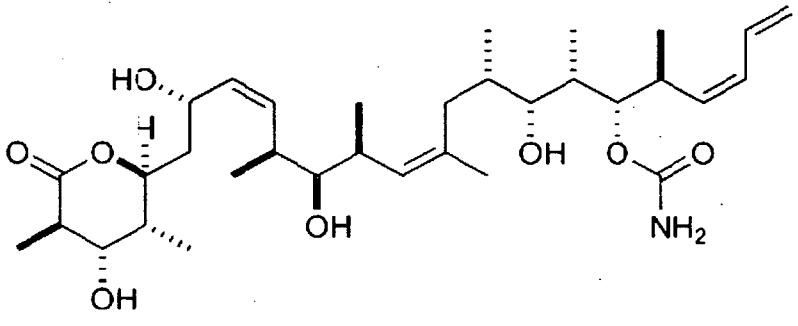
PL-6

Studies of the Potent Microtubule Stabilizing Marine Sponge Polyketide (+)-Discodermolide

S. P. Gunasekera

Smithsonian Marine Station at Fort Pierce, 701 Seaway Drive, Fort Pierce, Florida 34949, USA
E-mail: gunasekeras@si.edu

In 1990, chemistry and biology groups at Harbor Branch Oceanographic Institution (HBOI) working together reported the isolation, structure determination and preliminary biological activities of the marine sponge derived anticancer compound (+)-discodermolide. Scientists have studied the chemistry and biological activities of this compound for two decades. Interestingly, more than 50 articles describing the chemistry and biological activities have been published in superior chemical and biological journals. In addition, nearly 50 patents have been issued to cover and protect the discoveries in synthetic, medicinal and biological chemistry.



(+)-Discodermolide

(+)-Discodermolide is a highly fictionalized polypropionate natural product first isolated from the marine sponge *Discodermia dissoluta*. My group at HBOI defined the structure by spectroscopic methods and confirmed by X-ray diffraction analysis. The absolute stereochemistry was subsequently established by total synthesis conducted by the Schreiber group. (+)-Discodermolide was first introduced as a cytotoxic and immunosuppressive agent, but then found to be a potent microtubule stabilizer that binds with remarkable affinity to the taxoid site on β-tubulin in microtubules. Unlike paclitaxel, the known microtubule-stabilizing anticancer drug with clinical utility, (+)-discodermolide is not a substrate of P-glycoprotein pump. (+)-Discodermolide maintains antiproliferative potency against β-tubulin mutant cell lines that are resistant to epothilones and paclitaxel. Further, (+)-discodermolide and paclitaxel can act synergistically, and the combination increased the activity as well as decreased the toxicity in both cell lines and xenograft-bearing mice. This mechanism of action, antiproliferative activity better than paclitaxel and novel structure made it a promising candidate for clinical development as an anticancer drug. The limited supply of (+)-discodermolide from the natural source delayed the development of it as an anticancer drug and thus prompted the scientific community to prepare synthetic (+)-discodermolide.

The unique chemical structure with 13 stereogenic centers posed a major synthetic challenge for the preparation of sufficient material to allow for the pre-clinical and clinical studies. Over 15 publications describe the synthetic approaches of discodermolide. A major milestone in the development of (+)-discodermolide was the progression of a large-scale synthesis of (+)-discodermolide by the Smith group. This coupled with other synthetic schemes, the Novartis Pharmaceutical Corporation (NPC) led to a refined process in which over 60 g of synthetic (+)-discodermolide was produced. NPC who licensed the compound from HBOI conducted Phase I clinical trials for solid tumor malignancies at the Cancer Therapy and Research Center in San Antonio, Texas.

The low availability of the natural (+)-discodermolide and the complexity of its molecular structure for synthesis, the scientists initiated programs to prepare analogues of discodermolide for structure-activity relationship (SAR) studies. The Schreiber group was the first to prepare discodermolide analogues for SAR studies. My group at HBOI prepared large number of analogues using natural (+)-discodermolide and also isolated three analogues from the natural source. In addition, a series of minor analogues were purified from the by-products resulted from the final stages of NPC full synthesis of 60 g of (+)-discodermolide.

The chemistry, biological activities including the effects on microtubule architecture, perturbation of the cell cycle on A549 cells, their ability to induce polymerization of purified bovine brain tubulin and the results of the Phase I clinical trials of (+)-discodermolide will be presented. In addition, the synthesis of analogues and the evaluation of these for in vitro cytotoxicity against A549, P388, MFC-7, NDC/ADR, PANC-1 and VERO cell lines and their effects on microtubule architecture studies towards the identification of the pharmacophore of (+)-discodermolide will be discussed.