

New Moffitt And USF Collaboration Reunites Scientists

By Randolph Fillmore

It belongs in the “small world” category.

Saïd Sebti, Ph.D., Garcia Endowed Professor and Chair, Drug Discovery Department at Moffitt Cancer Center, and Robert Deschenes, Ph.D., the newly arrived University of South Florida chair of Molecular Medicine, were graduate students in the same biochemistry program at Purdue University in the early 1980s. Now they are sitting across the same table in Tampa, a table to which they are bringing their two distinct areas of expertise - drug discovery/molecular medicine from Dr. Sebti and molecular and structural biology from Dr. Deschenes - to figure out innovative ways to fight cancer.

“It’s a great opportunity,” says Dr. Sebti. “We have a new initiative in drug discovery to build a structural biology component. When I heard Bob was being recruited by USF to be the chair of Molecular Medicine, I was delighted and looked forward to collaboration. This is the way it was meant to be - Moffitt and USF working together.”

For Dr. Deschenes, the new collaboration now in the works is also a great opportunity.

“Saïd has built an impressive program in drug discovery,” he says. “By working together, by strengthening structural biology beyond what he has done, and by working with USF and Moffitt chemists, we can do great things.”

So, what is structural biology and how does it fit into the grand plan of drug discovery Moffitt researchers have been developing over the years?

“Our three goals in drug discovery remain the same,” explains Dr. Sebti. “Our first aim is to identify and validate cancer-causing genes and their proteins as molecular targets for therapy. Second, we want to design drugs that block these molecular targets and, ultimately, take those drugs from the scientist’s bench to the patient’s bedside. The structural biology component adds the ability to look at proteins

Moffitt and University of South Florida researchers are using X-ray crystallography equipment (shown here) and nuclear magnetic resonance spectroscopy to study the molecular basis of cancer through a better understanding of the structure and function of proteins.

in three dimensions and the expertise to make recommendations to medicinal chemists on how to develop the most effective compounds to bring to the fight against cancer."

While the collaboration is about the reunion of two scientists and friends, it is also about the joining of two technologies: X-ray crystallography and nuclear magnetic resonance spectroscopy, or NMR.

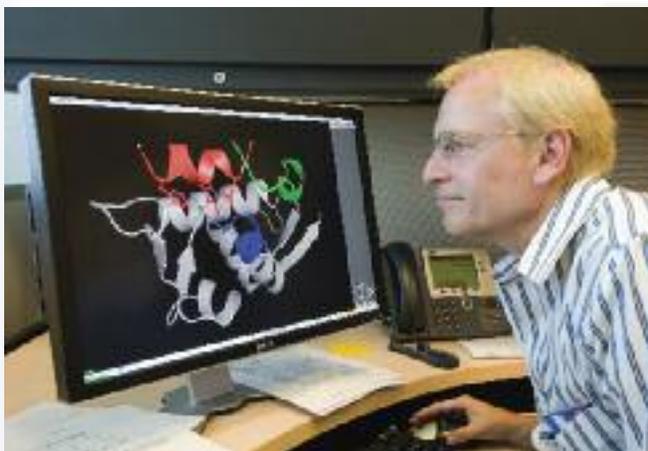
Scientists at Moffitt have been using X-ray crystallography to model protein structure at the atomic level. Now, USF has purchased a sophisticated NMR made specifically to examine proteins. The NMR will be able to look at small proteins and generate a three-dimensional graphic of their structures.

"Every protein has a unique shape that is related to its function. Understanding how that shape is related to function is what molecular medicine is all about."

"Not every institution has an 800-megahertz NMR," says Dr. Deschenes. "With Moffitt's X-ray crystallography and USF's new NMR, we will be able to better study the three-dimensional structure and function of proteins. It provides us with an enormous advantage when we can rotate the image and see more than just a two-dimensional structure."

Now, Moffitt and USF scientists have the best of both worlds.

"Both techniques let us see the three-dimensional structure of proteins at the atomic level," explains Ernst Schonbrunn, Ph.D., professor, Drug Discovery Department, and scientific director of Moffitt's Structural Biology Core. "The difference between the two lies in the size of the protein molecule we want to study. NMR gives us a look at the smallest, while crystallography lets us examine some small to extremely large protein complexes. However, some proteins may not crystallize, making NMR the better choice. Both techniques provide valuable information for drug design."



Ernst Schonbrunn, Ph.D., views a protein structure of MDM2, a protein that is involved in about half of all cancer cases. So far, no drugs that target this protein are available for use in the clinic setting.



Left to right: Robert Deschenes, Ph.D., Gary Daughdrill, Ph.D., and Saïd Sebt, Ph.D.

The NMR, says Dr. Schonbrunn, can quickly evaluate the binding properties between a potential inhibitor and a given protein. 5

Gary Daughdrill, Ph.D., of the Center for Biomolecular Identification and Targeted Therapies at USF, is heading the NMR phase of the collaborative effort.

"Proteins are the molecules responsible for performing most of the chemical and physical functions that sustain life," explains Dr. Daughdrill. "Every protein has a unique shape that is related to its function. Understanding how that shape is related to function is what molecular medicine is all about."

