MEDICAL GOLD RUSH – IN DEEP SEA
Suman Pratihar, Rudra Prasad Nath & Jayanta Kumar Kundu
Molecular Biology Research Unit, Department of Zoology
Vidyasagar University, Midnapore -721102, West Bengal, India.

ABSTRACT
There is a medical gold rush going on, not in our laboratory system but on the deep sea floor. The search for new drugs is now become increasingly urgent. The marine environment holds incredible resources for unique biodiversity. Marine organisms are very rich source of therapeutic drugs. In recent years, a significant number of novel metabolites with potent pharmacological properties have been discovered from the marine organisms. Although there are only a few marine-derived products currently on the market, several robust new compounds derived from marine natural products are now in the clinical pipeline, with more clinical development. Some promising role of these organism have been found in treatment of diseases like cancer (brayostatin 1, didemnin b, dolastatin 10), HIV (lamellerin α-20 sulfate), tumor, Alzheimer (Gts21), metastatic activity etc.


INTRODUCTION
Life began in the sea, and three-quarters of the Earth’s surface is covered by water. Innumerable organisms, displaying rich biodiversity, populate the ocean depths. There are extremely diverse species of invertebrates – fixed or sessile – many in plant form and others capable of slow, primitive movement. These invertebrates possess no physical defenses such as protective shells or spines; instead, they have developed biologically active molecules – secondary metabolic substances – that they use to attack prey or defend their habitat. The fascinating variety of marine organisms hints at a myriad of new possibilities for drug discovery (Kijjoa et al., 2004). Marine life is a vast resource, providing food, medicine, and raw materials, in addition to helping to support recreation and tourism all over the world. At a fundamental level, marine life helps determine the very nature of our planet. Marine organisms contribute significantly to the oxygen cycle, and are involved in the regulation of the Earth's climate. Exploration of the sea and its organisms is still at a relatively early stage. Although the oceans contain much greater biodiversity than is found on land, efforts to exploit this biodiversity by identifying new compounds have hardly begun. At present there are some 11000 marine derived natural products compared with more than 1,55,000 natural, terrestrial products. To date, researchers have isolated approximately 7000 marine natural products, 25 percent of which are from algae, 33 percent from sponges, 18 percent from coelenterates (sea whips, sea fans and soft corals), and 24 percent from representatives of other invertebrate phyla such as ascidians (also calledtunicates), opisthobranch molluscs (nudibranchs, sea hares etc), echinoderms (starfish, sea cucumbers etc) and bryozoans (moss animals) (Kijjoa et al., 2004). There are several phases in marine product research: specimen collection; establishing taxonomy; extracting possible active molecules; using screening techniques to evaluate therapeutic activity; identifying and isolating the structure responsible for the activity; and using organic synthesis to ensure a supply (Newman et al., 2004). Patent applications are immediately filed for promising molecules. These molecules are then tested and, if the results are positive, studies are carried out on human subjects in clinical trials. Once this last phase has been completed, the product is registered as a new drug and brought to. (Faulkner, 2000) Some potential therapeutic compounds which are derived from marine sources are shown in table I.

BRAYOSTATIN 1 (C_{47}H_{80}O_{17})
The tunicate Trididemnum solidum (chordata) is the source of this drug. 20 different bryostatins have been isolated till date (Hale et al., 2010). It has an anti-canceral and immunosuppressive activity. Bryostatins act synergistically with other anti-cancer drugs and modulate protein kinase C (PKC) activity (Mackay et al., 2007). Bryostatins has appeared very promising memory enhancer in animal models. It is now being investigated in human testing, possible for treatment for alzheimer. (Sun et.al, 2005)

DIDEMMIN B (C_{27}H_{66}N_{15}O_{15})
The tunicate Trididemnum solidum (chordata) is the source of this drug. It is an anti-cancer agent via protein synthesis inhibition. Didemmin B interrupts protein synthesis in target cells by binding non-competitively to palmitoyl protein thioesterase. Didemmin B is a strong anti-viral agent against both DNA and RNA viruses like Herpes Simplex Virus type 1 (Montgomery et al., 1985). It has completed phase II human clinical trials against adenocarcinoma of the kidney and advanced epithelial ovarian cancer.

