is a man who's familiar with having a foot in two different worlds.

Some days as a radiation oncologist in Moffitt Cancer Center's clinics, he says, something just seems to click. He might be seeing prostate cancer patients or maybe those with other types of genitourinary cancers, "and suddenly I realize I'm seeing a consistent problem. I'm thinking - we can do better here! It begins to form the basis of a hypothesis that can be tested," explains the scientist in Dr. Yamoah. "Those are 'aha' moments!"

Except, he notes with a chuckle, for the manager of his Moffitt research laboratory, who knows what's coming. "He'll say - 'When Kosj gets that look, that's crazy dangerous, because his mind begins to go wild!'" More than once, Dr. Yamoah's wild thoughts reduced to a one-page draft have become studies that his office and lab staff hadn't exactly been expecting. "And they'll say - do you know how much work you just unleashed on us?"

Hard work is how he's gotten this far in just 37 years; a man with dual careers and dual citizenship on two continents.

A PASSION TO HELP OTHERS.

Long before he became a physician, a researcher and the father of a child with cancer, Kosj Yamoah was a child of Ghana, a country roughly the size of the state of Michigan on the Gulf of Guinea in western Africa. Ghana has its own dichotomies – traffic and all the trappings of the western world in its capitol Accra, with mud huts 20 miles away. Growing up in Accra's suburbs, Kosj was driven by two passions: a desire to help others and a need to learn. He was the youngest of four, teaching himself to

TOP LEFT: Kosj Yamoah, age 17, teaching as a medical student in Ghana and presenting a research hypothesis. TOP RIGHT: Young Yamoah with his father Rev. Dr. John Yamoah and Rev. Amartey-Amarh, the assistant headmaster of Achimota Secondary School, after orientation day when he was admitted to high school at the age of seven. It was a national sensation to be the youngest in the whole of Africa to enter high school at that age.

"I wanted to work with people globally to look at one common problem from both the advanced world and the developing world."

read by borrowing his siblings' textbooks. He made national news after acing Ghana's high school entrance exam – at age seven. When young Kosj was allowed to join his older siblings at boarding school, he quickly became its de facto health officer, accompanying older students to hospital as a liaison with their physicians. "As much as I enjoyed studying and making my own discoveries," he reflects, "I felt most alive when I was helping people recover."

By age 19, he'd completed Ghana's two-year medical school track and applied for graduate studies at Mount Sinai in New York City. Here he discovered the path to serve both his passions, as a physician and a researcher, through its medical scientist training program. Within three months, his work in the research lab led to groundbreaking publications. No wonder his application for permanent U.S. residency under the national interest waiver was granted. Before he'd completed his residency and radiation oncology fellowship, he'd been awarded two competitive research grants.

And through his mentors, he'd identified the perfect intersection for his research and clinical interests: prostate cancer and its inordinate incidence and mortality among black men.

According to the National Cancer Institute (NCI), African-American men have the highest rate of aggressive prostate cancer and related deaths of any ethnic group in the United States. And in sub-Saharan Africa, prostate cancer is the second leading cause of cancer deaths among men.

PROSTATE CANCER: A PROBLEM IN BOTH WORLDS

"Prostate cancer is a problem among black men in Ghana and throughout Africa – just as it is in the United States," observes Dr. Yamoah. "It made sense to focus my efforts on this disease. I wanted to work with people globally to look at one common problem from both the advanced world and the developing world."

As an assistant member of Moffitt's Cancer Epidemiology Program, Dr. Yamoah's research focuses on the biologic factors behind prostate cancer disparities. Global scientific collaborations can help researchers tease out the details of underlying biology by comparing subsets of patients from far-flung corners of the world. Whatever holds true despite differences in diet, environment, socioeconomic status or other confounding factors is often meaningful. It can also be helpful to look at subpopulations of patients whose genetic makeup is less of a melting pot than of those in the U.S., where self-identified African Americans may unknowingly have a multi-ethnic heritage.

Among Dr. Yamoah's more than 30 peer-reviewed publications, one study identified a subset of genes known as biomarkers which define an aggressive type of prostate cancer more common in black men of African origin, whether they are now "from Jamaica, the Bahamas, Nigeria, Senegal, Ghana, the U.S., you name it," he says. He hopes that further study of these genomic biomarkers will lead to development of better treatments, much like identification of BRCA gene mutations in women led to more personalized treatment plans for breast cancer.

COLLABORATING TO REDUCE DISPARITIES

With his strong ties to Ghana, Dr. Yamoah was tapped by a mentor to become a co-investigator with an NCI-funded consortium called MADCaP (Men of African Descent and Carcinoma of the Prostate), which brings together researchers from the U.S., U.K., Africa and the Caribbean. It's work he's continued and expanded upon at Moffitt. Dr. Yamoah's goal with this group is to develop a biorepository – a retrospective data bank of information from prostate cancer patients in 18 participating countries to aid in creating protocols for use globally. He's also part of a subgroup called Bio-MADCaP, focused on eventually collecting biospecimens for collective study of the biology of prostate cancer.

Funding for such ambitious initiatives can be challenging, with tightening competition for government and philanthropic grants. That's one reason why Dr. Yamoah has also become involved in the George Edgecomb Society at Moffitt. This unique opportunity seeks to partner with the community in generating support for research aimed at reducing racial disparities in cancer incidence, mortality and survivorship.

