Biomaterials

Cornell has long been a leader in materials science and engineering. This experience allows Cornell faculty to make rapid progress in the development of new materials for medicine such as the drug delivery systems covered here.

Robert Barker/CU

C. C. Chu, Textiles and Apparel, designs new materials with biological activity (such as nitric oxide), biomaterials for drug delivery, and biomaterials as substrates for tissue engineering.

C. C. Chu, Textiles and Apparel, has an active research program centered on the design and synthesis of biomedical materials. Currently, Chu is most excited about designing new materials with biological activity (such as nitric oxide), about biomaterials as the delivery vehicles for drugs, and about biomaterials as substrates for tissue engineering. The new biomaterials, with nitric oxide function, are synthesized from both synthetic biodegradable polymers (such as aliphatic polyesters) and hybrids of synthetic and natural-based biodegradable polymers (such as polyester-amides derived from nontoxic α-amino acids).

Nitric oxide is a very small but highly reactive and unstable free radical with many known biological functions. However, the molecule itself is extremely short lived, lasting about 6 to 10 seconds. Chu and his coworkers have created biodegradable materials that possess long-lasting nitric oxide function, which may be useful for reducing the incidence of stent restenosis after balloon angioplasty procedures in heart-attack patients. Stent/balloon procedures suffer a restenosis rate of about 40 percent due to excessive growth of tissue into stents.

*W. Mark Saltzman**
BP Amoco/H. Laurance Fuller Professor of Chemical Engineering

**Saltzman acknowledges assistance from faculty members in BME*

For more information:
http://biomedeng.cheme.cornell.edu

Medical Research in the College of Arts and Sciences Yields Insights on Cancer and Its Treatment

Research in the College of Arts and Sciences is designed to increase fundamental understanding of the world around us, but this emphasis on understanding does not exclude practical applications. Research on cancer, for example, has yielded important insights into such basic biological processes as cell growth and development and the flow of biological information along molecular pathways. Understanding these processes in detail can ultimately lead to the development of useful drugs for the treatment of cancer, and one group of Cornell researchers is working to translate an improved understanding of cancer into useful treatment.

Cancer develops when accumulated errors in a cell's genetic material lead to unregulated cellular proliferation. The various forms of cancer reflect different mutations and different cellular locations, but all cancers originate from damaged genes. Typically, the damaged genes that lead to cancer involve cell signaling pathways, along which information is passed from molecule to molecule in a cell. Figure 1 shows a typical cellular signaling pathway. An external signal tells a cell to grow or to stop growing and specialize (differentiate). The information in the external signals goes from molecule to molecule along a complex network of molecular interactions. A frequent cause of cancer is a mutation in one of the proteins along the signaling pathway. Mutations that cause the growth signal to persist can lead to the unregulated cell growth that is the hallmark of cancer. Once the mutated signaling protein has been identified, a small molecule—a drug—that corrects the faulty signal can, in principle, be designed and synthesized. The very recent success of Gleevec (STI571) in treating chronic myelogenous leukemia is an example of this approach: genetic analysis pinpointed the fault in the signaling pathway and a small molecule that corrects the faulty signal was developed from a detailed analysis of the mutated signaling molecule.

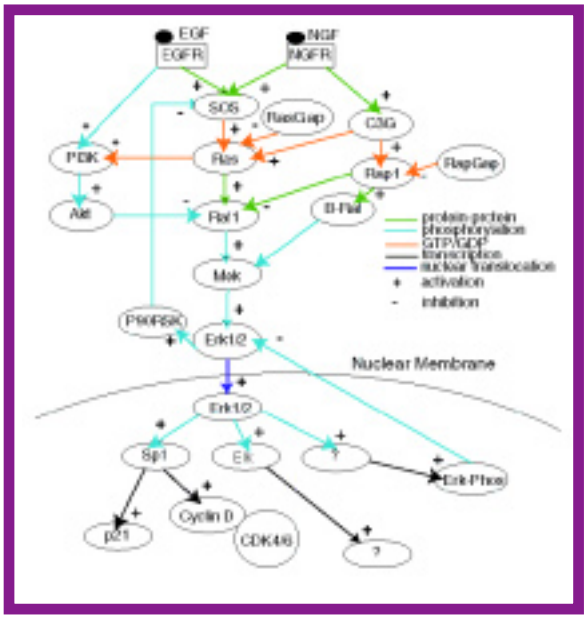

Figure 1

Richard Cerione, Molecular Medicine, and Chemistry and Chemical Biology, is an expert on deciphering cell-signaling pathways. In many cancers, a small protein called Ras is hyperactivated by mutations; the faulty signaling from Ras plays a key role in causing the cancer. Mutated Ras has proved to be a difficult drug target because the typical cancer-causing mutations in Ras are not amenable to correction by a small-molecule drug. Another protein named Cdc42, which Cerione discovered some years ago as a signaling partner of the epidermal growth factor receptor, turns out to be absolutely essential for the activation of Ras and some of its

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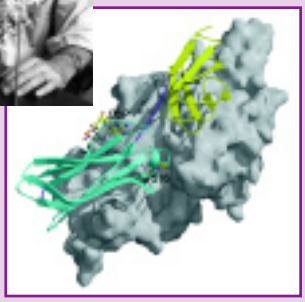
other signaling partners. Modulating Cdc42's activity should tune down Ras signaling, even the Ras signaling from mutated forms. Developing appropriate inhibitors to modulate Cdc42 and its targets requires several steps. The first step was to determine the three-dimensional structure of Cdc42 by using x-ray crystallography, which took advantage of Cornell's MacCHESS facility. Multiple studies were needed to investigate Cdc42 and its signaling partners, and expertise in molecular and cell biology was crucial to identifying these partners. The task of unraveling the roles of Cdc42 and its partners in normal and malignant cells is ongoing, and the search for small molecules that will specifically influence the activation of Cdc42 and consequently Ras has just begun.

