From Nature to Bench to Bedside

History of the Discovery and Development of Taxol and Camptothecin

CAMPTOTHECIN Timeline

1958

Only one extract displays strong anitcancer activity, Camptotheca acuminata

1965

Camptothecin isolated in pure form/

1966-69

Preclinical development

1970

Clinical trials of camptothecin sodium salt initiated 1985

In 1963, Drs. Wall, Wani and colleagues began isolating, purifying, and

characterizing the anitcancer components of Camptotheca acuminata, whose anticancer activity was first identified in the late 1950s. In 1966,

they published the discovery of camptothecin in the Journal of the American Cancer Society. Poor water solubility and side effects stalled

camptothecin's unique mode of action was reported in 1985. In the

mid-1990s, two camptothecin analogs, topotecan and irinotecan, received FDA approval for use against ovarian, lung, breast, and colon cancers.

clinical trials in the early 1970s, but interest was renewed when

Unique mechanism of action determined: trapping of DNA topoisomerase I in covalent complexes with DNA

1996

Topotecan (SmithKlineBeechum) and CPT-II (Daiichi, Japan) were approved by the FDA for clinical use in the US

2003

RTI's Natural Products Laboratory bestowed National Historic Chemical Landmark

1957

Dr. Wall (then at the USDA) sends 1000 plant extracts to NCI for anticancer testing

1960

Dr. Wall founds the Natural Products Laboratory at RTI

1963

Large sample assigned to RTI for bioactivitydirected fractionation

1966

The structure of of C. acuminata camptothecin is reported in the J. of the Am. Chem. Society

1974

Due to lack of efficacy, clinical trials are discontinued

1986

Revival of interest in camptothecin. Synthesis of analogs that retain potency and are water soluble

1994

CPT-II (Daiichi, Japan) was approved for clinical use in Japan

2002

A number of CPT analogs are currently in clinical evaluation. 9-Nitro-CPT (rubitecan). NX211 (lurtotecan), DX-8951F (exetecan) are in Phase II trials and homocamptothecin, BN 80915, karenitecin, silatecan, and macromolecular prodrugs of CPT, MAG-CPT, and PEG-CPT are in Phase I trials.