Kristin Bartlett Grace

UF Drug Development Researchers Are Forging New Trails To Cancer Treatments

By Melanie Fridl Ross

Molecular Mountaineers

David Ostrov fancies himself a molecular mountaineer of sorts. It's an apt description for a scientist who is just as comfortable scaling the world's tallest peaks as he is staring down some of the most challenging questions in science.

Ostrov got a toehold on the sport as a teen scrabbling up 60-foot cliffs in Connecticut. He headed off to lofty locales like Colorado for college and Seattle for graduate school, and managed to climb his way across the West along the way. His tally? Fifteen mountains taller than 14,000 feet, including heavily glaciated formations in the Pacific Northwest. Not to mention Joshua Tree in the Mojave Desert, and the rock faces of Yosemite.

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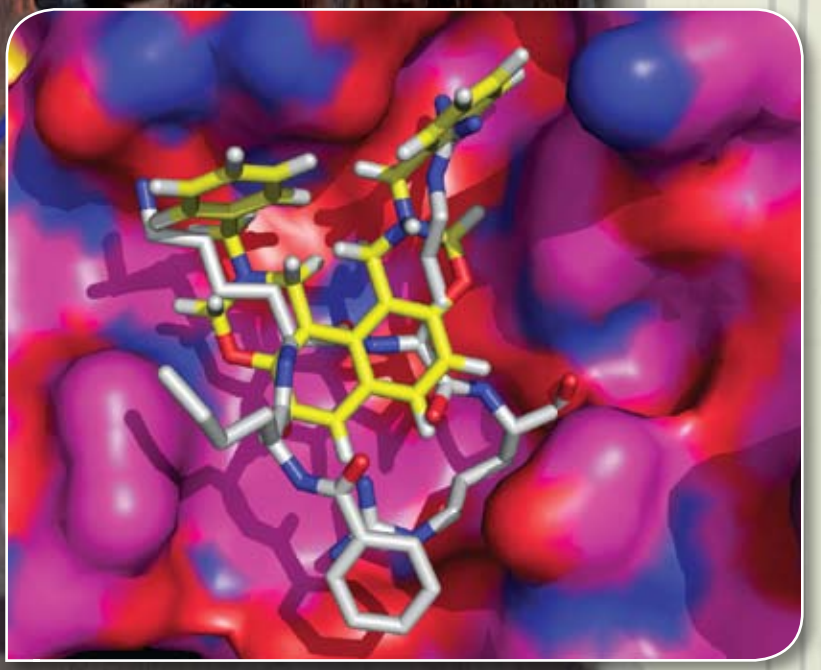


These days, Ostrov's goals are no less daunting, but you're much more likely to find him with two feet on the ground. As an X-ray crystallographer, he's hard at work designing new drugs for an array of conditions, including many novel therapies for cancer. To do so, his research team harnesses the ability of one of the most powerful supercomputers on the planet to process as many as 300,000 potential drug compounds within two hours.

The machine — and the minds behind it — make the drug discovery and development process faster, cheaper and more precise than ever before. The approach means the window to usher in a new drug candidate that could be tested in people could soon shrink from the industry average of seven years to a mere 12 months.

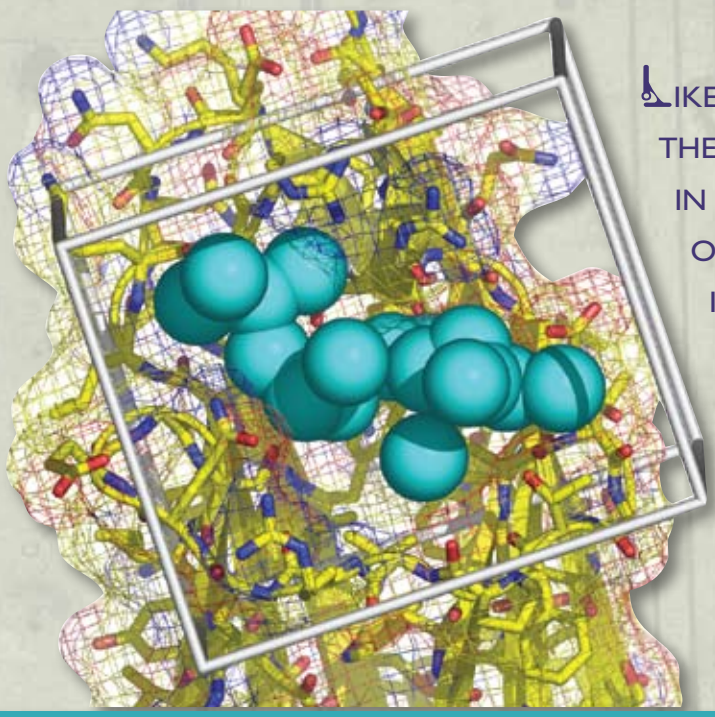
Like a rock face studded with small crevices and tiny outcroppings ideal for an ascent, proteins, enzymes and DNA molecules — all common targets of anticancer agents — are covered in surface contours that represent potential areas to attack using a new drug compound.

