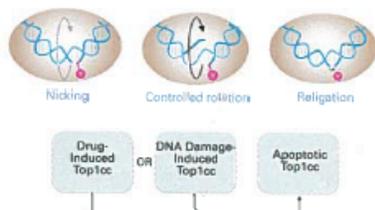


CORRIDOR COLLABORATIONS

Develop Effective Treatments

"This couldn't have been done anywhere else."

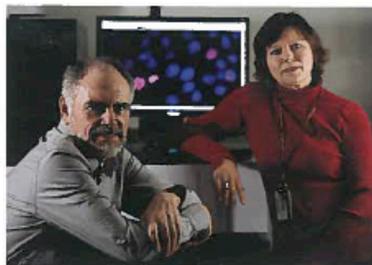
Top1 Cleavage Complex (Top1cc)



"Imagine DNA as a hopelessly twisted garden hose. Topoisomerase 1 acts like a pair of scissors that cuts the hose and holds both ends while the tangles are removed, then reconnects the two ends so the hose is back in working order," explains Dr. Pommier. "Top1 inhibitors prevent the 'scissors' from gluing back the two ends. The drugs act as a wedge so that the DNA can't settle back into its coiled conformation, and trouble for the cancer cell begins."



Dr. Yves Pommier. Photo credit: Rhoda Baer



Dr. William Bonner and Dr. Olga Sedelnikova. Photo credit: Rhoda Baer

Like the Natural Product, Only Better

Topoisomerase 1 (Top1) is an essential enzyme that enables tightly coiled DNA to unwind and open up so that transcription and replication can take place. It then assists the DNA in closing back up again, restoring the DNA double helix. Dr. Yves Pommier, Chief of CCR's Laboratory of Molecular Pharmacology, received an NIH Merit Award for his comprehensive approach to devising drugs that block that action and selectively kill cancer cells.

For a long time, camptothecin, a natural product that comes from the *Camptotheca acuminata* tree, was the only drug that could attack topoisomerase 1. "Our goal was to find more options," says Dr. Pommier. In 1991, his team was the first to propose how camptothecin traps the enzyme and DNA in open conformation. It takes advantage of a key difference between normal cells and cancer cells. "Cancer cells are impatient," explains Dr. Pommier. "They can't hold on while the drugs keep the DNA break open. It's toxic to them. Normal cells have the ability to wait out the damage."

The Pommier team's hypothesis proved correct when they solved the crystal structure of the three-way complex of camptothecin, Top1, and DNA in 2005. They also showed that many naturally occurring anticancer drugs (vinblastine, Taxol™, and rapamycin) and some antibiotics use the same mechanism. "Our data show that researchers should be looking for new agents that stabilize open conformations," Dr. Pommier notes.

Camptothecin is effective, but it has weaknesses. Dr. Pommier and his colleagues set out to find more potent cousins. They searched for drugs that are stable longer in the blood and trap DNA-Top1 complexes in

an open conformation for longer periods than camptothecin can. They succeeded. Using NCI cell lines and COMPARE analysis (a chemical and cellular screening database to reveal similar patterns of activity), they searched through thousands of drugs in the NCI's Developmental Therapeutics Program (DTP). "I asked the late Dr. Ken Paull in DTP to look for something that looked like camptothecin," Dr. Pommier says. "We found a group of drugs called indenoisoquinolines. This couldn't have been done anywhere else."

The progress made in developing new Top1 inhibitors was possible because of a strong collaboration between CCR and the Developmental Therapeutics Program, researchers at Purdue University, and private industry. NCI and Purdue now share a patent for these new Top1 inhibitors. Of about 400 indenoisoquinolines found through the NCI screen, eight lead compounds are in high-priority development by NCI. At least one has been licensed to a drug company for further development.

This Biomarker Will Help

Thanks to Dr. William M. Bonner's discovery of a biomarker for the double-strand breaks in damaged DNA, upcoming Phase 0 and Phase I clinical trials of the indenoisoquinolines will be more conclusive. When these breaks in DNA occur, many molecules of histone H2AX quickly become phosphorylated. Dr. Bonner, also in the Laboratory of Molecular Pharmacology, has developed and patented an antibody to phosphorylated H2AX that will enable clinicians to monitor whether the drugs have hit their molecular target and caused DNA damage.