Charles Harrington/CU

Jon Clardy, Chemistry and Chemical Biology



Certain breast cancer cells have abnormally large amounts of transglutaminase (a signaling protein) and are difficult to kill with standard chemotherapeutic agents. The first step to obtaining its structure was determining its three-dimensional structure by x-ray crystallography. Clardy's lab obtained the transglutaminase structure a few months ago.

A second signaling protein, transglutaminase, is receiving a great deal of attention from Cornell researchers as a potential anticancer agent. Transglutaminase is a puzzling protein since it is regulated in a way similar to Ras and Cdc42, and it is also a crosslinker that connects growth regulatory proteins to small molecules. Transglutaminase protects cells from dying when they are stressed or undergoing growth-arrest in order to differentiate. Certain breast cancer cells have abnormally large amounts of transglutaminase, and they are difficult to kill with standard chemotherapeutic agents. Could a small molecule that affects transglutaminase be a useful therapy for these breast cancers? To answer this question, a multidisciplinary effort has begun to reveal transglutaminase's secrets. Once again, the first step was to determine the three-dimensional structure of transglutaminase by x-ray crystallography. The first transglutaminase structure was obtained in Jon Clardy's

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Frank DiMeo/CU

Richard Cerione, Molecular Medicine; Chemistry and Chemical Biology

Nicola Kountoupes/CU

James Sethna, Physics

Charles Harrington/CU

Bruce Ganem, Chemistry and Chemical Biology

"A group of chemists and physicists working together have come up with some very clever ideas for prioritizing new drug targets and thereby speeding up the drug discovery process."

Charles Harrington/CU

Steven Strogatz, Theoretical and Applied Mechanics

"The research on cdc42 and transglutaminase illustrates how molecular biology, crystallography, and chemistry work together to develop anticancer agents."

laboratory, Chemistry and Chemical Biology, a few months ago. Cerione's laboratory uses molecular biology to prepare mutant forms of transglutaminase that, when considered in combination with the three-dimensional structure, should lead to a fuller understanding of transglutaminase and its potential as a target for cancer therapy.

The research on Cdc42 and transglutaminase illustrates how molecular biology, crystallography, and chemistry work together to develop anticancer agents. Cornell scientists are looking at the typical cell-signaling pathway (see Figure 1). Are there other molecules on the pathway that would make good drug targets? A large number of signaling molecules are being revealed by genome sequencing, and a reliable procedure to determine which of the many signaling molecules is most likely a drug target would be very valuable. A group of chemists and physicists working together have come up with some very clever ideas for prioritizing new drug targets and thereby speeding up the drug discovery process. The group includes James Sethna, Physics; Richard Cerione, Molecular Medicine, and Chemistry and Chemical Biology; Bruce Ganem, Chemistry and Chemical Biology; Kelvin Lee, Chemical Engineering; and Steven Strogatz, Theoretical and Applied Mechanics. An ambitious group of graduate students from these faculty members' research groups organized an interdisciplinary research team, the Cornell Computational Cancer Group, to think about how the products of genes are organized into networks and which of the nodes in these networks might make good drug targets. A local start-up company, Gene Network Sciences, will try to translate these basic discoveries into new anticancer drugs.

Cancer research of the sort described here requires a synthesis of genetic understanding of mutations, pathway analysis, three-dimensional structure determination, and chemical synthesis. Cornell is fortunate to have strengths in all of these areas.

Jon Clardy
Horace White Professor of Chemistry
Associate Dean, College of Arts and Sciences

For more information:
http://www.arts.cornell.edu

Biomedical Research in the Division of Nutritional Sciences Probes Links Between Maternal and Child Nutrition and Lifelong Health

Amazing progress in medical research over the past 30 years has resulted in effective treatments and even cures for major diseases affecting the U.S. population. While the curative aspect of the biomedicine revolution receives much of the headlines, another revolution is taking place in preventive medicine. It is increasingly recognized that many diseases afflicting the U.S. population are preventable with changes in life-style. These include heart disease, cancer, and diabetes—the top three killers of Americans. Diet and nutrition are major components of life-style over which people have considerable control. The Division of Nutritional Sciences (DNS) has played a leading role for more than 25 years in improving the public's knowledge of the importance of nutrition in disease prevention and health promotion.

DNS has been a leader in human nutrition research, in part, because it approaches human health from a multidisciplinary perspective. Surrounding a core of scientists trained in the traditional discipline of nutrition are faculty who represent such diverse basic science disciplines as biochemistry, molecular and cell biology, and physical chemistry as well as translational and applied disciplines such as toxicology, public health, epidemiology, psychology, sociology, anthropology, and economics. Integration of methods and theories from these disciplines has allowed DNS to investigate the whole person within the context of the family, community, and society into which the individual is born, raised, and functions through adulthood and into old age. Thus, a major approach to nutrition is through a life course perspective that recognizes the importance of genetic endowment and its varied expression in the individual depending on the environment encountered from conception to death. Nutrition is an indispensable component of that environment which is known to affect the way genes are expressed. It is in this context that the science of nutrition is expected to make important contributions to biomedical and public health research.

One area of research that involves a large number of DNS faculty relates to the nutrition problems surrounding pregnancy and early infancy. Research in maternal and child nutrition has implications for both the United States and developing countries, and DNS researchers are active in both arenas. This research bridges the basic and applied sciences in DNS. Recent laboratory research in the Division of Nutritional Sciences has contributed to new knowledge about the mechanisms of genetic control of nutrient metabolism associated with fetal malformation, the contribution of