The drug design process starts by imaging the molecule's crystalline structure using X-ray beams that map the type and placement of each atom. The method differs from traditional approaches because it capitalizes on UF software that enables researchers to identify the sites on a molecule most likely to interact with a drug.

"One of the most powerful advantages of our method compared to other methods in terms of discovering and developing novel therapies to treat diseases is our ability to pinpoint the location of where we want drugs to bind," says Ostrov, an assistant professor in the College of Medicine's Department of Pathology, Immunology and Laboratory Medicine who is affiliated with the UF Shands Cancer Center. "We can specifically select small drug-like molecules capable of interacting with very specific portions of a target protein."

With the supercomputer humming away 24-7 in UF's Physics Building, researchers can run a molecular docking program they designed that attempts to fit each prospective compound into selected structural pockets on a target protein that are most vulnerable to attack.

Like a virtual Rubik's Cube, the program rotates the compounds in a thousand different orientations to identify which is likely to work best and in what position. The winning candidate, the "lead compound," can then be synthesized by a chemist, tested in the lab and — if it proves promising — eventually in people.



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"It's a way of short-tracking the identification of a novel agent against targets that are known to be important in the disease or in cancer," says Carmen Allegra, chief of the Division of Hematology and Oncology at UF's College of Medicine and associate director of clinical and translational research at the UF Shands Cancer Center. Allegra, who came to UF last year from the National Cancer Institute, is working with Ostrov's team to find new drugs to treat colorectal cancer.

"It's a way of identifying lead compounds much, much quicker. And it also gives you the opportunity to optimize the compounds," he says.

The work has led to numerous grants, publications and patent applications — about 20 patents related to discoveries made using Ostrov's method have been applied for so far — and more are on the way. And the approach isn't used just for cancer, but also for heart disease, diabetes, Alzheimer's and other conditions.

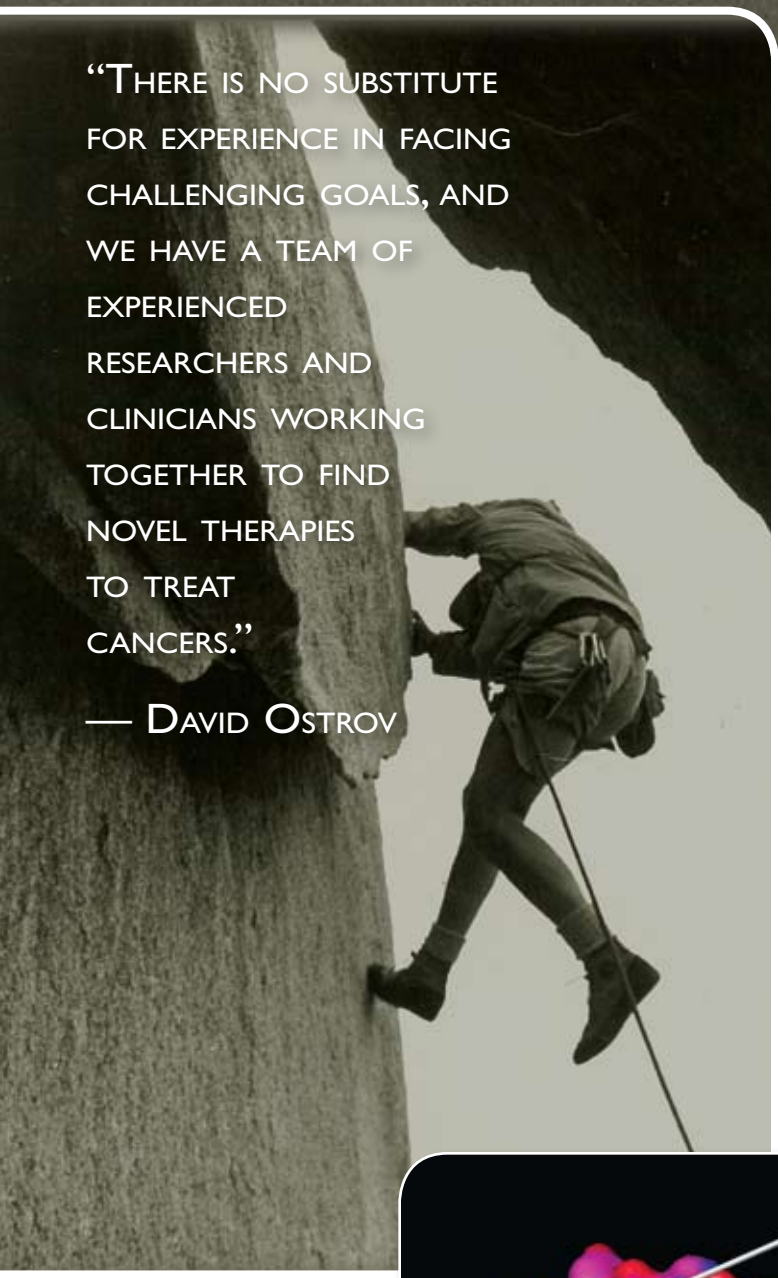
"We can screen drugs more rapidly than in industry. We can conduct preclinical testing in vitro and in vivo, in many cases using the same, or better, animal models as industry," Ostrov says. "We have a very active clinical trials unit well-suited to our rapid approach. Moreover, our College of Medicine is enthusiastic to pursue this all-inclusive strategy to develop novel therapies entirely within the university."