It's exactly the type of research that Dr. Yamoah has undertaken, both in the U.S. and in Ghana. He continues collaborative work between Moffitt and the University of Ghana Medical Center in search of ways to predict aggressive prostate cancer in men of African origin. The two institutions are working to develop the Ghanaians' prostate cancer program into a center of excellence with Moffitt oversight. Some of Dr. Yamoah's Moffitt colleagues are also discussing a collaborative project involving breast cancer among younger women, another increasing problem in Ghana.

These collaborations extend to programs like M-POWER, the Moffitt Program for Outreach Wellness Education and Resources, to address cultural and behavioral barriers to cancer screening and treatment. "You'd be surprised how much similarity there is in the attitudes on both continents," he adds with a laugh. "Patients say, 'I don't want to get checked!'"

WORKING TOGETHER TO LIVE HEALTHY

The key, says Dr. Yamoah, is dispelling the notion that physicians are the bearers of bad news. "We need to change that mindset - and establish that we can show you how to live healthy. That change can only come from people like us who can say – I am at risk as much as you are. And we want to work together to prevent this."

Dr. Yamoah's connection to his patients has deepened through personal experience. His son Zion was just four years old when he succumbed to brain cancer in July of 2016. Zion's cancer battle began just as Dr. Yamoah joined the faculty at Moffitt. He spent many days and nights in the hospital with his son on "the other side" of the consultation table, this time as the father of a patient rather than physician.

While Zion bravely dealt with chemo, radiation and surgery "like a champion," his father continued researching and seeing patients at Moffitt whenever possible. Not all of Dr. Yamoah's patients knew about Zion's battle. It's a story he shares selectively, when he thinks it will help the patient. Those that knew, he says, often couldn't wrap their minds around how he was able to function and be present for their care.

"I still have moments where it's very difficult when I hear patients talking about their grief, because it reminds me of my own pain," he reflects. "But I have realized that sometimes sharing that moment of connectivity with their problems and what I've been through can give them the strength to move forward."

Dr. Yamoah keeps his smiling boy's photos throughout his office, along with pictures of his daughter Zoe-Elle. His wife, Jaymi, keeps alive the memories of the baby boy who "sang and danced in her womb" through the non-profit she founded, called Out of Zion. It provides a creative program including music, dance and the arts – things that Zion so loved - for children with medical and special needs at no cost to the caregivers. Pediatric cancer patients and their families were the first to benefit from an Out of Zion program at the Children's Cancer Center in Tampa. More kids in the Tampa area and in New York City had the opportunity to "Shine Like a Superhero" at Out of Zion summer programs; celebrations that serve as a balm for the Yamoahs first year without their precious young boy.

"We miss him," Dr. Yamoah says simply. "And I don't know what the whole experience means to my journey, my story - why couldn't I, an oncologist, have changed things? We may never be able to understand."

"What I do know is that I have to keep on moving forward with him in my heart, and that's where I'm at."

For that part of the journey, Dr. Yamoah draws strength from his faith, family and the work that remains his passion. After all, there is still so much to learn – and so many more to help.

Dr. Kosj Yamoah is a Moffitt radiation oncologist whose clinical focus is genitourinary malignancies. His collaborative work focuses at reducing cancer disparities across the globe.

International Search for Answers

MOFFITT RESEARCHERS LEAD GLOBAL TEAM SCIENCE EFFORTS

By Ann Miller Baker

Moffitt researchers will go to great lengths in pursuit of the next breakthrough in understanding, treating or preventing cancer. Some are studying data from patients literally a half a world away – Israelis with colon cancer, Swedes with melanoma, even Australians with ovarian cancer.

Their work is done in offices or labs on our Tampa campus. It's shared via email, internet, occasional international meetings and regular conference calls at all hours to accommodate multiple time zones.

They are on the forefront of a concept called global team science: contributing to and analyzing patient data from numerous cancer studies worldwide in collaboration with their scientific colleagues around the globe.

To understand why such collaboration is vital, it helps to understand the type of research involved. Unlike experimental studies that use a new intervention or treatment in animal models or clinical trials and compare the results to those of existing standards of care, global team science efforts often involve observational, case-control studies. These studies compare two groups of people: one group with a certain type of cancer (cases) and another group without that cancer (controls). They are called observational because researchers don't assign participants to a treatment or intervention. The study volunteers may only be known as data on a spreadsheet or specimens to be processed. The premise is to look for differences (genetics, environmental exposures, other factors) between the two groups in hopes of explaining why and how the cancer occurred – information that is a first step toward new treatment or prevention strategies. Valid research results require large numbers of observations, not easily accomplished when the cancer under study is rare.

Photography: Jeremy Peplow

Peter Kanetsky, PhD, MPH, chair of Moffitt's Cancer Epidemiology Department, leads several such efforts. "I had dark hair when I started," he says half-jokingly, recalling his early days at the University of Pennsylvania where he recruited families at high risk for melanoma to a study called GenoMEL. Established in 1997 as a non-profit consortium of melanoma research groups worldwide, GenoMEL was founded to study variation in a gene called CDKN2A that predisposed these families to melanoma. GenoMEL now counts Dr. Kanetsky as one of three principal investigators. He also is instrumental in two more international research consortia: GEM (Genes, Environment and Melanoma) studying melanoma patients from the U.S., Canada, Italy and Australia; and TECAC (the International TEsticular CAncer Consortium) with testicular cancer patients from throughout the U.S. and European countries including Germany, the Netherlands, Norway, Denmark, Italy and the U.K.