DOLASTATIN 10 (C_{63}H_{108}N_{10}O_{9}S)
This drug found in Indian Ocean sea hare Dollabella auricularia (mollusca). It acts as Tubulin interactive agents. The intracellular targey of Dolastatin 10 is tubulin. The peptide inhibits microtubule assembly and tubulin dependent – GTP binding. Dolastatin 10 causes metaphase arrest in wide variety of animal and human cancer cell...
line. Dolastatin 10 induces apoptosis in certain human lymphoma cell line. (Kijjoa et al., 2004).

ECTEINASCIDIN 743 (C_{39}H_{42}N_{19}O_{15})
The tunicate Ecteinascidia turbinata (chordata) is the source of this drug. It has anti-cancer agent via apoptosis induction. ECTEINASCIDIN 743 (ET-743) induces apoptosis only during active gene transcription (Kijjoa et al., 2004). This makes activity dividing cancer cell more vulnerable to drug toxicity than normal cell because they exhibit greatly accelerated transcription & translation rate. This drug showed effectiveness against advanced stage breast cancer. (Newman et al., 2004)

HALICHONDRI B (C_{66}H_{96}O_{39})
The Japanese sponge Halichondria okadai (porifera) is the source of this drug. It’s activity resides in macrocyclic lactone C1-C38 moiety. It’s synthetic analog NSC 707389 or E7389 (licensed by Eisai) act like its parent natural compound is classified as a tubulin depolymerizer. It acts to disrupt the polymerization at the microtubules necessary in mitosis. (Newman et al., 2004).

TABLE1: some promising potential therapeutic compounds derived from marine source

<table>
<thead>
<tr>
<th>Condition</th>
<th>Compound</th>
<th>Source organism</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Brayostatin 1</td>
<td>Brayozoan</td>
<td>Gulf of California</td>
</tr>
<tr>
<td></td>
<td>Didemnain b</td>
<td>Tunicate</td>
<td>Caribbean</td>
</tr>
<tr>
<td></td>
<td>Dolastatin 10</td>
<td>Sea hare</td>
<td>Japan</td>
</tr>
<tr>
<td></td>
<td>Et 743</td>
<td>Tunicate</td>
<td>Hawaii</td>
</tr>
<tr>
<td></td>
<td>Helicondrin b</td>
<td>Sponge</td>
<td>Deep sea</td>
</tr>
<tr>
<td></td>
<td>Kahalaide f</td>
<td>Shark</td>
<td>Caribbean</td>
</tr>
<tr>
<td></td>
<td>Nevostat</td>
<td>Shark</td>
<td>Palau</td>
</tr>
<tr>
<td></td>
<td>Squalamine</td>
<td>Sponge</td>
<td>Australia</td>
</tr>
<tr>
<td></td>
<td>Discodermolide</td>
<td>Tunicate</td>
<td>Palau</td>
</tr>
</tbody>
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HIV

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<thead>
<tr>
<th></th>
<th>Cyclodimennisrol trisulfate</th>
<th>Tunicate</th>
<th>Palau</th>
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</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Lamellarin α 20 sulfate</td>
<td>Tunicate</td>
<td>Palau</td>
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Alzheimer

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<thead>
<tr>
<th></th>
<th>Gts21</th>
<th>Nematode</th>
<th>Mediterranean</th>
</tr>
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Asthma

<table>
<thead>
<tr>
<th></th>
<th>Contignasterol</th>
<th>Sponge</th>
<th>New Guinea</th>
</tr>
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Pain, Headch, Nausea

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<thead>
<tr>
<th></th>
<th>Zincnotide</th>
<th>Mollusc</th>
<th>Philippines</th>
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</table>

KAHALAIDE F (C_{20}H_{34}N_{19}O_{16})
Hawaiian sacoglossan Elysia rufescens (mollusca) is the source of this drug. Kahalaide F appears capable of disrupting lysosome membranes within certain target cells, thereby initiating apoptosis. The drugs also appears to inhibit the expression at certain specific genes that are involved in DNA replication and cell proliferation, thereby inhibiting tumor spreading and growth. (Kijjoa et al., 2004).

