

O-04: MINING THE NCI OPEN REPOSITORY FOR MOLECULAR-TARGETED ANTITUMOR NATURAL PRODUCTS

Dale G. Nagle and Yu-Dong Zhou

School of Pharmacy, University of Mississippi, Oxford, MS

Extracts from the NCI Open Repository of marine invertebrates and algae were evaluated using cell-based reporter assays for the ability to regulate the antitumor molecular targets Hypoxia-Inducible Factor-1 (HIF-1) and Peroxisome Proliferator-Activated Receptor-gamma (PPAR- γ). HIF-1 is a transcription factor that promotes tumor cell adaptation and survival under hypoxic conditions and is an important molecular target for anti-cancer drug discovery. A T47D breast tumor cell-based reporter assay was used to evaluate extracts for HIF-1 inhibitory activity. Bioassay-guided fractionation of an active extract from an *Axinella* sp. yielded new sodwanone and yardenone triterpenoids that were shown to inhibit HIF-1 activation in T47D breast tumor cells and in PC-3 prostate tumor cells. PPAR- γ is a ligand-activated transcription factor. Ligands of PPAR- γ have been shown to inhibit growth, promote terminal differentiation, and induce apoptosis in human breast tumor cells. A MCF7 breast tumor cell-based reporter assay was developed to examine extracts for the ability to activate PPAR- γ . Bioassay-guided isolation of an active extract from the marine sponge *Pseudoceratina rhax* yielded psammaplin A. Molecular modeling studies suggest that psammaplin A may interact with binding sites within the PPAR- γ ligand-binding pocket and activation of PPAR-regulated gene expression may play a role in the ability of these natural products to induce apoptosis in tumor cells.