Dr. Kanetsky co-authored a paper with his international TECAC colleagues that appeared in Nature Genetics this June. Their results uncovered eight new genetic markers associated with an increased risk of developing testicular germ cell tumors (TGCT), the most common cancer in men aged 20 to 39 years in the U.S. and Europe. Testicular cancer is relatively rare with only 8,850 cases expected this year in the United States, and 95 percent of all cases begin in the testicular germ cells responsible for producing sperm.

The modest number of TGCT patients illustrates one need for global collaboration. "When you're studying common cancers such as breast cancer or prostate cancer one might be able to get away with a local study," explains Dr. Kanetsky. "In a rarer cancer where numbers are scarce, you have to reach further. Very often that means reaching to other continents, to other collaborators who might be doing similar research in the rarer cancer that you are studying." For their June 2017 paper, TECAC researchers analyzed combined data from more than 3,500 TGCT cases in five previous international studies.

Dr. Kanetsky says there are two sides to power in numbers. While they are necessary to observe genetic differences for rarer cancers, he points out, "you can also observe more modest effects as you increase those numbers. The more numbers we get into our studies, the better our ability to make inferences about small effects."

And when it comes to genetic predisposition to cancer, small effects can add up to big problems.

Clear genetic culprits, like high-risk BRCA genes in breast cancer or CDKN2A in melanoma, have been identified by studying

IT'S BEEN SAID THAT, WHEN SEARCHING FOR NEEDLES IN A HAYSTACK, IT HELPS TO BRING A MAGNET. SEARCHING FOR GENETIC CONTRIBUTORS TO CANCER RISK HAS BECOME A LOT LIKE THAT HAYSTACK.

families who've had multiple members diagnosed with these cancers. While these high-risk genes dramatically increase a person's risk for the cancer, they account for only a small portion of cancer cases overall.

That leaves investigators searching for lower-risk genetic variations, like needles scattered throughout the haystack of a person's genome. This haystack's magnet is an innocent looking piece of plastic no bigger than a thumb drive. Called a microarray, it's a chip containing hundreds of thousands of microscopic spots. Each one corresponds to strategically selected markers of genetic variation called "snips," or single nucleotide polymorphisms (SNPs). Everybody has countless SNPs in their genome. They may have little or no impact at all. The SNPs measured in these arrays have been picked from points throughout the genome because they're associated with certain heritable traits or a variety of diseases.

DNA swabbed from a person's cheek, isolated from saliva or extracted from a tube of blood is loaded onto the chip and scanned by automated lab machines to see how strongly it matches the array's SNPs. Matches that turn up more frequently in people with a particular cancer than in healthy controls are said to be associated with the cancer. And they can be more common than you might think.

"Typically, these genetic factors are common variants – meaning, anywhere from five to 50 percent frequency in the overall general population - and on average, have very small effects on disease risk," explains Stephanie Schmit, PhD, MPH, an assistant member in Moffitt's Cancer Epidemiology Department. While BRCA or CDKN2A can magnify a person's cancer risk 400 to 700 percent, these variants might only increase the odds of developing cancer by a few percent. "Because the effect sizes are so small," she says, "it takes a lot of people to be able to detect them."

Dr. Schmit has been in the lab studying colorectal cancer with one such array since she was a PhD student. Much of her work has been in conjunction with two global efforts: the Molecular Epidemiology of Colorectal Cancer Study (MECC), a population-based case-control study of over 10,000 individuals in northern Israel, and the ColoRectal Transdisciplinary Study (CORECT), an international consortium studying nearly 100,000 participants. She is the lead author of a paper pending publication that identifies 11 previously unknown risk variants for colorectal cancer.

"I didn't recruit a single one of these 100,000 research participants myself," says Dr. Schmit, "but I'm taking advantage of this wonderful research infrastructure and resource that hundreds of investigators and their teams have built over more than 30 years. Progress is incremental - it's going to take time, but we're really making some good strides."

Variants like those identified by Dr. Schmit's global group provide new points on the genome to investigate. But unlike high-risk genes, these low risk-conferring variants don't lead almost unequivocally to cancer. It may take many of them - along with environmental and lifestyle factors - to tip a person into a high-risk category for a given cancer.

Once new variants are found, the question becomes – what do they do? And how might we intervene to lower the risks? Moffitt's contribution to those answers comes in part from a researcher with his own global connections.

PROBING HOW THEY WORK

Alvaro Monteiro, PhD, trained as a scientist in his native Brazil, France, Belgium and Japan. In the late 1990s he worked in the labs of New York City's Rockefeller University which counts dozens of Nobel Prize laureates and Lasker Award recipients among its scientists. It wasn't until his daughter was born and New York's Twin Towers came down that he seriously entertained an offer to come to Tampa from his colleague, Moffitt Center Director Tom Sellers, PhD, MPH.

