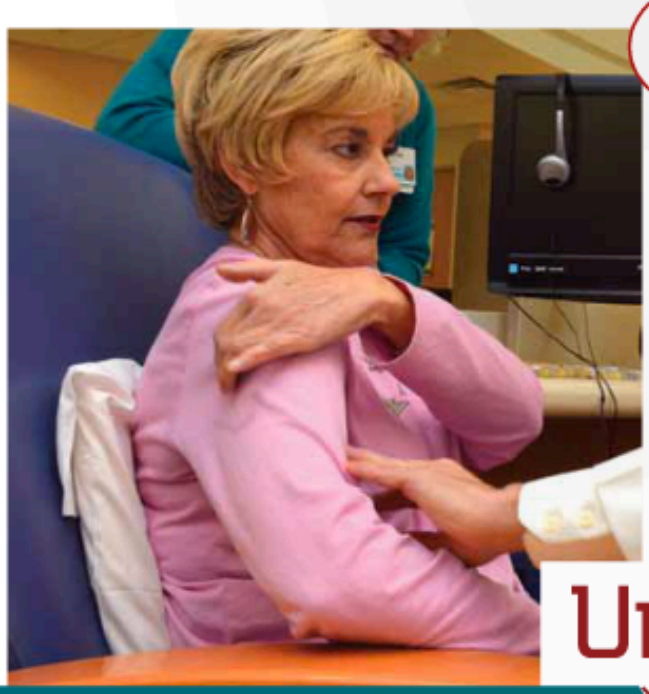
Taking a Shot at Cancer

CLINICAL TRIALS ENSURE CUTTING-EDGE TREATMENT



JOYCE CHAVIS GRU Clinical Trials Patient

After Joyce Chavis of Aiken, S.C., underwent surgery and chemotherapy for stage IV colon cancer in 2009, her treatment went well—so well, she says, that there were no signs that the cancer would ever come back.

Until it did.

