Various active anticancer agents are derived from plants and terrestrial microorganisms. The isolation of C-nucleosides from the Caribbean sponge, Cryptotheca crypta, four decades ago, provided the basis for the synthesis of cytarabine, the first marine-derived anticancer agent to be developed for clinical use. Cytarabine is currently used in the routine treatment of patients with leukaemia and lymphoma. Gemcitabine, one of its fluorinated derivatives, has also been approved for use in patients with pancreatic, breast, bladder, and non-small-cell lung cancer. Over the past decade, several new experimental anticancer agents derived from marine sources have entered preclinical and clinical trials. This field has expanded significantly as a result of improvements in the technology of deep-sea collection, extraction, and large-scale production through aquaculture and synthesis. In this paper, examples of marine-derived experimental agents that are currently undergoing preclinical and early clinical evaluation are briefly discussed. A summary of the available information on the results of phase I and II trials of agents such as aplidine, ecteinascidin-734 (ET-734), dolastatin 10 and bryostatin 1 is also presented.

Since ancient times, we have relied on nature for our basic needs – food, protection, clothing, transport and pharmaceuticals. The medical armamentarium includes many examples of important agents that were first isolated from plants and microorganisms and that are now in routine clinical use. In the field of anticancer therapy, many active cytotoxic agents were originally developed from natural sources (Table 1). Until recently, the only major contribution to anticancer therapy from the sea was the synthetic nucleoside analogue cytarabine, which is commonly used in the treatment of leukaemia and lymphoma. The development of cytarabine was initially inspired by a series of C-nucleoside-derived compounds isolated from the Caribbean sponge Cryptotheca crypta. More recently, a fluorinated derivative of cytarabine, gemcitabine, has shown significant activity in patients with solid tumours, such as pancreatic, breast, bladder, and non-small-cell lung cancer.

The oceans cover about 70% of the earth’s surface, and the marine environment includes tremendous biodiversity; all but two of the 28 major animal phyla are represented. Over the past few years, about 3000 new compounds from various marine sources (Figure 1) have been described and some have entered clinical trials. This activity has been largely due to improvements in the technologies involved in deep-sea sample collection and large-scale drug production through aquaculture and drug synthesis which took place in the 1980s. These developments suggest that, in the future, the oceans will become an important source of novel chemical classes not found in the terrestrial environment (Table 2).

New agents undergoing clinical evaluation

Tunicate derivatives

Of the marine-derived compounds that have entered phase I and II trials as antitumour agents, didemnin B, aplidine, and ET-743 are derived from tunicates. Didemnin B is a cyclic depsipeptide isolated from the tunicate Trididemnum solidum. It has shown impressive antitumour activity in human tumour models in vitro as well as in tumours growing in athymic mice. In initial clinical trials, patients with various solid tumours or non-Hodgkin lymphoma...
Aplidium albicans (Figure 1) and later called aplidine. The preclinical findings for aplidine suggested potentially high antitumour activity in preclinical models after longer drug exposure, phase I trials were initiated at various drug schedules, ie 1 h, 3 h, 24 h and 72 h intravenous infusions. Notably, antitumour activity was observed in patients with advanced solid tumours, such as renal-cell carcinoma, breast cancer, melanoma and ovarian cancer included in phase II trials for ET-743 confirm its therapeutic potential in various soft tissue sarcomas and breast cancer.22-26

Another depsipeptide, dehydrodidemnin B, was subsequently isolated from the Mediterranean tunicate, Aplidium albicans (Figure 1) and later called aplidine. The preclinical findings for aplidine suggested potentially high antitumour activity against various different, rapidly proliferating tumour types, as a result of interference with cell-cycle progression at G1.13 Aplidine appears to be more active than didemnin B in preclinical models and so far has not shown evidence of life-threatening neuromuscular toxicity. Because aplidine appears to have higher antitumour activity in preclinical models after longer drug exposure, phase I trials were initiated at various drug schedules, ie 1 h, 3 h, 24 h and 72 h intravenous infusions. Notably, antitumour activity was observed in patients with advanced solid tumours, such as renal-cell carcinoma, breast cancer, melanoma and ovarian cancer included in phase II trials for ET-743 confirm its therapeutic potential in various soft tissue sarcomas and breast cancer.22-26