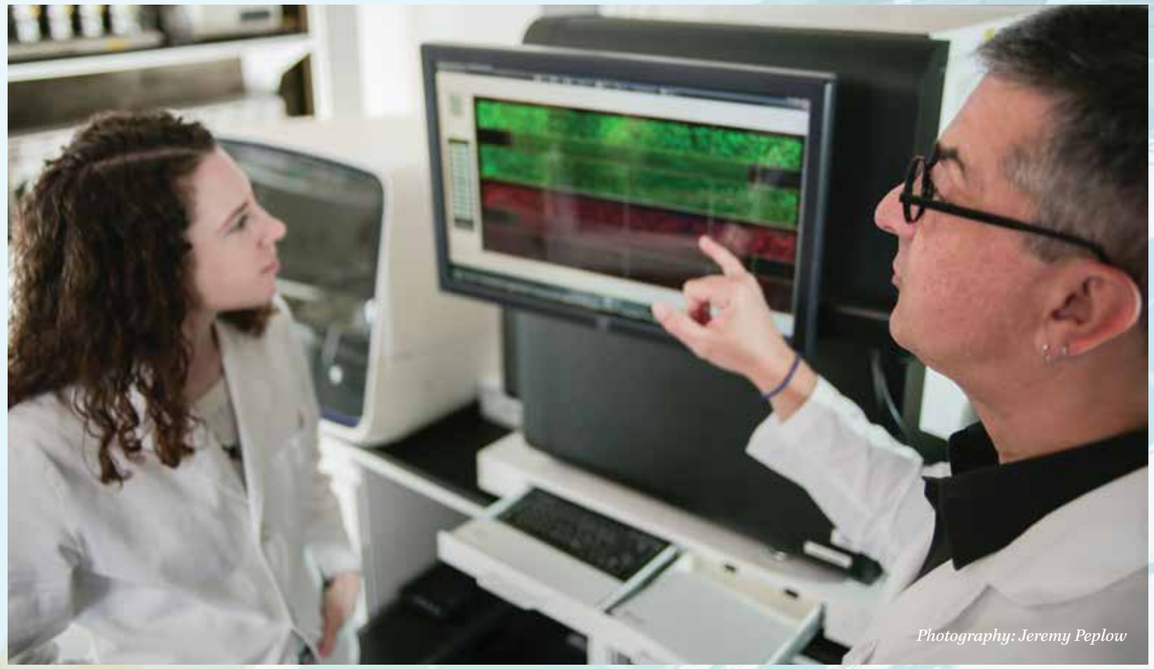
Early in his career, Dr. Monteiro focused on figuring out how high-risk genes predispose families to certain cancers. Dr. Sellers wanted him to set up a Moffitt lab to analyze a number of low-risk variants found through an international project they both participated in, called COGS (Collaborative Oncological Gene-environment Study). COGS was a huge undertaking, uniting four global consortia focused on genetic susceptibility to breast, ovarian and prostate cancers. It designed its own custom array with over 200,000 SNPs, producing a vast amount of data. Dr. Monteiro set up his lab in Moffitt's Cancer Epidemiology Department, and joined the effort to explain how the newly discovered variants worked to increase cancer risk.

In earlier studies of familial cancers, each anomaly mapped neatly to a gene responsible for building a protein. Scientists inferred that the mutated genes make defective proteins, leading to cancer. But with the new COGS variants, says Dr. Monteiro, "the first thing we saw right off the bat was that 90 percent of them are located in regions of the genome that do not code for proteins."

It turns out many of these low-risk variants are regulatory elements. "We think they have smaller effects on cancer risk because, instead of producing a bad protein, they just change the levels of proteins that are produced," says Dr. Monteiro. But regulatory region anomalies don't map so neatly to their targeted protein-coding genes. The two may not even be physically close,

Photography: Jeremy Peplow

ALVARO MONTEIRO, PHD (LEFT), AND STEPHANIE SCHMIT, PHD, MPH



Photography: Jeremy Peplow

"The first thing we saw right off the bat was that 90 percent of them are located in regions of the genome that do not code for proteins."

instead relying on the folds that fit a six-foot strand of DNA into a tiny cell to bring them together.

Finding the connections would require an entirely new approach. "None of the methods were there," says Dr. Monteiro. "We've spent the past five to seven years adapting the experimental methodology and the standard operating procedures of how we go about figuring this out."

Through its work with a National Cancer Institute consortium called GAME-ON (Genetic Associations and Mechanisms in Oncology), Dr. Monteiro's lab helped to develop a framework with bioinformatics and custom arrays to sift through the massive amounts of data produced worldwide by all of these genome-wide association studies, looking for the mechanisms of how variants increase cancer risks.

Understanding the mechanism is the key to expanding or designing new treatments or prevention therapies, says Dr. Monteiro. "And once you identify what's gone wrong with the biology, you can make generalizations. You might have a person who doesn't have exactly the same variant, but their cancer has the same mechanism and therefore might respond to any therapies we develop in these cases."

He says it also changes the way scientists think about developing those new drugs and therapies. It's no longer simply a matter of finding a way to interfere with the gene that's producing a defective protein. Since over 90 percent of the new, low-risk variants being discovered are regulatory elements, researchers now broaden their focus to interfering with faulty regulation of the genes.

Each new variant identified provides another clue to how myriad forces interact to cause cancer. Dr. Monteiro was one of several Moffitt Cancer Center researchers who took part in a major international study published in Nature Genetics this March. It identified 12 new genetic variants associated with an increased risk of developing epithelial ovarian cancer, the most common and dangerous type of the disease. All 18 previously identified ovarian cancer risk variants were also confirmed. The study, led at Moffitt by Dr. Monteiro's Cancer Epidemiology colleague, the late Catherine Phelan, MD, PhD, MMS, was a collaborative effort of more than 400 scientists from the U.S., U.K. and Australia. It utilized a next-generation tool called OncoArray to survey and compare over a half a million SNPs among nearly 100,000 women worldwide.

