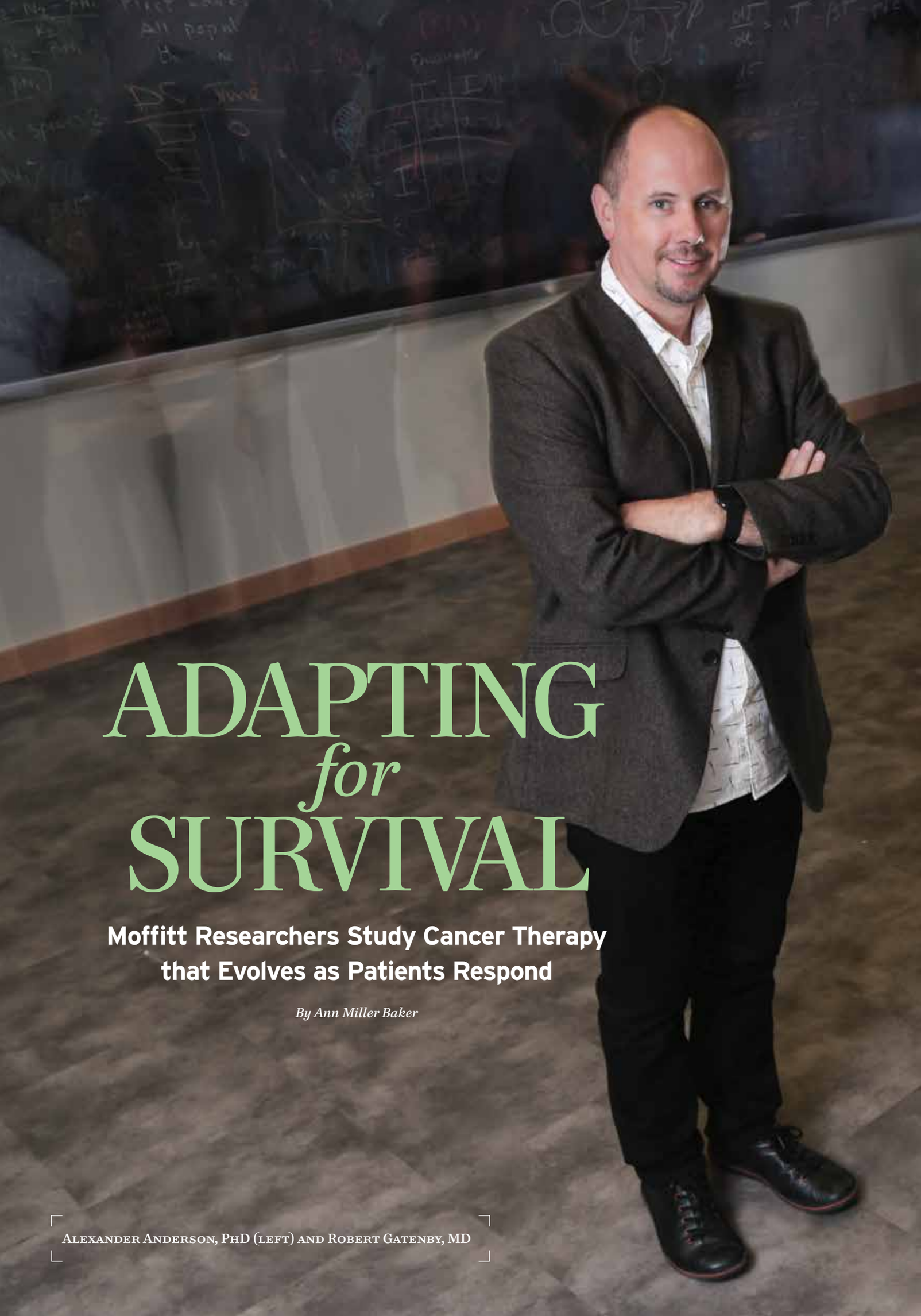


ADAPTING *for* SURVIVAL

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

Photography: Jeremy Peplow

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."

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.

Photography: Jeremy Peplow

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.

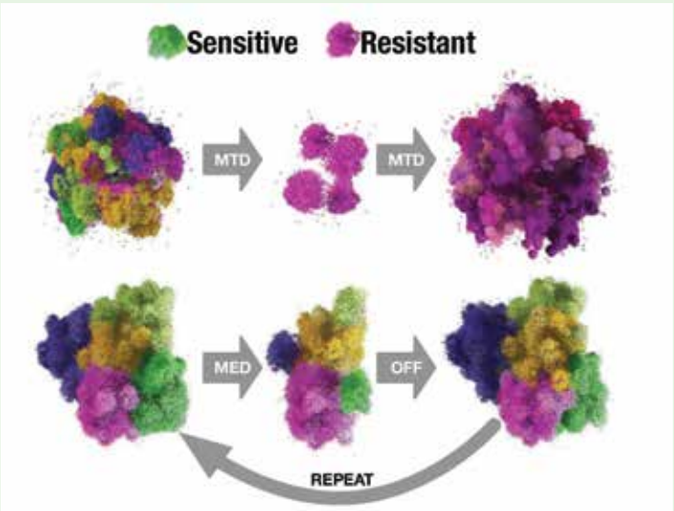
"It's like developing a personal spaghetti plot of a patient's cancer over time.

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 Mr. 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."

Photography: Rachel Lawrence

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.