**Table 2. Marine-derived experimental anticancer agents**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Group</th>
<th>Metabolite</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trididemnum solidum</td>
<td>Tunicate</td>
<td>Didemnin B</td>
<td>Caribbean</td>
</tr>
<tr>
<td>Bugula nentina</td>
<td>Bryozoan</td>
<td>Bryostatin 1</td>
<td>Gulf of California</td>
</tr>
<tr>
<td>Ecteinascidia turbinata</td>
<td>Tunicate</td>
<td>Ecteinascidin-743</td>
<td>Caribbean</td>
</tr>
<tr>
<td>Halichondria okadai</td>
<td>Sponge</td>
<td>Halichondrin B</td>
<td>Okinawa</td>
</tr>
<tr>
<td>Dolabella auricularia</td>
<td>Sea hare</td>
<td>Dolastatin 10</td>
<td>Indian Ocean</td>
</tr>
<tr>
<td>Portiera homemannii</td>
<td>Red alga</td>
<td>Halomon</td>
<td>Philippines</td>
</tr>
<tr>
<td>Aplidium albicans</td>
<td>Tunicate</td>
<td>Aplidine</td>
<td>Mediterranean</td>
</tr>
<tr>
<td>Aplysia kurodai</td>
<td>Sea hare</td>
<td>Aplyronine A</td>
<td>Japan</td>
</tr>
<tr>
<td>Elysia rubefascens</td>
<td>Mollusc</td>
<td>Kahalalide F</td>
<td>Hawaii</td>
</tr>
<tr>
<td>Mycale sp.</td>
<td>Sponge</td>
<td>Mycosphere B</td>
<td>Thailand</td>
</tr>
<tr>
<td>Micromonospora granulata</td>
<td>Actinomycete</td>
<td>Thiothoracin</td>
<td>Mozambique</td>
</tr>
<tr>
<td>Ascidian didemnin</td>
<td>Tunicate</td>
<td>Granulatimide</td>
<td>Brazil</td>
</tr>
</tbody>
</table>

malignant melanoma, tumours of neuroendocrine origin, and medullary carcinoma of the thyroid.14-16 The main toxic effects observed so far have been nausea and vomiting, myalgia, transient disturbance of liver function, and local irritation at the injection site. Muscular toxicity was circumvented by the concomitant administration of L-carnitine (E Raymond, unpublished). Aplidine will start phase II trials in various solid tumours in the near future.

The euteinascidins are derived from the Caribbean tunicate Ecteinascidia turbinata (Figure 2) and also show significant antitumour activity in both murine and human tumour cell lines.27 Of the many euteinascidins that have been isolated, ET-743 was selected for clinical trials (Figure 3). It is a tetrahydroisoquinoline alkaloid that acts by selective alkylation of guanine residues in the DNA minor groove.18 It therefore differs from the other DNA-alkylating agents so far introduced in the clinic. It also interacts with nuclear proteins.19

The main drug-induced toxic effects of ET-743 in early clinical trials were pancytopenia, fatigue, emesis and transaminitis. Local toxicity was also observed in patients who received short-term intravenous administration. There were objective and long-lasting tumour responses in patients with advanced resistant mesenchymal tumours, breast cancer, melanoma and ovarian cancer included in phase I clinical trials of ET-743.10,11 Initial results from pilot phase II trials for ET-743 confirm its therapeutic potential in various soft tissue sarcomas and breast cancer.12-20

**Dolastatins**

The dolastatins are cytotoxic cyclic and linear peptides derived from the sea hare, Dolabella auricularia (Figure 4), a mollusc found in the Indian Ocean. Dolastatins 10 and 15 are small peptides; dolastatin 10 was selected for clinical trials because of its more favourable preclinical profile.27 It inhibits microtubule assembly, causing cells to accumulate in metaphase4,20 and is extremely potent in vitro. Dolastatin 10 caused bone-marrow toxicity in initial clinical trials, as well as local irritation at the injection site and mild peripheral neuropathy. Phase I and II trials involved
Marine-derived anticancer agents

Cyclic peptides and depsipeptides are found in blue-green algae (cyanobacteria).41 Depsipeptide (NSC 630176) is a bicyclic peptide isolated from a strain of Chromobacterium violaceum. It decreases mRNA expression of the c-MYC oncogene and inhibits the growth of Ha-RAS-transformed NIH-3T3 cell line, RAS-1, causing cell-cycle arrest at G0–G1.42 It acts as an inhibitor of a histone deacetylase.43 Depsipeptide showed cytotoxic activity in various human solid-tumour cell lines in vitro and also in athymic mice.44 Phase I trials of depsipeptide will begin soon.