"The importance is that we are clawing into that fraction of the genetic contribution to cancer that is not explained right now," says Dr. Monteiro. "We're making dents on it," he adds, hopeful that eventually all of those dents will yield the answers we seek.

With help from Moffitt, this global team of scientists is set on providing answers for cancer patients worldwide.

Photography: Raj Rejes

A Passion to *Transform Lives*

COMMUNITY LEADER MOVES MOFFITT VISION FORWARD

By Ann Miller Baker

Valerie Goddard didn't have to search for role models and direction in her life.

Growing up in a military family that traveled the world gave her an appreciation for the richness of diversity – and an extended family and friends that she jokes is like "a little United Nations."

VALERIE GODDARD
BOARD MEMBER + ADVOCATE

HER AUNT HAD A CAREER STRAIGHT OUT OF "HIDDEN FIGURES," except that this math genius was exploring oceans as one of the Navy's first nautical cartographers for submarines.

And her grandmother Altamese Brodie, "the love of my life," says Goddard, was a transformational influence in the lives of children and families in the Tampa Bay area for over 55 years as the administrator at Helping Hand Day Nursery, Inc.

Great strength, compassion and desire to serve others shaped Goddard's life as a wife, mother of two and now as CEO and Chief Strategist of The Goddard Group.

No wonder, then, when she hosted a Moffitt Cancer Center health disparities summit in 2010 as chair of the Children's Board of Hillsborough County, she became intrigued by a new opportunity to serve. Moffitt's vice president of Diversity, Public Relations and Strategic Communications B. Lee Green, PhD, invited Goddard to tour the hospital and learn more, in hopes that she might join the Moffitt Hospital Board.

Goddard recalls being moved by the cancer center's history and excited about its clinical pathways work. "I value data and utilize data-driven decision-making while assisting my clients in achieving their organizational goals" she explains, "and here were personalized care models with strategy, data and outcomes tracked for each patient." But what really sold her was the tour – "such a jewel! Even with all my community involvement, I had never been to Moffitt before that day. Shortly after joining Moffitt's Hospital Board in 2011, that passion became even more personal for Goddard when her mother was diagnosed with colon cancer. Though her parents initially planned to simply rely on a local physician for care, Goddard insisted they seek a second opinion at Moffitt – an option they'd never realized was open to them.

Photography: Ray Reyes

"My mom is here today because she came to Moffitt for care," says Goddard, who this year joined the Moffitt Institute Board of Directors. "If my parents didn't think Moffitt was an option, how many other families in our community face cancer not knowing that Moffitt is here to help? It's my duty to share with others that they, too, can experience Moffitt's expertise and compassion like we have."

"My mom is here today because she came to Moffitt for care."

Misperceptions may be part of the reason why some community members don't think of Moffitt as their hospital, says Goddard.

Even something as simple as its valet parking "might be interpreted that Moffitt is just for the wealthy," Goddard explains, "when it's really for the comfort and convenience of all patients going through the rigors of treatment."

But far larger issues can interfere with access to care for underserved communities - and result in cancer health disparities with grave consequences . Those issues led Goddard to accept another role, chairing the George Edgecomb Society which raises funds for Moffitt research into cancer health disparities within the black/African-American community.

Goddard says the commitment to grow the Edgecomb Society is one she takes personally. "We can transform lives through this initiative," she says, "because through this research and with the doctors focusing on these issues, we're going to help develop a new generation of health care professionals who gained their expertise and experience at Moffitt Cancer Center. It's important to have health care leaders who can relate to our community and culture."

The Society was named in memory of Hillsborough County's first African-American judge, a close friend of then-state representative H. Lee Moffitt. Judge Edgecomb's death from leukemia spurred Moffitt's vision to create Florida's only National Cancer Institute-designated Comprehensive Cancer Center. It's a story that still inspires Goddard.

"Mr. Moffitt faced great odds in fulfilling his vision, but nevertheless he was courageous," adds Goddard. "Because of his courage, we can have courage, too. If one man can build his vision, my team and I can move it forward."

GUT BACTERIA

A KEY TO IMPROVING RESPONSE TO CANCER TREATMENT

By Cathy Clark

The word in modern scientific circles is that we are not 100% human. We are only 10% human, and the microbes in our bodies comprising the other 90% hold keys to health.

So claims author and biologist Alanna Collen in her book titled *10% Human*.

The percentages do not pertain to the weight of the cells, but rather correspond to the numbers of microorganisms (including bacteria, fungi and viruses) in and on your body compared to the number of your own various types of cells. Nevertheless, some scientists estimate the average human microbiome weighs in at a hefty two and a half pounds. The density varies throughout the body with most of the microbiome residing within the intestinal tract.

The human microbiome is considered the collection of microbes, which include bacteria, viruses, fungi, that exist in and on our bodies – and also in our environment.

"Everything is littered with microbes – every surface you touch, the air you are breathing – and every part of your body has a different community of bacteria and viruses and fungi," says Moffitt epidemiologist Christine Pierce, PhD, MPH.

That being the situation, why aren't we sick more often? Actually, it is the microbes – that is, microbes in balance – that keep things in check, says Dr. Pierce.

She describes the three general types of human-microbe relationships:

COMMENSAL
Commensal means there is usually a benefit to the microbe and a rather neutral experience to the human. We would not benefit from the presence of commensal microbes nor would they harm us, but the microbe benefits.