NEOVESTAT (AE 941)
This drug found in Shark, Scoliodon sorrrakowah. It is potent anti-tumor drug and anti-metastatic drug. AE 941 component specific any prevents the binding of VEGF to its receptors (vascular endothelial growth factor) to its receptor, which is an important factor in pre prevention and containment of tumor growth. It inhibits MMP’s, induction of endothelial cell specific apoptosis, increase in the level and activity of tissue plasminogen activator (t-PA). (Falardeau et al., 2001).

SQUALAMINE (C_{26}H_{45}N_{13}O_{8})
The shark Squalus acanthus (chordata) is the source of this drug. It is anti-tumor agent; anti angiogenic agent. Squalamine starves tumors by preventing the typical proliferation of blood vessels they require for nourishment. Squalamine appears capable of inducing endothelial cell inactivation and apoptosis through inhibition of integrin (specialized receptor protein) expression and the disruption of cytoskeletal formation. (Newman et al., 2004).

DISCODERMOLIDE (C_{13}H_{22}NO_{4})
This drug is found in Caribbean deep-sea sponge Discodermia dissolusa (porifera). Discodermolide has been shown to inhibit the proliferation of human cells by arresting the cell cycle in G2- and M-phase. It hyper-stabilizes microtubules, especially prevalent during cell division. Hyper-stabilization of the mitotic spindle causes cell cycle arrest and cell death by apoptosis. (Faulkner et al., 2000).

LAMELLERIN A-20 SULFATE
Tunicates are the source of this drug. Lamellerin α – 20 Sulfate was tested against wild type HIV and form to inhibit early steps of HIV replication. Lamellerin α -20 Sulfate inhibited integration in vitro by authentic HIV-1 replication intermediates isolated from infected cells.

GTS 21 (DMXB-A)
Nematodes are the source of this neuro protective drug. As Alzheimer’s progresses, nicotine receptor in the brain gradually disappear. GTS – 21 compound aims to stimulate the surviving nicotine receptors and delay the onset at this debilitating desaiage. Test at GTS-21 is rats showed boosts in memory and a slowing at nerve cell degeneration. (Meyer et al., 1998).

CONTIGNASTEROL (C_{29}H_{42}O_{7})
The sponge Petrosia contignata (porifera) are the source of this drug. It is anti-asthma agent. Some of the novel compounds derived from contignasterol were shown to demonstrate activity as histamine blockers in in vitro rodent cell cultures. IPL 576, 092 (contignasterol...
derivative) completed phase-II trails in 2002, has entered clinical trails as a treatment for disease causing inflammation of the eyes and skin. (Langlands et al., 1995).

ZICONOTIDE (C_{10}H_{172}N_{16}O_{32}S_{7})

This drug is found in Derivative of a conotoxide of cone snails Conus geographicus, Conus magus (mollusca). The mechanism of Ziconotide has no yet been discovered in humans. Result in animal studies suggest that Zinconotide blocks N-type calcium channels on the primary nociceptid nerve in the spinal cord. (McGivern et al., 2007).

CONCLUSION

In summary very promising anti-cancer, anti-tumor, anti-alzheimer, anti-metastatic activity has been found for several naturally occurring compounds (or their chemically synthesize analogs derive from organisms that inhibit the tropical reefs or various parts of the sea all over the World). It is a real fact that the importance of marine organism as a new substance is growing. Marine organisms represents approximately a half of the total global diversity. These biomolecules have a huge medicinal value. Several of these compounds have advanced to human trails, and the results remain encouraging. Further expansions of the knowledge base for aqua culturing the nominal producing organism can only help this effort.

REFERENCES