Bottleneck to Breakthrough

University scientists can hit a roadblock when it comes to developing novel drugs, says Ostrov. It's an expensive proposition, and academic institutions typically play a more peripheral role. But therein lies opportunity.

UF scientists recently embarked on a new alliance with the H. Lee Moffitt Cancer Center and Research Institute, and Ostrov continues to collaborate with Gary W. Litman, a faculty member in Moffitt's cancer biology program. Their joint efforts have already led to solving seven crystal structures.

And researchers are increasingly working in collaborative teams as the National Institutes of Health's "Roadmap"



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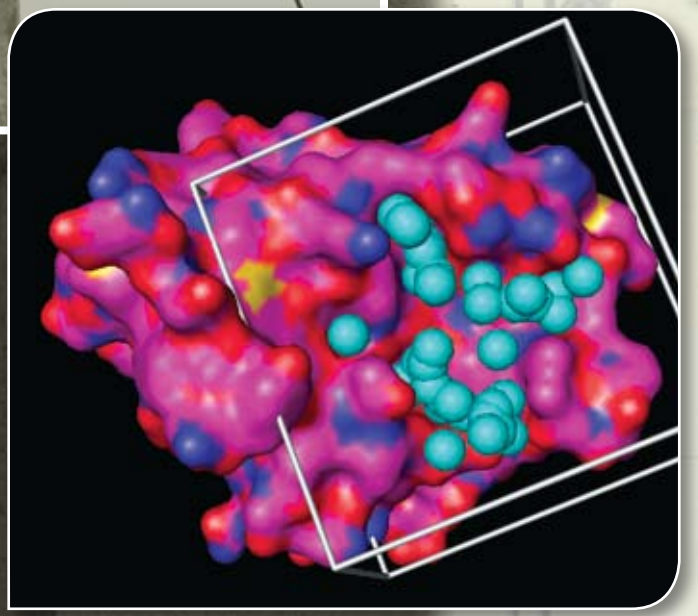
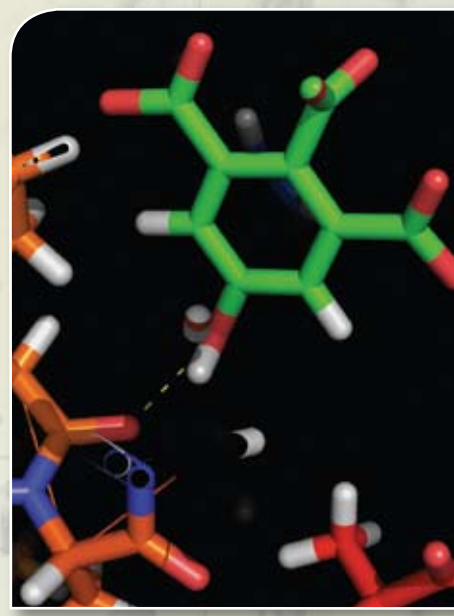
directive continues to encourage the approach, pushing the model as a way academicians can rapidly translate bench discoveries to the bedside. UF's newly designated Clinical and Translational Science Institute, or CTSI, will be a campuswide resource for facilitating research and training in clinical research and also for translating discoveries in the laboratory into clinical practice.

Preclinical drug development is a key aspect of the institute's efforts, and speeding new drugs to cancer patients will be one focus.