SYMBIOTIC
Symbiotic means that both the microbe and the human would benefit by the presence of the symbiotic microbe.

PATHOGENIC
Related to the word pathogen, pathogenic microbes are harmful to the human and are often disease causing.

Our bodies are usually pretty good at keeping things in balance, and that balance of microbes helps lead to health. Having ecological balance between the commensal and symbiotic microbes – and preferably very few of the pathogenic microbes – then we usually are healthy and things are in a good, calm state.

But when our bodies' microbes are out of balance, disease occurs. And that is where the association with cancer comes in.

MICROBES, collectively, include bacteria, viruses, fungi, and parasites. The microbiome is the collection of all microorganisms residing in a given environment, including parts of the human body, such as the digestive system.

"We now are starting to understand how the microbiome can actually impact the development of our immune system and that absolutely ties in with cancer," says Dr. Pierce. "The scientific community has been investigating the role of infections, particularly viruses and bacteria, in cancer development for a long time. But how these microorganisms contribute to cancer remains understudied."

Dr. Pierce became interested in understanding how infections can contribute to chronic diseases when she was in graduate school.

We know that certain microorganisms are involved with cancer. For example, Helicobacter pylori is known to cause stomach cancer, and infection with some types of human papillomavirus (HPV) can lead to cellular changes that, if untreated, may progress to various types of cancers, notes Dr. Pierce. But the study of a collection of organisms – the microbiome – is emerging, with numerous studies in place and more clinical trials on the horizon.

Christine Pierce, PhD, MPH (left), and Lary Robinson, MD

Photography: Ray Reyes

"Everything is littered with microbes – every surface you touch, the air you are breathing, and every part of your body has a different community of bacteria and viruses and fungi"

EPIDEMIOLOGY AND SURGERY INTERSECT

Dr. Pierce's research focuses on understanding complex interactions between the human microbiome and the immune system. Her aim? To understand how the microbiome influences the effectiveness of cancer therapies, especially immunotherapy. The studies will improve our understanding of the role of the microbiome in cancer treatment and it might also help in the development of personalized strategies to optimize anticancer therapies through interventions that involve personalized microbiota-based interventions.

This is where her research interests and those of Moffitt thoracic surgeon and senior member Lary Robinson, MD, converge.

An accomplished surgeon, Dr. Robinson says he enjoys helping patients by removing cancers – something he has successfully been doing for a long time. His extensive career includes having served as a Flight Surgeon at the rank of Major, USAF, and in 1975 was awarded the Air Force Commendation Medal for Meritorious Service in Thailand.

About eight years ago he began reading up on Crohn's disease because a family member had been diagnosed with the illness. As he read, he became curious about the relationship between the disease and gut bacteria. This led to more reading, and he became increasingly interested in how microorganisms contribute to cancer.

"We now understand that approximately 20 percent of cancers are known to be caused by some type of microorganism," says Dr. Robinson. HPV causes virtually all cases of cervical cancer, the majority of oropharyngeal cancer, vaginal cancer, penile cancer, anal cancer and a number of other cancers.

Hepatitis B and hepatitis C viruses cause liver cancer. A variety of different viruses, such as Epstein Barr virus, cause some types of lymphoma.

But while many cancers have a strong microbial cause, the mere fact that one is exposed to a pathogen known to cause cancer does not necessarily mean that an exposed person will develop cancer. Other factors, including genetic differences, environmental factors and immune suppression all influence how the body responds to various infections and whether cancer develops.

HOW ONE'S BUGS AFFECT THE IMMUNE SYSTEM

Dr. Pierce and Dr. Robinson are conducting studies to better understand how changes in the gut microbiome affect cancer patients who are undergoing immunotherapy. They believe that an understanding of these variations will help to explain associations between a patient's gut microbiome and response to treatment. They hope their findings will shed light on the potential use of microbes as biomarkers of clinical response and allow for potential microbial modification (through diet, prebiotics or probiotics) to improve treatment response.

Dr. Pierce provides the scientific expertise required in these types of studies, and Dr. Robinson provides the clinical perspective, resulting in a successful collaboration.

"Your bugs determine your immune system…how well it works," says Dr. Robinson. "And the more diversity of bugs in one's colon the better."

Two different melanoma studies from other centers involving the relationship between immunotherapy outcomes and the microbiome were recently presented at the 2017 American Society of Clinical Oncology meeting. The investigators obtained gut bacteria through fecal samples before the patients underwent immunotherapy for melanoma. In these observational studies, they found that the composition of the gut bacteria made a difference in how well the patients responded to immunotherapy.

Finding a strong correlation between gut bacteria and response to treatment in melanoma by other investigators encouraged Dr. Pierce and Dr. Robinson to conduct a study in patients with lung cancer at Moffitt. Preclinical research shows promise, but no one has done such a study yet in humans with lung cancer.

Photography: Rachel Lawrence

Research coordinator Maria Gomez works in Dr. Christine Pierce's lab, where stool samples are processed as part of a study involving evaluation of the potential role of microbes in response to cancer immunotherapy.

CENTER FOR INFECTION RESEARCH IN CANCER

Dr. Robinson and Dr. Pierce actively work with other members of Moffitt's Center for Infection Research in Cancer (CIRC). Dr. Robinson is one of the founding members of the center of excellence, led by Moffitt HPV research expert Anna Giuliano, PhD. The CIRC is designed to identify additional cancer-causing agents, learn more about the role of these infectious agents in the origin of cancer and to translate this knowledge into novel and effective strategies for the prevention and treatment of cancer.

