Scripps Scientists Achieve Total Synthesis of Taxol

La Jolla, CA. February 10, 1994 — Scientists at The Scripps Research Institute (TSRI) have succeeded in solving a complex scientific problem that has eluded scores of scientific teams for more than 20 years: the total chemical synthesis of one of the most significant chemotherapeutic agents known. Taxol, a substance originally isolated from the Pacific Yew tree (Taxus brevifolia), has been synthesized by a team of Scripps chemists led by K.C. Nicolaou, Ph.D.

"The main advance lies in our newly acquired ability to synthesize in the laboratory a plethora of designed taxoids that may prove superior to the naturally occurring substance," according to Nicolaou. "Even though this synthesis represents a first giant step, the method needs further refinement before a practical way to produce taxol synthetically will emerge. Our hope is to produce a simpler molecule that mimics taxol's biological activity."

Richard A. Lerner, M.D., President of The Scripps Research Institute said, "This synthesis meets a formidable academic challenge and is a wonderful example of the value of basic biomedical research in its ultimate application to the alleviation of human suffering. Dr. Nicolaou’s achievement will have far-reaching implications for the field of anti-cancer therapeutics."

The scarcity of taxol and the ecological impact of harvesting it have prompted extensive searches for alternative sources of the compound including semisynthesis, cellular culture
production and chemical synthesis. Despite considerable efforts, the latter has been thwarted until now due to the magnitude of the synthetic challenge.

The work will be reported in the February 17 issue of Nature Magazine in an article entitled, "Total Synthesis of Taxol," by K.C. Nicolaou, Z. Yang, J.J. Liu, H. Ueno, P.G. Nantermet, R.K. Guy, C.F. Claiborne, J. Renaud, E.A. Couladouros, K. Paulvannan, and E.J. Sorensen. In addition to his appointment as Chairman of the Department of Chemistry and Darlene Shiley Professor of Chemistry at TSRI, Dr. Nicolaou also is a Professor of Chemistry at the University of California, San Diego.

Recognized as a potentially promising anticancer therapy more than 30 years ago and approved a year ago by the U.S. Food and Drug Administration for use in the treatment of ovarian cancer, taxol was discovered during extensive screening of plant materials for anticancer agents during the late 1960s under an initiative sponsored by the National Cancer Institute.

Scientific study of the compound has been extensive. Physicians currently are studying its effects on nearly every known neoplasm. Biologists are using it to study the mechanisms of cell function. Synthetic chemists are exploring every conceivable pathway for its synthesis.

As early as the 1970s, scientists discovered taxol's unique mechanism of action; it kills cancer cells in a way unlike that of any other drug.

Nearly all cells have a complex structure within them called the cytoskeleton, an intricate scaffolding of minute fibers called microtubules. The cytoskeleton enables each cell to maintain its appropriate shape, to move and to interact with neighboring cells -- in short, to function correctly. This scaffolding also is dynamic and changes according to the functional
state of the cell, alternately appearing and disappearing as the microtubules break down and then reassemble.

Prior to their investigation of taxol, cell biologists had discovered a number of compounds that could inhibit this reassembly of microtubules, some of them anti-cancer agents. Microtubules play a critical role in cell division and when they are prevented from forming cells, they cannot divide. Initially, taxol was believed to be one of these inhibitors.

But, in fact, it had the opposite effect. Rather than breaking down the internal structure of cells, taxol paralyzed them, making them so stable as to prevent movement, replication or division. It was a mechanism of action that was unprecedented and represented a way of killing cancer that was never seen before.

While the interest in taxol increased as it began to demonstrate efficacy against some of the most virulent forms of cancer, several daunting problems remained, including the issue of limited supply, side effects and difficulty of administration to patients.

Chemistry could provide a solution to these problems. The achievement of total synthesis could help scientists to devise a scheme for making large amounts of taxol relatively cheaply, and by modifying the structure of taxol the scientists could increase its water solubility.

The Nicolaou group began serious work on the total synthesis in January, 1992, when it committed itself to a convergent strategy involving assembling the molecule from scratch using simple starting materials through a pyramidal scheme. The plan included initial construction of the two six-membered rings of taxol, joining them to form the central eight-membered ring, and installing the four-membered ring very late in the synthesis. The last two ring formations were considered by many chemists to be notoriously difficult to piece

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together and the group invested many months of work before they knew if it were possible to achieve.

By the end of 1992, the group had assembled the left and right hand fragments of the molecule, the two six-membered rings, and were ready for their coupling. Because of the complexity of the anticipated maneuvers, Nicolaou divided the group into three subunits: one to study methods for joining the two segments of the molecule, one to find a way to close the central ring of the target, and one to study the "endgame" of the projected synthesis using materials derived from taxol itself.

By the middle of 1993 the group had achieved the first and second goals using simpler model compounds and later the fully elaborated fragments. By September, 1993, the third team had made considerable progress, paving the way for the final steps of the synthesis. Several difficult tasks, including the introduction of the final oxygen atoms and construction of the fourth, oxetane ring remained. Shortly thereafter, members of the group reached the final target and had achieved total synthesis.

Dr. Nicolaou noted, "Considering the fierce competition to achieve this goal and the extreme difficulties of the task, it is gratifying to have been able to assemble such a talented group of students and postdoctoral fellows with whom I have collaborated on this project and to see them succeed in such a short time."

The Scripps Research Institute provided both facilities and funding for this work. With the exception of Eric Sorensen, who is a graduate student at UCSD, the other members of the group are students and postdoctoral fellows at The Scripps Research Institute. Additional funding was supplied by NIH, and through several graduate and postdoctoral fellowships.