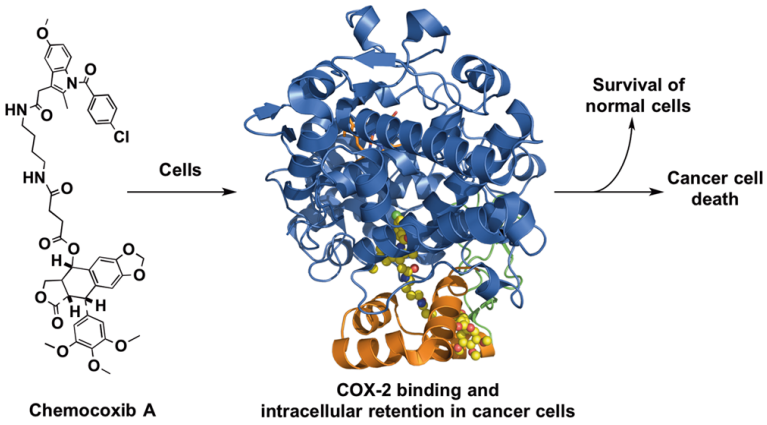
Chemical Research in Toxicology

Spotlight

pubs.acs.org/crt

ANTICANCER DRUG CONJUGATE SELECTIVELY TARGETS AND INHIBITS THE INTRACELLULAR PROTEIN COX-2 IN *IN VIVO* TUMORS



Adapted from M. J. Uddin et al. (2016) *ACS Chem. Biol.*, DOI: 10.1021/acschembio.6b00560. Copyright 2016 American Chemical Society.

The enzyme cyclooxygenase-2 (COX-2) is an intracellular protein highly expressed in a range of malignant tumors. Jashim Uddin, Lawrence J. Marnett, and their team synthesized and evaluated a series of chemotherapeutic agents targeting COX-2 in cancer cells and discovered a podophyllotoxin−indomethacin conjugate named chemocoxib A that displays selective antitumor activity *in vivo* ((2016) *ACS Chem. Biol.*, DOI: 10.1021/acschembio.6b00560).

The researchers tethered derivatives of indomethacin, a slow, tight-binding COX inhibitor, to the nonalkaloid toxin lignan podophyllotoxin, which is inactive against COX-2. These conjugates successfully inhibited COX-2 selectively *in vitro*. One of these, chemocoxib A, displayed high potency in inhibiting COX-2 *ex vivo* in intact cells of head and neck squamous cell carcinoma and dramatically reduced the number of cells present 48 h post-treatment. While this reduction was not observed in nontumorigenic primary human mammary epithelial cell cultures, chemocoxib A was also active against many other neoplastic cell types, regardless of COX-2 expression level. *In vivo*, however, chemocoxib A demonstrated COX-2-dependent selectivity; it was ineffective against COX-2-negative tumors in mice after 14 d of treatment, yet reduced COX-2 positive tumor growth by 50% without any systemic toxicity. The success of chemocoxib A provides proof-of-concept for the strategy of targeting an intracellular protein *in vivo* with an antitumor agent.

Abigail Druck Shudofsky

DOI: 10.1021/acs.chemrestox.6b00408
Chem. Res. Toxicol. 2016, 29, 1791−1792