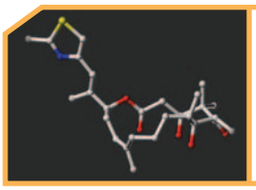
Chemistry Research at MSKCC

Making Molecules with the Goal of Helping Patients



Memorial Sloan-Kettering chemists play an important role in developing new cancer treatments. The drug dEpoB (shown at left), a member of a new class of drugs called the epothilones, is one molecule developed at MSKCC that may prove to be effective in fighting cancer.

When people think of chemistry, many recall the periodic table and its rows of one- and two-letter symbols, or smelly Bunsen burners and scratched beakers from high school science class. Chemistry, however, is an exciting, dynamic field that plays a central role in many scientific advances, including those important to cancer research.

Memorial Sloan-Kettering is known for its patient care and its clinical and biology research, but the Center also boasts a collection of talented chemists. These chemists work on a variety of projects, from designing new drugs to making vaccines to developing tools for studying the fundamental processes in cells.

In more-traditional settings such as universities, chemists often work separately from biologists and medical researchers. By contrast, chemists at MSKCC say the ease with which they can join forces with investigators from a wide range of disciplines makes their work especially rewarding. "Often people who do basic science don't get to see the connections between their work and helping people," said Derek Tan, who recently was appointed to head the new Laboratory of Chemistry and Chemical Genetics. "But here at Sloan-Kettering, you have the seamless connection from early research all the way to the clinic."

Samuel Danishefsky, head of the Bioorganic Chemistry Laboratory, developed several molecules that are now being used to treat patients. For example, he created a method for combining multiple antigens (substances that stimulate the body's immune system) into a single molecule to produce more effective cancer vaccines. Some of those vaccines are now in early clinical trials for cancers including breast and prostate.

"When you're in the Sloan-Kettering environment, you select projects that are likely to have an impact on patients."

SAMUEL DANISHEFSKY, CHEMIST

Dr. Danishefsky also has generated techniques for synthesizing a new class of drugs called epothilones. In the test tube, these drugs block cell division and prevent cancer cells from multiplying. Their mechanism is similar to that of the well-known cancer drug Taxol, but epothilones seem to work even on tumor cells that have become resistant to Taxol and other cancer drugs. Clinical trials for one of the epothilones, dEpoB, are expected to begin soon at Memorial Hospital.

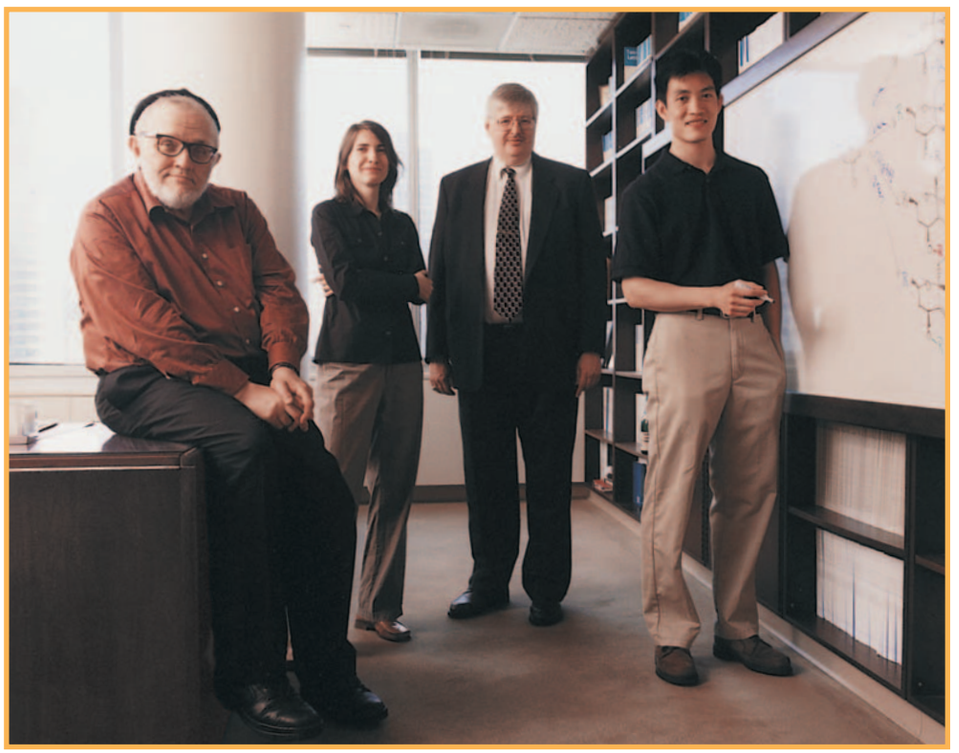
The epothilones and many other drugs developed at MSKCC are based on natural products. "Historically many drugs have come from natural products," Dr. Danishefsky explained. Natural product compounds can be isolated from anything found in nature — from plants to microorganisms in the soil to creatures found in the oceans.