"We now understand that approximately 20 percent of cancers are known to be caused by some type of microorganism"

Now Drs. Robinson and Pierce are collaborating with other physician-scientists to find, prospectively, whether the gut microbiome makes a difference in treatment response in humans with lung cancer. This endeavor has far-reaching potential because lung cancer is the most frequently diagnosed cancer and the leading cause of cancer death worldwide. The primary purpose of the study is to understand how the gut microbiome of individual patients with advanced lung cancer affects their response to immunotherapy. Ultimately, the changes in the gut microbiome will help explain the associations between the gut microbiome and treatment response and shed some light on the potential use of microbes not only as biomarkers of clinical response, but also offer the prospect of potential microbial modification (through diet, prebiotics or probiotics) to improve treatment response.

So far, no patients are deliberately being treated with anything different that might affect the microbiome since this is an observational study only.

Antibiotics are lifesavers, yet they also are known to temporarily distort the healthy diversity of gut bacteria. Dr. Robinson cites a retrospective study by another group (not yet published) comparing renal cell cancer patients who received antibiotics within two months of starting immunotherapy with patients who did not receive antibiotics. The patients who received antibiotics had a significantly decreased response to immunotherapy. They are now retrospectively looking at Moffitt patients to see if the same negative effect is seen in lung cancer patients receiving antibiotics before immunotherapy.

Photography: Rachel Lawrence

WHAT ARE PROBIOTICS AND PREBIOTICS?

Probiotics are live microorganisms that are intended to have health benefits. Products sold as probiotics include foods (such as yogurt) and certain dietary supplements.

Prebiotics are types of sugars in some foods and supplements that humans can't digest but they nourish or stimulate the growth and activity of certain beneficial bacteria / probiotics.

"What we really want to do is manipulate the gut bacteria in a way that benefits treatment, but we won't do this until initial studies show that it makes a difference," says Dr. Robinson. He adds that the gut bacteria can easily be changed within two to three weeks through diet, probiotics and prebiotics.

FIRST, PROVE A CORRELATION

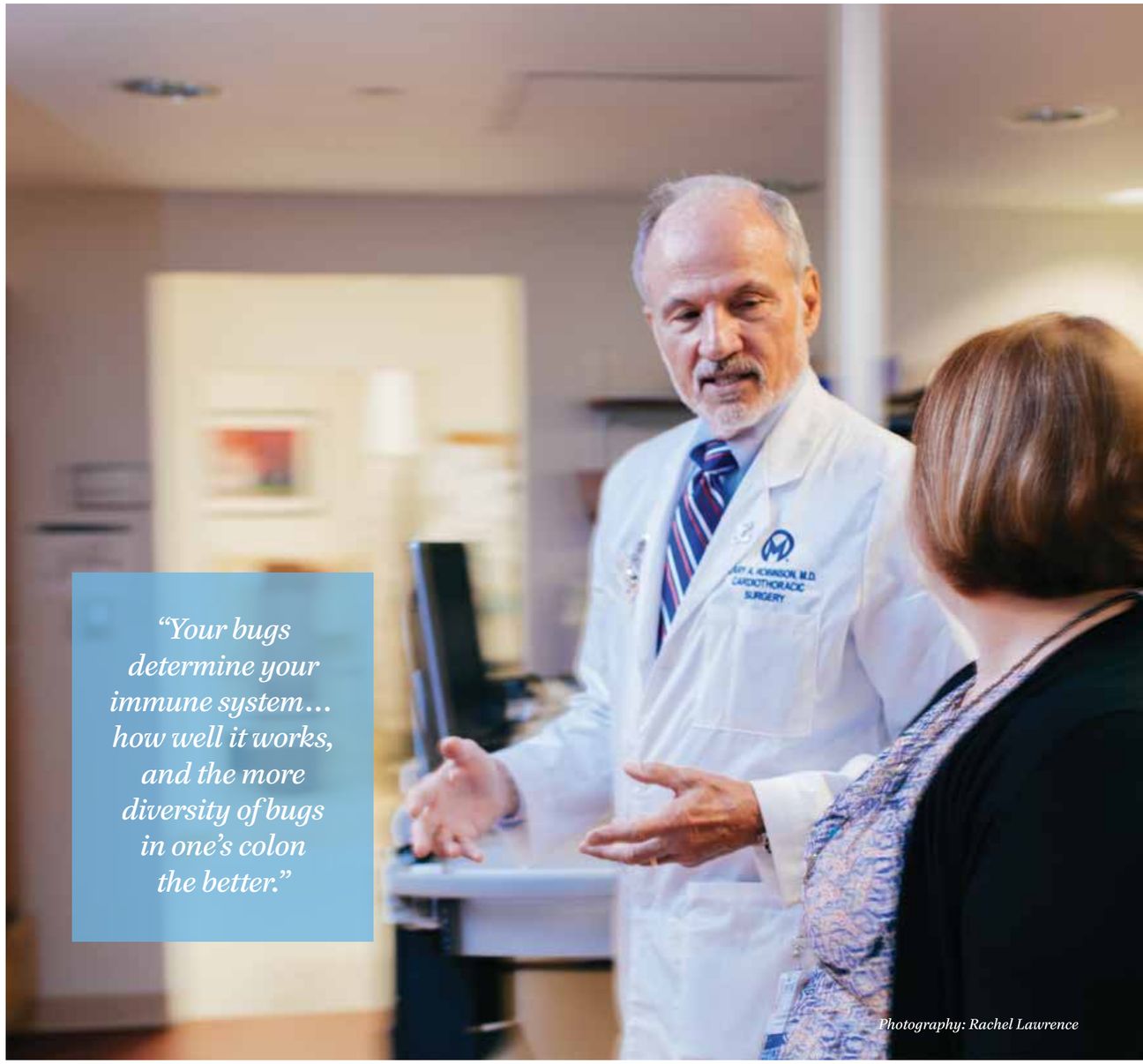
Dr. Pierce and Dr. Robinson eagerly anticipate moving their work beyond retrospective chart reviews and prospective observational collections of fecal samples that they are analyzing for the microbiome.

