"TROJAN HORSE" ANTI-CANCER AGENTS
DESIGNED AND SYNTHESIZED BY LA JOLLA SCIENTISTS

La Jolla, CA 3 pm May 21, 1992 -- A new class of molecules that represents some of the most potent anti-cancer agents ever tested has been designed and synthesized by a team of scientists from The Scripps Research Institute (TSRI) and the University of California, San Diego, both located in La Jolla, California.

The molecules, called enediyynes (pronounced een dye ines), also have shown "remarkable selectivity" in their ability to destroy cancer cells while leaving healthy cells intact.

"Provided their selectivity against tumor cells versus normal cells can be maintained and enhanced in animal models and humans, these molecules may emerge as powerful drugs against cancer," the scientists wrote in the current issue of Science, the journal of the American Association for the Advancement of Science.

K.C. Nicolaou, Ph.D., who is TSRI's Darlene Shiley Professor and chairman, Department of Chemistry, as well as a UCSD professor of chemistry, said "we are really excited about these compounds because of their potency, but most importantly, because of their selectivity."

Nicolaou, the study's principal investigator, cautioned that further studies to assure the molecule's safety and effectiveness are required before it can be tested in patients.

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The study's co-authors are Wei-M. Dai, Ph.D.; Susan C. Tsay, Ph.D.; Virginia A. Estevez, Ph.D.; and Wolfgang W. Wrasidlo, Ph.D., all from The Scripps Research Institute.

The new molecules are synthetic versions of naturally occurring toxins isolated from unique bacteria that use chemicals to defend themselves from other bacteria. By definition, these chemicals are considered antibiotics.

Discovered in 1987, these molecules have attracted international attention among academic researchers and drug companies intrigued by what Nicolaou describes as their "phenomenal biological activity."

In essence, the molecules work by creating highly reactive chemicals called radicals that attach themselves to the cell's DNA, the helically shaped repository of heredity, and then -- at the appropriate signal -- break it into pieces.

When introduced to the first member of the enediyne family, Nicolaou recalled, "It looked so diabolical, I couldn't believe it was real."

As described in the Science paper, each molecule is equipped with three domains that, when combined, create a potent weapon: a molecular "warhead" that houses the active region of the enediyne; a delivery system that directs the molecule to its target; and a triggering device that, at the right signal, initiates a cascade of reactions that leads to the generation of the DNA damaging molecules.

"You could compare this process to a 'Trojan horse' of Greek mythology," said Nicolaou. "The molecules enter the cell intact and upon activation, destroy the genetic material via both single- and double-strand DNA cuts."

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Although the naturally occurring molecules have shown "remarkable" anti-cancer activity, they fail to differentiate between healthy cells and tumor cells. To be useful, the synthesized versions of the molecules had to be designed by the chemists to take advantage of the potent anti-cancer activity, while leaving healthy cells intact.

"We are trying to mimic the action of these molecules by designing our own warheads, and we are trying to make them as simple as possible so we can produce them in the laboratory in large quantities," Nicolaou said.

During the last couple of years, Nicolaou's labs at both TSRI and UCSD have designed and synthesized several molecules based on the naturally occurring compounds, with a few modifications.

In the Science paper, the researchers described experiments with a synthetic version of the anti-cancer antibiotic called dynemicin A, which is one of four enediyynes that are produced naturally by bacteria originally found in soil. "Although we're exploring mimics of other enediyynes, we concentrated on dynemicin models because they are the easiest to make," Nicolaou said.

In these experiments, the synthetic molecules were designed with a modified warhead, combined with a molecular triggering device and built-in lock. Also designed into the molecule were tethering devices, to allow subsequent attachment of other chemical groups to aid in the delivery of the molecule; and, in some cases, detection devices designed to help monitor the results.

"Our molecules proved to be more potent than the naturally (more)
occurring substances in test tube studies," Nicolaou said.

The studies further showed the molecules to be more potent than known anti-cancer agents including cis-platin, doxorubicin, vinblastine and bleomycin, and even more potent than the highly promising and much-discussed anti-cancer agent known as taxol.

Surprisingly, small amounts of the molecules showed "dramatic selectivities" in killing certain types of tumor cells, particularly leukemia cells, without destroying normal cells, Nicolaou added.

"A most remarkable feature of these compounds is their low toxicity in animals. This is a real plus because it makes these new agents prime candidates for clinical development," added Wrasidlo, the head of the biological team at TSRI.

"Something happens within the cell that opens up the lock (of the triggering mechanism), but we're not quite sure yet what that is," Nicolaou said.

Three possible explanations might be: the potential existence of tumor-associated factors that might activate these cells preferentially; differences in the permeability of membranes to these compounds; differences in the ability of the healthy vs. cancerous cell machinery to repair DNA damage caused by these agents.

Nicolaou said he and his research team are trying to find out which, if any, of these explanations is correct. He is also attempting to design a delivery system to home in on tumor cells or DNA sequences responsible for cancer.

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