

CMD5



Second year chemistry graduate student Wai Sheung Ma displays a high resolution NMR spectrum collected at a magnetic field strength of 11.7 Tesla (500MHz NMR spectrometer) at the USF Interdisciplinary NMR Facility, a Chemistry and CMD5 facility. The spectrometer is the highest magnetic field strength currently in existence at USF. Spectra like the one displayed on the monitor are used to study potential drugable protein sites by molecules that are synthesized by CMD5 researchers.

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USF researchers are creating biologically active compounds with pharmaceutical properties



By Randolph Fillmore
Photos by Joseph Gamble

As the University of South Florida enters its next 50 years, one of the pivotal moments future USF historians will likely cite as both a turning point in the University's commitment to research and an advancement that helped put USF research into the top echelons of university-based research, will be the establishment of CMD5—the Center for Molecular Diversity in Drug Design, Discovery and Delivery.

“CMD5 represents both a synergy and a consensus-driven venture between USF scientists from several diverse research disciplines,” says USF Chemistry Professor and Department Chair Mike Zaworotko. “CMD5 members are creating and using the most recent advances in molecular science to understand the causes of human disease and develop new ways to prevent and treat disease.”

What Zaworotko is most enthusiastic about is the ability of CMD5 and USF to commercialize new drug lead compounds that participants in CMD5 discover. Those compounds, says Zaworotko, will be on the front lines of the next generation of pharmaceuticals that are not only designed for individuals as “personalized medicine,” but are also delivery-controlled to molecular sites of action within the body.

According to Zaworotko, the outside world has created ‘fertile ground’ for the initiative for the USF-based venture into drug discovery and design by interdisciplinary teams of medicinal chemists, biologists, and biochemists.

“The business model for drug discovery, getting new drugs through the pipeline and into the marketplace, has changed dramatically,” explains Zaworotko. “Because the costs of early stage drug discovery are high and the rewards are very low, major pharmaceutical companies are relying more on small companies and university-based research groups to come up with novel lead compounds.”

That evolving business model puts CMD5 in the “catbird seat.” The outside world of pharmaceuticals changed even as the USF Chemistry Department’s developing critical mass in medicinal chemistry was

coalescing. As a result, CMD5, he says, is “open for business.”

In short, USF medicinal chemists will be inventing new molecules and coming up with unique compounds. They are in the business of discovering new molecules with medicinal properties.

According to Zaworotko, the number of new, potential molecules is greater than the number of atoms in the universe. Two million molecules have been “archived,” but the number of combinations is endless. However, figuring out which new molecular structures will have medicinal properties is an enormous job.

“The goal of the medicinal chemist, and what we do in CMD5, is to create biologically-active compounds with special pharmaceutical properties and try to understand why they do what they do and how to make them perform better,” says CMD5 Director and Chemistry Professor Edward Turos, Ph.D. “We take an academic approach by which the professor works with students and post docs closely, often drawing new molecular “target”



A variety of procedures and techniques are required for the preparation of biologically active compounds. The rotary evaporator (shown above) is commonly used at the very end to obtain the pure compound in a powder form.

structures on the office blackboard. The investigators then going into the lab to chemically synthesize the compound for further study.”

According to Turos, it is of paramount importance to study the chemical literature to see what may already be known about the molecule or its activity, and if it is totally new, to then file a disclosure to begin the process of obtaining a patent.

Turos notes that at this point early in the discovery process detailed information about the effectiveness or even the toxicity of most new molecules is not well known. The new compound is just at the very beginning of the pipeline.



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Dr. Ted Gauthier and graduate student Lisa Malgren, above, discuss the mass spectrum of a drug precursor. Below, third year chemistry graduate student Jaime Effatt Heimbegner adjusts the position of an NMR sample tube containing a purified natural product which will be studied in the 400 MHz nuclear magnetic resonance spectrometer utilized by CMD5 researchers.

