1. INTRODUCTION

Type I and II DNA topoisomerases are the targets for numerous clinically efficacious antitumor agents. Over the last decade, considerable effort has been expended in developing camptothecin (CPT) derivatives that selectively target DNA topoisomerase I (TOP-I) (1). The prodrug irinotecan (CPT-11) is approved for treatment of colon carcinoma and has demonstrated significant activity against numerous other cancers in adults and
children. Topotecan is approved for treatment of platinum- or taxane-resis-
tant ovarian carcinoma and has demonstrated broad-spectrum activity (2).
Other analogs are in clinical development, such as D5198f and the homocamptothecins and liposomal formulations of CPT derivatives, and offer the potential for prolonged plasma exposures.

Agents targeting TOP-I in clinical trials have proceeded through the preclinical stages of identifying cytotoxic potency and confirmation of in vivo antitumor activity. Acceptable toxicity in rodents and other species, as mandated by regulatory agencies, had been studied before clinical evaluation. CPTs have demonstrated remarkable activity against animal models (3). However, less dramatic clinical activity has been reported, resulting in the discontinuation of at least one agent, 9-aminocamptothecin (9-AC).

In this review, we examine this preclinical-clinical interface with respect to understanding the value and limitations of preclinical models. Hopefully, lessons learned regarding development of camptothecins can be applied to the future development of drugs that induce cytotoxicity through their interactions with TOP-I. This article will focus on preclinical models used to assess antitumor activity and toxicity for TOP-I–targeted drugs and how information derived from valid models may be used to direct the design of clinical trials.

2. EARLY STUDIES

CPT was studied extensively in the Cancer Chemotherapy National Service Center of the National Cancer Institute during the 1960s. It was formulated in carboxymethylcellulose and administered by intraperitoneal (ip) injection using the Walker 256 rat carcinosarcoma model as the test system. Relative to other drugs evaluated, camptothecin had relatively poor activity (4). However, the sodium salt of CPT demonstrated significant activity in increasing survival time in several lymphocytic leukemias (5). Based on a lack of cross-resistance to dichloromethotrexate, BCNU, cytosine arabinoside, 6-mercaptopurine, and other agents, it was proposed that CPT had a novel mechanism of action. In contrast to the significant activity observed in these preclinical models, CPT, evaluated as the sodium salt, was found to be ineffective in patients with advanced disseminated melanoma or gastrointestinal malignancies (6,7). Severe toxicities included myelo-suppres-
sion, vomiting, diarrhea, and hemorrhagic cystitis and resulted in the discontinuation of the clinical trial of sodium CPT. Other studies in China, however, demonstrated activity of 10-hydroxycamptothecin in treatment of head-and neck-and bladder cancers (reviewed in ref. 8).

Studies by the Liu laboratory defined TOP-I as the target for CPT and the observation that the CPTs caused trapping of TOP-I on DNA and induced single-strand breaks (9,10) served as an impetus to reexplore this class of agent. Although CPT is frequently referred to as an “inhibitor” of TOP-I, it