According to Dr. Daughdrill, when collaborators from Moffitt and USF study the molecular basis of cancer, they are looking for changes in a protein's shape and how those changes have altered the protein's function in such a way as to cause cancer. The NMR assists in this effort by allowing scientists to understand the electromagnetic properties of atoms in proteins. With that information they can use the computer to build a molecular model of the protein that is most like the picture drawn by X-rays in X-ray crystallography. NMR can also track changes in protein molecule structure.

Over the last 20 years, says Dr. Daughdrill, science has determined the shapes of over 50,000 proteins using the X-ray and NMR combination.

"Now we have a much better understanding of how proteins evolve and function," he says. "In our collaboration,

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scientists at Moffitt and USF will examine how protein shape and mobility change when two proteins interact or when a protein binds to a potential drug."

Using the ability of USF's Chemistry and Molecular Medicine Departments to generate proteins, Drs. Sebti, Deschenes, Daughdrill and colleagues will be able to begin looking at a variety of proteins. The goal is to develop compounds that can be tested as candidates for preventing the kinds of protein-protein interactions that cause cancer.

"We know that, for example, when protein A combines with protein B, this combination causes cancer, but we need to know how they bind," says Dr. Sebti. "Once we know the precise way they bind, we can figure out how we can disrupt this binding and design a novel anticancer drug."

For structural biologist Dr. Deschenes, getting a detailed, three-dimensional look at a protein is invaluable when that information is added to information about enzyme activity and genetic screening that can provide information about mutations. Much of that information comes from Dr. Deschenes' work with yeasts and understanding protein and enzyme activity in the genetically tractable yeast system.

"If it's important, it's in yeasts," says Dr. Deschenes with a smile. "All the fundamental machinery is there. What we know about cell cycles, we know from yeast cell cycles."

Likewise, what we know about pathways and enzymes to determine targets for drugs comes from knowledge of yeasts as well, says Dr. Deschenes. However, finding the right proteins, enzymes and pathways for designing new drugs could be a needle and haystack search scenario without X-ray crystallography, NMR and USF and Moffitt chemists simplifying and speeding up the process.

The collaboration also creates a firmer and a more frequently traveled "bridge," not only between Moffitt and USF, but also among the three scientific components - molecular medicine, medicinal chemistry and structural biology.



Stephane Betzi, Ph.D., postdoctoral research fellow, works to solve a protein structure in a Moffitt Drug Discovery laboratory.

"The 'bridge' already exists," points out Dr. Sebti. "USF researchers have been working with us all along."

USF chemists Roman Manetsch, Ph.D., Wayne Guida, Ph.D., and Mark McLaughlin, Ph.D., have worked on numerous projects, and Dr. Manetsch has worked closely with Moffitt Drug Discovery Professor Hong-Gang Wang, Ph.D. (who has since left the Cancer Center).

"We not only develop new, biologically active compounds, we are also interested in developing a new way of screening compounds using what is called 'target-guided synthesis,'" explains Dr. Manetsch. "This method allows us to find the most biologically active compounds in one step."

Dr. Manetsch and Dr. Wang have been working with proteins in the Bcl-2 family, which they call "validated drug targets" containing "apoptotic switches." Apoptosis is the name for a kind of programmed cell death that can kill cancer cells; finding the 'switch' to turn that process on is critical.

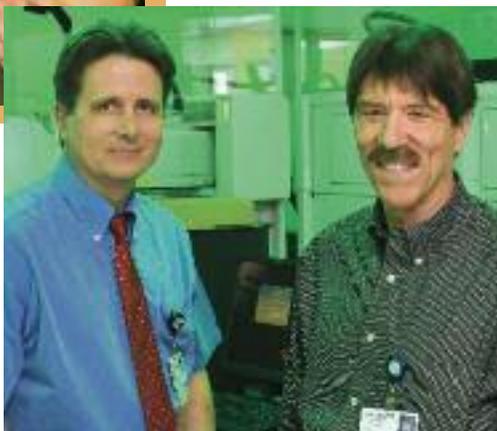
The trip back and forth across the USF-Moffitt "research bridge" begins with the structural biologist identifying the structure of proteins and how they bind. Next, chemists work to come up with compounds to prevent binding. Then the biochemists and the cell biologists evaluate the compound's efficiency in fitting into the protein structure picture by blocking, or unlocking, the precise spot where the proteins are known to cause cancer by their docking. Dr. Sebti calls this back-and-forth process "structural activity relationship," or SAR.

"Once we find the drug that disrupts the binding cycle, we can proceed with testing in preclinical models and eventually move to clinical trials," says Dr. Sebti. "This is just the beginning."

"The identification of new targets for cancer therapy and the development of drugs that specifically destroy cancer are the ultimate goals sought by these investigators," concludes W. Jack Pledger, Ph.D., Moffitt's executive vice president and associate center director, Basic Science. "This exciting association of Moffitt and USF through the research interactions of Drs. Sebti and Deschenes brings together two outstanding research groups that can make significant advancements in the development of new therapeutics for the treatment of cancer."



Roman Manetsch, Ph.D.



Mark McLaughlin, Ph.D. (left), and Wayne Guida, Ph.D.