Other compounds in preclinical development

New classes of anticancer drugs isolated from marine organisms in different parts of the world show cytotoxic activity in a variety of preclinical models. Discodermolide, a metabolite of the deep-sea sponge Discodermia dissolute collected in the waters of the Bahamas, induces microtubule stabilisation.45–47 Halichondrin B was initially purified from the sponge Halichondria okadai in Japan and has shown in vivo activity in melanoma and leukaemia models. It can also be obtained from the deep-water sponge Lissodendoryx, which is found in New Zealand. This compound is also active in various human tumour-cell models in vitro and in vivo and appears to interfere with microtubule function.48

The Brazilian tunicate, Ascidian didemnum granulatum, is the source of the aromatic alkaloids granulatimide and isogranulatimide, which appear to act as G2 checkpoint inhibitors.49 These compounds have been synthesised, and several analogues are being developed for further testing. In addition, new bisindole alkaloids of the topsentin and hamacanthin classes have been isolated from the Mediterranean sponge Rhaphisia lacazei, and these compounds also showed significant antiproliferative activity against a series of human cell lines in vitro.50

Five new sesquiterpenes, parahigginols, and parahigginic acid, have been isolated from a Taiwanese marine sponge Parahippuris sp. Initial studies revealed that these compounds were cytotoxic against murine P-388 and human KB16, A549, and HT-29 tumour cells.51 Another group of marine compounds, the makaluvamines, also show significant antitumour activity in animal models, probably through the induction of dose-dependent DNA cleavage via topoisomerase II.52

Dinoflagellates, unicellular marine protozoons, produce some of the largest and most complex polyketides identified to date. The biological activities of these molecules are quite diverse.53 More recently, the manipulation of the biosynthetic pathways of microbial polyketides through...
Finally, preclinical models and is due to start phase I trials in Hawaii, showed substantial antitumour activity in early stages of clinical evaluation.57 A synthetic cryptophycin derivative (LY355703, CRYPTO 52) is in the agents obtained from cyanobacteria. A synthetic cryptophycin is a family of antitubulin antitumour agents obtained from cyanobacteria. A synthetic cryptophycin derivative (LY355703, CRYPTO 52) is in the early stages of clinical evaluation.57

Future prospects

Nature has supplied several active anticancer agents (eg, the vinca alkaloids, anthracyclines, epipodophyllotoxins, and taxanes), which have significantly improved the management of many types of human cancers.2,4,5,58 These marine-derived compounds are extremely potent in culture, with inhibitory concentrations generally in the nanogram range. The recommended doses of didemmin B, aplidine, and ET-743 for phase II trials were 6.3, 6.0, and 1.5 mg/m², respectively. One can speculate that these organisms require potency and rapid penetration of cellular membranes for protection against predators, since their aquatic environment will rapidly dilute their poisons.2,4,5

The challenge of identifying new anticancer agents in the oceans has been taken up by a group of scientists who have formed a worldwide collaboration to investigate the organisms found on coral reefs and in deep ocean thermal vents. This field is also expanding thanks to advances in deep-sea collection techniques, aquaculture, and the technology needed to extract nucleic acids from biological materials. The manipulation of microbial biosynthetic pathways through genetic engineering has also led to the production of interesting new molecules. These living organisms represent a rich reservoir of genetic and metabolic diversity, which is ready to be exploited and which will certainly make anticancer drug discovery even more challenging in the next few years.

References


Search strategy and selection criteria

Published data for this review were identified by searching MEDLINE, CancerLit, UKCCR Register of Cancer Trials, and references from relevant articles. Relevant researchers and drug companies were also contacted.

Figure 4. The bryozoan Bugula neritina.
Marine-derived anticancer agents

47 Kowalsky RJ, et al. The microtubule-stabilising agent discodermolide competitively inhibits the binding of paclitaxel to tubulin polymers, enhances tubulin nucleation reactions more potently than paclitaxel, and inhibits the growth of paclitaxel-resistant cells. Mol Pharmacol 1997; 52: 613–22.