# Molecule that could aid organ transplantation synthesized by La Jolla Researchers K.C. Nicolaou, Ph.D., professor of chemistry and Darlene Shiley, professor and chairman, Department of Chemistry

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Media Contacts: Warren R. Froelich, UCSD, (619) 534-8564 Robin Goldsmith, TSRI, (619) 554-8134

MOLECULE THAT COULD AID ORGAN TRANSPLANTATION SYNTHESIZED BY LA JOLLA RESEARCHERS

A biologically significant molecule being studied for its ability to suppress the immune system for organ transplantation has been synthesized by a team of scientists from the University of California, San Diego and The Scripps Research Institute (TSRI), both located in La Jolla, California.

The molecule, called rapamycin, is being viewed by some as a potential rival to cyclosporin--the only immunosuppressant drug available today to prevent rejection from transplantation.

During the past decade, more than 250,000 patients have undergone successful transplantation of organs including kidneys, heart and lung, thanks largely to the use of cyclosporin.

However, the drug has triggered side effects in some patients--including kidney and liver damage, in addition to hypertension, abnormal hair growth and gum disorders.

"Many people see rapamycin as a promising alternative to cyclosporin," said K.C. Nicolaou, Ph.D., UCSD professor of chemistry, and TSRI's Darlene Shiley Professor and chairman, Department of Chemistry.

Nicolaou, principal author of a study appearing in today's issue of the Journal of the American Chemical Society (JACS) emphasized that his approach would not replace the current fermentation techniques for growing rapamycin, originally isolated from a naturally occurring fungus found on Easter Island in the South Pacific.

Though promising, rapamycin--produced by Wyeth-Ayerst in New Jersey and currently in patient trials--is considered to be chemically and metabolically unstable, requiring continuous patient monitoring.

For this reason, chemical synthesis represents a new avenue toward the development of molecular cousins of rapamycin, with increased stability and more clinical promise.

"Our hope is to create chemical analogs with greater potency, higher stability, and less side effects," Nicolaou said.

The study's co-authors are Tushar K. Chakraborty, a visiting scientist from the Indian Institute of Chemical Technology; Anthony D. Piscopio, an NIH Postdoctoral fellow at UCSD, now at Pfizer, Inc.; Nobuto Minowa, a visiting scientist from Meiji Seika Kaisha, Ltd., in Japan; Peter Bertinato and Koide Kazunori, both graduate students at UCSD.

Although discovered about 20 years ago, rapamycin didn't begin to attract attention until organ transplantation became medically accepted during the past decade, and the demands for cyclosporin to prevent rejection began to increase dramatically. Today, worldwide sales for cyclosporin reach nearly a $1 billion.

However, researchers in university and pharmaceutical laboratories around the world are looking for alternatives to cyclosporin that would suppress the immune system at least as well, but also would leave patients with fewer side effects.

Two potential molecules have received the most attention: FK506, isolated from a fungus by a Japanese drug company; and rapamycin, discovered by Wyeth-Ayerst researchers. Both molecules have undergone intensive study, each probed with a variety of sophisticated tools to learn more about its physical and chemical structure, atom by atom.

Among other things, researchers have discovered that both molecules work in combination with a cellular protein called FKBP. Once the molecules are bound to this protein, a series of signals that influence the production of T-cells, important cells that trigger the immune response, are blocked. Researchers are now trying to find the precise targets to which these complexes bind.

"There is now a big race among biologists to find out where this complex binds," said Nicolaou.

"This step is crucial to discover what triggers immunosuppression," he added. "Such basic knowledge will be invaluable to further design immunosuppresants that will be better than the existing ones."

As a first step toward the design of such drugs, Nicolaou and his team describe in the JACS article what they call a "rather daring approach" for the total synthesis of rapamycin.

In essence, the researchers built their molecule using an open chemical chain or precursor, whose ends--consisting of carbon atoms--were stitched together via a chemical fragment or "bridge" to form a large ring.

The process, called "stitching cyclization," is being used by Nicolaou's team to help create new versions of the molecule, which subsequently can be tested for biological activity.

"Now we have the ability to bring in different kinds of fragments, stitch them into this common precusor, to make a variety of analogs that differ from rapamycin in this region," said Nicolaou.

He added that each new version of the molecule could take weeks or months to create, since rapamycin is "one of the most complex molecules to ever be synthesized.

"Our goal is to try to design simpler and simpler analogs," he said, "so that one day we may find simple compounds that will be effective in immunosuppession that could be made in a laboratory in a practical way."

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