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Race to Synthesize Cancer Drug Molecule Has Photo Finish

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Correction Appended

AFTER decades of excruciating effort and cutthroat competition, chemists have at last synthesized taxol, a cancer drug that is arguably the most complex molecule ever cobbled together by human hands.

The achievement, announced last week by two rival laboratories, is a major coup in synthetic chemistry, said Dr. Matt Suffness, program director of biochemistry and pharmacology grants at the National Cancer Institute in Bethesda, Md. "At least 40 to 50 research groups around the world have been working on the synthesis of taxol since 1971," he said. "It is a very challenging molecule."

Now that taxol can be made in the laboratory, Dr. Suffness said, researchers have new tools to improve the molecule. Taxol, hailed in much of the news media as a miracle cure for ovarian cancer, has not lived up to those early claims, Dr. Suffness said, but has nevertheless proved to be a very effective and important anti-cancer agent in ongoing clinical trials.

Two chemists emerged as winners in a photo finish in the race to synthesize taxol. First by a nose is Dr. Robert Holton, a professor at Florida State University whose report will be published Feb. 23 in The Journal of the American Chemical Society. Second is Dr. K. C. Nicolaou, a chemist at the Scripps Research Institute in La Jolla, Calif., whose work is described in next week's issue of the journal Nature. Although Dr. Holton's article appears later, it was submitted and accepted for publication before Dr. Nicolaou's and therefore, by the rules of scientific races, Dr. Holton is the winner.

Although the scientists used different methods to construct the taxol molecule, they faced the same challenge. Taxol, a substance isolated from the Pacific yew tree, was found to have cancer killing effects in the early 1960's, and its structure was delineated in 1971.

Chemists groped for words to describe the complexity of its structure, Dr. Holton said. Among those used were "diabolical," "congested," "strained" and "crowded."

At its core, taxol contains four carbon rings that are folded up in a cup shape. One ring has eight
carbon atoms, two have six carbon atoms and the fourth has four atoms. Hung all over this structure are so-called functional groups, dangling clumps of oxygen and nitrogen atoms that interact with each other and with outside molecules.

In deciphering such molecules, synthetic chemists study the structural elements, spin them around in their mind's eye and on computer screens and then try to find ways to stitch them together in the test tube. "You design a strategy on paper and go to the laboratory to try it," Dr. Nicolaou said. "Often it doesn't work. So you retreat and try again. And again."

This molecule was so complex that it took new chemical methods to make it. For example, the Florida group used a unique method to build the eight-member ring out of camphor. Later it added the functional groups and attached the other rings.

The Scripps scientists took a different tack. They constructed the two six-member rings and loaded them with functional groups. Then, using a special chemical reaction that uses titanium to fuse the ends of a chain of carbon atoms, they made the eight-member ring. Finally they installed the four-member ring and hooked everything together. "Voila," Dr. Nicolaou said, "We have taxol. It is exactly the molecule that occurs in nature with the same chemical, physical and biological properties."

Neither method will lead to the mass production of taxol, the scientists said. There is already plenty of taxol around. It is being extracted from yew needles, a process that does not require cutting down the tree, and results in a renewable source of the drug. The payoff, they said, is that the synthesis suggests new methods for constructing complex molecules. Specifically, it may help researchers design analogues of taxol that are superior to the natural molecule.

"Nature provides a lead," Dr. Nicolaou said. "We chemists can fine-tune the structure" to make it better.

In tinkering with the molecule, researchers have already stripped away functional groups and added others to see what happens. "Whenever you knock off functional groups, a thousand things can happen," Dr. Holton said. "Every change of shape changes function."

But now that the molecule can be built up step by step from scratch, the scientists said, there are more opportunities to try to make a version that is more effective, less toxic and easier to administer.

Of the drug’s effectiveness, Dr. Suffness said: "We have seen very few complete remissions with taxol, but we have seen partial remissions and life extension. The drug is fairly well tolerated." Cancer drugs work best in combination, Dr. Suffness said, and taxol is now being tested as an ingredient in various cancer drug cocktails. "We'll have to see how they do," he said. "We think we'll see enhancement."

Diagram: "A Drug's Tangled Structure" At the core of the taxol molecule are four carbon rings
folded up in a cup shape, outlined in the schematically unfolded drawing below. One ring has eight carbon atoms, one at each point, two have six and the fourth has four. From this structure hang functional groups, clumps of oxygen and nitrogen atoms that interact with each other and with outside molecules. (Source: Dr. Robert Holton/Florida State University)