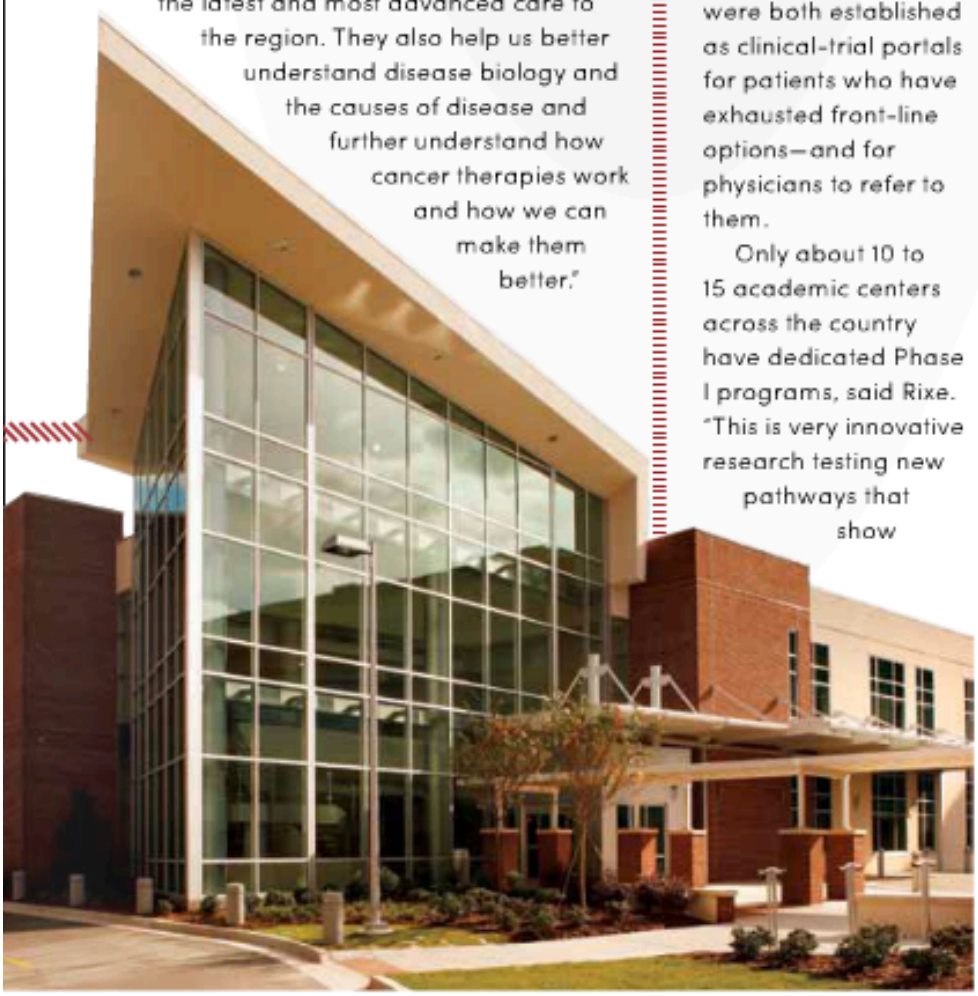
BY DANIELLE WONG MOORES

Last December, her doctor found that her cancer had metastasized to her liver. Because Chavis was on blood thinners, she was no longer a candidate for a standard therapy combining chemotherapy and Avastin. Instead, her oncologist referred her to the Georgia Regents University Cancer Center's new Phase I clinic.

The clinic and a new partner immunotherapy clinic are just two indications of the major changes spilling out of the center's newly reinvigorated clinical trials program. And there's much more to come, said Dr. Samir N. Khleif, who just completed his first year as Director of the GRU Cancer Center.

Khleif has articulated his goal of National Cancer Institute designation, making GRU's only the second such center to be so designated in Georgia. Last year, Gov. Nathan Deal pledged $5 million in state funding to support the initiative—a major component of which is a vibrant clinical trials program, offering innovative treatments available nowhere else in the region.

"One of the roles of a cancer center—particularly one that is National Cancer Institute-designated—is to provide not only research and not only clinical care, but the latest combinations of research and clinical care," said Khleif. "That means clinical trials, which help us provide the latest and most advanced care to the region. They also help us better understand disease biology and the causes of disease and further understand how cancer therapies work and how we can make them better."



* Read about Rixe's business, SISENE Oncology, on page 30.

A True Phase I Program

Three days after her doctor referred her to GRU Cancer Center, Chavis was talking to Dr. Asha Nayak, a medical oncologist who specializes in gastrointestinal cancers, and Dr. Olivier Rixe*, who joined GRU in 2012 as the cancer center's Director of Experimental Therapeutics following similar roles at the University of Cincinnati and National Cancer Institute.

The Phase I clinic and the immunotherapy clinic were both established as clinical-trial portals for patients who have exhausted front-line options—and for physicians to refer to them.

Only about 10 to 15 academic centers across the country have dedicated Phase I programs, said Rixe. "This is very innovative research testing new pathways that show benefits for patients, with real Phase I experts, a dedicated clinical team and a connection with basic research to identify patients based on molecular characteristics," he said. "And that's just the tip of the iceberg in terms of what a Phase I program can offer."

What is most important is that patients unable to undergo standard treatments can potentially see benefits from early drugs that may not be approved for worldwide use until five or 10 years from now. Chavis, for example, is taking part in a study looking at PD-L1 inhibitor—a drug that can potentially help her immune system recognize and fight the cancer cells in her liver.

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Targeted Therapies

Research into immune therapies as well as molecular targeted agents—either alone or combined with standard treatments—started about 20 years ago. Today, this research is experiencing a wave of heightened interest nationally and internationally for its promise in arming the body itself to fight cancer with fewer, and less toxic, side effects than chemotherapy or radiation.

DR. OLIVIER RIXE Director of Experimental Therapeutics

The GRU Cancer Center is building on its expertise in this area, with the ultimate goal of personalized medicine, which would individualize treatment depending on patients' specific biomarkers.

