Chemistry and Mechanism of Action of Marine Natural Product Antitumor Agents

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The world's oceans cover greater than 70% of the Earth's surface, and taking into account volume, the oceans represent better than 95% of the biosphere. All but 2 of the 28 principal phyla in the animal kingdom are represented in aquatic environments; 8 phyla including the Cnidaria, Porifera, Ectoprocta and Echinodermata are exclusively aquatic, largely from saline habitats. Greater than 95% of all animal species are invertebrates and conservative estimates are that there are over 1 million species represented in the world's oceans. Nonetheless, natural products from terrestrial plants and soil microorganisms have historically played the more important role in human medicine. The search for anticancer agents from the marine environment is a relatively young field as compared to other natural products disciplines. The search began in earnest about 20 years ago with the beginning of clinical trials with didemnin B. During the last two decades approximately 8000 compounds have been isolated from marine organisms. Part of what makes marine natural products unique is that the majority of these are from invertebrate animals. To place this in perspective, according to the Dictionary of Natural Products approximately 150,000 compounds have been isolated from terrestrial organisms, primarily from plants and microbes. Although there are no approved chemotherapy drugs from marine organisms there are ten compounds currently in clinical development.

With the exception of the bryostatins which target a signal transduction process associated with tumor promotion, the marine natural products in clinical trial function by classically cytotoxic mechanisms. As a consequence, they tend to suffer from lack of selectivity for tumor cells, and cause collateral damage to normal tissue.

Selectivity is of course a widely recognized problem and one reason why many drug discovery programs both academic and industrial, have developed targeted screening programs focused on cellular components or pathways commonly over-expressed or selectively expressed in tumor cell lines. The particular pathways we have focused on are the EGF and PI3K-AKT- mTOR growth factor signaling pathways, the S26 proteasome protein degradation pathway and HIF-1.