While different cancers share similarities, cells turn malignant for a variety of reasons. So UF researchers also are focusing on distinct molecules unique to various cancer types, including breast, prostate, gastrointestinal, brain, lung, skin and blood cancers.

"We're not putting all of our eggs into one basket. We're trying to apply our novel strategy to a diverse set of cancer cell types," Ostrov says. "A lot of people are under the impression that cancer is a single disease, but cancers are extremely different from each other, and it's well-acknowledged that there are different types of therapies that are more useful for specific types of cancers."



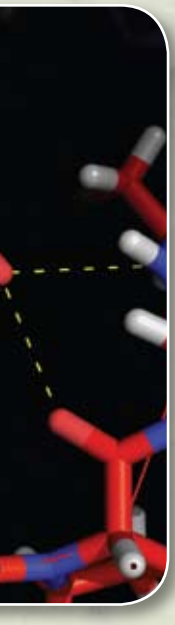


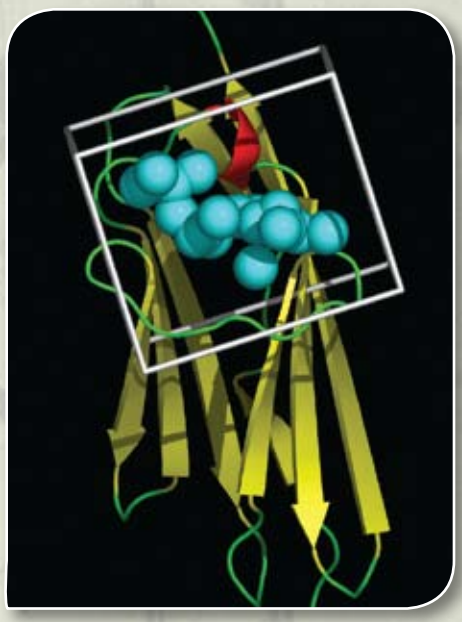
In the past year, UF efforts have included targeting a protein implicated in breast and pancreatic cancers. Researchers have successfully identified a compound that works in the test tube and in animals to shrink tumors without the harsh effects of chemotherapy, and Ostrov's team has solved the crystal structure of this molecule bound to its target. The effort is a collaboration with UF's chairman of surgery, Bill Cance, and his colleagues.

Peter W. Stacpoole, a professor of medicine and the CTSI program director, says Ostrov's contributions are at a very early stage of drug development, a critical one that capitalizes on a basic tenet of pharmacology: No drug does only one thing. Stacpoole and Ostrov, for example, have developed an investigational drug for the treatment of patients with genetic diseases that affect mitochondria, the cell's energy powerhouse. That compound was also found to exhibit antitumor effects in animals, human tumors and tissue culture.

"What we're doing together is to tap the National Cancer Institute repository of chemicals to identify some that have perhaps a special affinity for targets of proteins that we're interested in that we can then test," Stacpoole says.

"This has opened up a very, very exciting and widely publicized area of research in developing this compound as a potential anticancer agent," he adds. "And knowing what we know about how it works in mitochondria and understanding that mitochondria do not function normally in human cancers made us think we could identify new compounds that had not been looked at in this way before, but had been essentially on the shelf."





Scientific summits

One thing is certain: New drugs are desperately needed. Some of the agents doctors rely on are celebrating their 50th anniversary. Newer agents have recently been approved, but practitioners say they aren't enough.

"For many, many years in colon cancer we had a very small toolbox — like one drug, 5-FU," Allegra says. "Within the last decade we've seen that expand to five or six new tools, different agents that seem to have activity in the disease. I think everyone is trying to figure out how best to use them, how to sequence them, how to use them together. But it's not going to be enough."

A tall goal indeed, but one Ostrov says is within reach, just like the peaks he tackles.

Last summer, he was trying to climb the tallest mountain in the continental U.S., Mt. Whitney, and finally got to the steepest and most exposed section of the mountain. He had been moving since 3 a.m. and had only about 500 feet of exposed rock climbing to go.

"Just my luck, it started to hail," Ostrov says. "Many people would have turned back, as the rock was getting very slick. If you fell, you would die. There is no way I would have proceeded if I had not climbed many cliffs and mountains before. I knew that I had the experience to climb safely and made it to the top without a problem.

"There is no substitute for experience in facing challenging goals, and we have a team of experienced researchers and clinicians working together to find novel therapies to treat cancers," he adds. "We are moving forward with this experience and we intend to make it to the top. Our goal is to improve the quality of life of individuals suffering from human diseases. We want our work to result in improving the quality of life of patients."

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