They want to see patients undergoing immunotherapy first go on probiotics and prebiotics and change their diet so that their gut microbiome is in a healthy state that will enhance the effectiveness of therapy.

And if their studies prove the effectiveness of such an approach – which they believe they will – then they will expand their work further.

"Ideally, we will be able to do some of those interventions, or all of those interventions, prospectively in a trial with patients who are undergoing cancer treatment," says Dr. Robinson. "But first we must prove a strong correlation."

This field relating to bacteria keeps expanding. While their studies are centered on the gut microbiome, there are so many different types of microbiome – gut, oral, bronchial, and more. Dr. Pierce is even studying the microbiome within tumors.



Photography: Rachel Lawrence

We will be hearing and reading more about the human microbiome in the years ahead. Future anticipated areas of study include:

- Treatment based on the intestinal microbiome
- Manipulation of the intestinal microbiome before treatment
- Study of microbiome in the gut, mouth and other areas of the body
- Study of the microbiome on and within tumors
- Microbiome studies tied to genomics studies

They foresee, within the next five to 10 years, that the microbiome will revolutionize personalized medicine. At that time, they believe, treatment will be based not only on a person's genetics but also on an individual patient's microbiome and even on the tumor microbiome.

And in the future, physician-scientists may be doing some adjunctive treatments by way of diet, probiotics, prebiotics or other interventions not yet known to change a person's microbiome before treatment.

ABOUT MOFFITT CANCER CENTER

Moffitt Cancer Center in Tampa, Florida, has made a lasting commitment to the prevention and cure of cancer, working tirelessly in the areas of patient care, research and education.

MISSION

To contribute to the prevention and cure of cancer

VISION

To transform cancer care through service, science and partnership

SHARE YOUR THOUGHTS

/moffittcancercenter
/moffittnews
/moffittcancercenter
/moffittcancercenter

EDITOR@MOFFITT.ORG

H. Lee Moffitt Cancer Center & Research Institute, an NCI Comprehensive Cancer Center – Tampa, FL

Notable

HEARST, A MARKET LEADER IN HEALTHCARE TECHNOLOGY, ANNOUNCED AN EQUITY INVESTMENT IN M2GEN, A HEALTH INFORMATICS SUBSIDIARY OF MOFFITT CANCER CENTER. The partnership will help accelerate the discovery of innovative cancer therapies and improve care for patients nationwide. The collaboration will provide funding to expand the efforts of the nation's first major data sharing network among leading cancer institutions.

THE PREVIOUS ISSUE OF MOMENTUM MAGAZINE INCLUDED A FEATURE ON CAR T, AN EXPERIMENTAL IMMUNOTHERAPY THAT ENGINEERS A PATIENT'S OWN IMMUNE CELLS TO TARGET AND FIGHT CANCER. On Oct. 18, 2017, the U.S. FDA announced approval of Yescarta, Kite Pharma's Chimeric Antigen Receptor (CAR) T-cell Therapy for adults with diffuse large B-cell lymphoma. Moffitt Cancer Center has been critical to the advancement of this new, life-saving therapy. Dr. Frederick Locke, vice chair of Moffitt's Department of Blood and Marrow Transplant and Cellular Immunotherapy, was the co-principal investigator of the national multi-center trial that led to the approval of Yescarta. Moffitt is proud to be leading the way in the development of new immunotherapies like CAR T.

MOFFITT RESEARCHERS WERE AMONG THOSE FROM 18 COUNTRIES AND 105 STUDY SITES WHO FOUND THE NEWEST HPV [HUMAN PAPILLOMAVIRUS] VACCINE IS HIGHLY EFFECTIVE AT PREVENTING HPV INFECTION AND DISEASE. The study results, published in The Lancet, showed the 9vHPV vaccine (known as Gardasil 9) has long-term activity against HPV infection and disease. The study results support comprehensive vaccination programs and inform public health decision related to implementation, said Anna R. Giuliano, PhD, director of Moffitt's Center for Infection Research in Cancer, and one of the world's leading HPV experts.

Visit **MOFFITT.org** to find out about our upcoming events

WHEN YOU DONATE TO CANCER RESEARCH your gift will go directly to helping researchers and scientists develop the medicines and protocols that will advance cancer treatments and help cure patients. Simply put, your generosity will help save lives. Every gift, no matter the size, makes a difference. Now is the time to get involved and help make a difference. Visit **MOFFITT.org/Giving** to find out more.

MOFFITT CANCER CENTER

12902 Magnolia Drive, Tampa, FL 33612

TO CONTRIBUTE TO THE PREVENTION AND CURE OF CANCER