What the big pharmaceutical companies increasingly want, says Zaworotko, is to reduce both their financial risk and the costs in getting a new drug to market. That's why they are depending more and more on partnering with university-based efforts and university-based spin-off companies to do the initial work. University researchers are happy to do the research and their universities are hoping that there will be big payoffs at some point in the future.

Zaworotko and Tuross point to the recent \$8 million grant from the State of Florida paving the way for the establishment of a Florida Center of Excellence in biotechnology at USF. The grant is providing the funds to build the infrastructure, bring in faculty and support staff with additional expertise, and to purchase major

instrumentation, such as proteomics mass spectrometry and ultra-high field nuclear magnetic resonance (NMR) spectroscopy, that allow researchers to obtain detailed structural information about target molecules, essential for the scientific advances in modern drug discovery.

"Everyone wants to come up with the next Taxol," says Zaworotko, referring to the groundbreaking and effective cancer drug made from the Pacific yew tree. The compound's action, discovered and pushed forward by academic chemists in the 1960s, was eventually brought to market as Taxol® by Bristol-Myers Squibb in 1993.

Zaworotko is quick to point out that drug discovery and getting a successful drug to market is a long-term process and that patience, along with

"a molecular equal opportunity approach," is the way to go.

"We approach drug discovery by having a lot of irons in the fire," says Zaworotko.

While some research groups might focus all of their efforts on one compound, USF's CMD5 researchers do not put all of their molecular eggs in one basket. Nor do they focus on one disease. Graduate students, post docs, and their professors

work on a wide range of interesting possibilities, through collaborations with leading researchers at USF and throughout the world.

"The key to success is long and steady growth," predicts Zaworotko. "A large, synergistic group working together can lead to success. That's what CMD5 and the new Florida Center of Excellence is all about."





CMD5 scientists' patented devices available for licensure

That the drug discovery group is highly “decentralized”—in other words, takes a “shotgun” approach aimed at hitting as many biomarkers as possible—is a strategy that enables CMD5 researchers to make important advances in a multitude of different disease areas. This, in turn, leads to a full plate of intellectual property that can be owned by the University and ultimately licensed to pharmaceutical companies. CMD5 members already have an impressive list of patents and inventions available to license (see box).

Accordingly, new personnel interested in medicinal chemistry have come on board to help with the Chemistry Department's goals. In turn, these goals have taken on a university-wide flavor, with links to Engineering, Biology, and USF Health.

“It is not going to happen overnight,” admits Zaworotko. “We are just at the end of the beginning. We have made investments in personnel, half of which are new to the University in the last few years. We are building infrastructure and momentum. And, yes, we are open for business.”

CMD5 members are engaged in work ranging from targeting molecules that might be developed for pharmaceuticals to creating compounds isolated from natural products to researching enzymes and screening of chemical databases for novel therapeutic agents. For further information regarding these patents, and to see others available for licensure, please visit our website at www.research.usf.edu.

See-through nanotubes

This new manufacturing method for preparing transparent polymer-carbon nanotube composites using solar radiation allows for radiation-resistant biomedical devices and detectors of high radiation to work in space environments. USF partnered with NASA and Ames Research Center.

Melanoma treatment

An extract taken from sea squirts found in the Antarctic has been made into a compound (palmerolide) in USF laboratories. When tested by the National Cancer Institute against 60 cancer cell lines, palmerolide demonstrated three levels of magnitude higher activity against melanoma cells than against other cancer cell lines.

Neural anti-inflammatory agent

Diseases of the central nervous system connected to chronic inflammation can cause neurodegeneration. After finding a receptor on cells that play a role in inflammatory regulation, USF scientists identified a new and well-defined target for therapies or new drug discovery.

Drug delivery

A biodegradable, nontoxic polymer has been functionalized to deliver antibiotics. With FDA approval for use in the human body, the device has been shown to be effective against drug-resistant infections.

Anthrax fighter

A group of compounds has been developed to treat both anthrax and drug resistant staph infections (MRSA). Using beta-lactam agents developed at USF, researchers found that the compounds blocked bacterial fatty acid synthesis that anthrax and MRSA rely on.