Some of that work has already started. The GRU Cancer Center is part of a multicenter Phase 3 vaccine study for patients with glioblastoma, a fast-growing and aggressive brain tumor. The trial is testing a new cancer vaccine that targets the roughly 30 percent of patients with glioblastoma who have a genetic abnormality—a gene deletion known as EGFRvIII, said Rixe, who is overseeing the trial at GRU and has been involved in the early phase of development.

Patients with this gene deletion express a specific protein on the tumor's surface—the marker that is recognized by the vaccine and that gives these patients an important advantage. "We have been involved in preliminary studies with the vaccine, and now this is the last round to test the strategy," said Rixe. "The preliminary data from the earlier studies was very, very encouraging. While these results will need to be confirmed in large-scale studies here in the U.S., this is just one example of the very sophisticated and targeted studies we're bringing to this region, with the hope of being able to change the outcome of these tumors."

In addition, Khleif is the principal investigator on a clinical trial combining the prostate cancer vaccine Provenge with two other cancer-fighting drugs, CT-011 and cyclophosphamide. The vaccine already extends the life expectancy of certain men with prostate cancer by nearly 20 percent; preclinical animal studies in Khleif's lab found that the drug combination led to a significant increase in survival and complete tumor regression in more than 50 percent of mice.

"It's not about the Provenge," explained Khleif, who first began researching vaccines about 20 years ago. "It's a clinical trial combining a vaccine with two agents—one of which enhances further immune response with the vaccine, while the second prevents the inhibitory power of the tumor on the immune system. It's about combining multiple strategies to achieve additional patient benefits."

DR. SAMIR N. KHLEIF

Homegrown Invention

At about the same time that Khleif was doing his initial studies into cancer vaccines, Dr. David Munn, a pediatric oncologist and Associate Director of the university's Cancer Immunotherapy Program, together with Dr. Andrew Mellor, Director of the Immunotherapy Center, was making a significant finding of his own.

Certain enzymes send signals to the immune system that foreign objects—food, for example—are safe. Tumors, however, can evolve and mimic these signals to prevent the immune system from doing its job. "You don't have to worry about the dumb tumors. The immune system takes care of those," said Munn. "The tumors that come to clinical attention are the ones that have figured out some way to activate those enzymes and elude the immune system."

For example, an enzyme called IDO keeps the immune system from seeing a growing fetus as a foreign object. Munn hypothesized and confirmed that certain tumors use this same pathway to suppress immune response. About 14 years ago, he and Mellor discovered a new drug in their GRU lab—called one-methyl-tryptophan, or 1-MT—that would reactivate the immune system so that it would recognize and attack cancerous tumors.

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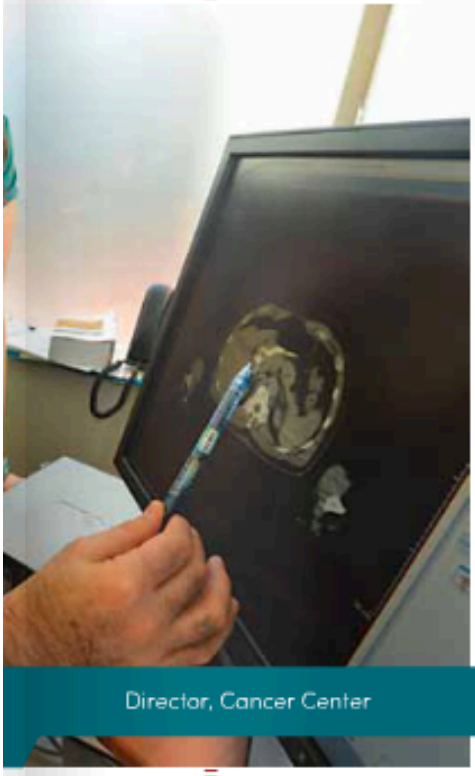

Director, Cancer Center

Innovative Clinical Trials

georgiahealth.edu/cancer/trials or 888-658-0422

To date, the GRU Cancer Center has 90 phase I, II or III clinical trials open, with 12 new trials set to launch soon, focused on cancers that affect Georgia and the Southeast. These new trials include:

A Pilot Study to Test the Feasibility and Immunologic Impact of Sipuleucel-T (Provenge™) Administered with or without anti-PD-1 mAb (CT-011) and Low Dose Cyclophosphamide in Men with Advanced Castrate-resistant Prostate Cancer

The trial is the first in the country to investigate prostate cancer treatment combining Provenge with two other cancer-fighting drugs, CT-011 and cyclophosphamide, and looks to improve survival rates.