"The argument in favor of studying natural products is that nature has seen fit to make these chemical structures, presumably with some goal in mind," Dr. Danishefsky said. That "goal" is usually some kind of biological activity, such as an interaction with proteins.

Gabriela Chiosis, an Assistant Attending Chemist in the Department of Medicine, has designed compounds that copy the shape of natural products and the way they interact with proteins, but have very different, more "drug-like" chemical compositions. "I try to understand why a compound binds to a protein and then come up with something that has the same function but not the drawbacks of natural products," Dr. Chiosis said. Natural products can be very large and complex, making them difficult to manufacture. Most drugs tend to be smaller molecules.

Dr. Chiosis is working with MSKCC cell biologist Neal Rosen and structural biologist Nikola Pavletich to develop drugs that bind to hsp90, a protein that is a potential target for cancer therapy. She is also collaborating with researchers in France to develop small molecules that resensitize bacteria that have become resistant to vancomycin, the drug of last resort for bacterial infections. One of the compounds disables the antibiotic-resistance mechanism.

Just because a molecule binds to a protein of interest in the laboratory, doesn't necessarily mean it will make a good drug. The molecule must be easy to administer to patients. In addition, the molecule may cause side effects because it interacts with other proteins in the body. William Bornmann, head of the Organic Synthesis Core Facility, is working with many



From left: Chemists Samuel Danishefsky, Gabriela Chiosis, William Bornmann, and Derek Tan collaborate with many MSKCC departments on a variety of projects.

clinicians within MSKCC to develop "analogs" of drug candidates (analogs often differ by a single atom or group) to create compounds that will make better therapies.

Dr. Bornmann was instrumental in determining the mode of action for STI-571 (also known as Gleevec, a new treatment for chronic myelogenous leukemia) and showing how it binds to its target protein, Bcr-Abl. His current research includes a collaboration to develop molecules that bind to Bcr-Abl and block its activity more effectively than STI-571 does. He is also working to develop analogs for actinonin — an antibiotic that induces cell death in leukemia and lymphoma cells — and thalidomide — a drug that is now being considered as a therapy for many types of cancer — as well as working on several vaccine projects.

Whereas much of the chemistry done at MSKCC involves the synthesis of individual molecules, called target-oriented synthesis, Dr. Tan's new laboratory will be taking a different approach, called diversity-oriented synthesis. "The idea is to synthesize very large collections of molecules, known as libraries, and then screen those libraries for biological activity using a variety of different tests, or assays," Dr. Tan said.

Dr. Tan hopes to contribute to the research of many biologists at the Center by developing molecules that can be used to study basic biological functions in cells. "We'd like to use these molecules to help map out the pathways that are defective in cancer and then to use that information as a jumping-off point for identifying potential targets for new therapies," he said.

"The benefit of doing chemistry research at MSKCC is tremendous," Dr. Danishefsky said. "There are more interesting chemistry projects out there than you could ever sensibly take on. When you're in the Sloan-Kettering environment, you have an additional key criterion for which projects you pursue: You select things that are likely to have an impact on patients." ☼

EXPERIMENTAL THERAPEUTICS CENTER CREATED

To make the most of drug-discovery research carried out by investigators at MSKCC, the Experimental Therapeutics Center (ETC) was recently established. Made possible by a donation from the Commonwealth Foundation for Cancer Research, created by Mr. and Mrs. William Goodwin, Jr., of Richmond, Virginia, the ETC will streamline the development of new therapeutics through early-stage clinical trials.

"The ETC will bring together individuals from different departments with a common goal of developing new agents for treating cancer," said David A. Scheinberg, who will lead the new center.

The Goodwins have pledged $5 million a year for four years, and MSKCC will match that amount. The funds will be used to enhance existing core areas (equipment and space used by many researchers) and create new ones dedicated to drug discovery and development, support initiatives in drug discovery and development, coordinate early investigation of new drugs and study their effects, and recruit new fellows and junior faculty.

"We have seen firsthand the tragic consequences of cancer and want to do what we can to help find better treatments and hopefully the ultimate cure for cancer," Mr. Goodwin said. "We believe Dr. Scheinberg and his staff are outstanding, and we are thankful that we are able to support their efforts with the development of the new ETC."

Mrs. Goodwin added, "Finding effective strategies to fight cancer is the goal of all involved. We are glad we have the resources to help." ☼