A Pilot study to test the feasibility of the combination of Gemcitabine and anti-PD1 monoclonal antibody (CT-011) in the treatment of resected pancreatic cancer

The treatment combines a standard chemotherapy drug with a monoclonal antibody that may help the immune system fight pancreatic cancer.

A Phase 1 Dose Escalation Study of BMS-982470 (Recombinant Interleukin-21, rIL-21) in Combination with BMS-936558 (Anti-PD-1) in Subjects with Advanced or Metastatic Solid Tumors

This Phase I study investigates the combination and clinical benefits of two cancer drugs in patients with locally advanced or metastatic cancer.

Phase III Study of Rindopepimut/GM-CSF in Patients With Newly Diagnosed Glioblastoma (ACT IV)

This study will investigate the efficacy and safety of an experimental cancer vaccine combined with the current standard in patients with recently diagnosed glioblastoma, a type of brain cancer, who have tumors that express the EGFR protein.

After years of bench and animal studies, the drug founded in a GRU lab is going into clinical trials. While it still may be some years before the treatment could be approved in children (trials typically must first be conducted and proved in adult populations), one of Munn's goals as a pediatric oncologist is to speed this process so that children most in need of these new treatments can benefit.

"We want to be able to enroll more pediatric patients into these early-phase clinical trials," he said. "But what makes this more challenging is that no one center really has enough patients for early-phase clinical trials just in its own center. Our hope is to reach out to several large clinical programs and join our science with their enthusiasm for moving these trials into children."

It's the type of work that could take a lifetime, and said Munn with a smile, "It has. And what's nice too is to have a local university cancer center offering something not invented in New York or elsewhere that trickled to us, but something that we actually invented here."

That is the promise of clinical trials—that the research done today will benefit the patients of tomorrow. For her part, Chavis is optimistic—after all, she's already seen what clinical trials can do: During her initial treatment for colon cancer, Chavis took a drug, now FDA-approved, that Rixe worked on developing earlier in his career.

And for Khleif, who once gave presentations titled "Taking a Shot at Cancer," the exciting recent work in the vaccine field gives him hope that cancer treatments, one day soon, could be as simple as a shot. "I'm proud I stuck to it," said Khleif. "It's great to know now after this many years that this growing field is extremely important and one of the milestones in cancer treatment." ✣

Speedy Sequencing

The GRU Cancer Center is now the only cancer research center in the state that can sequence the entire human genome in 24 hours for about $6,000—thanks to an upgrade in technology that researchers believe will allow them to develop more targeted therapies for cancer. Until very recently, the cost was more than $20,000 to sequence an individual genome.

Cancer researchers used to have to analyze individual genes—often many thousands of them in a process spanning several years—for mutations, scouring certain regions of the genome implicated in specific tumor types, said Lesleyann Hawthorn, a geneticist and Director of Shared Resources at the GRU Cancer Center. But over the past decade, years have morphed to weeks, and now hours, as technology has improved through a push by the scientific community for faster and less-expensive gene sequencing.

"Nationally, since 2001, scientists have been working toward sequencing the human genome within 24 hours and for under $1,000, and we are now approaching that," said Hawthorn, noting that the first draft of the human genome took 13 years and $3 billion to sequence. "As a result, our researchers are now able to work more effectively in identifying specific mutations in hard-to-treat tumors, to help us develop treatments targeted to that particular person and tumor type."

Along with the genome-sequencing upgrade, the GRU Cancer Center can now sequence single exomes—the protein coding part of the genome—on a single run of a new instrument called the MiSeq. All upgrades and new instrumentation were supported through a $2 million grant from the Georgia Research Alliance. ◆