Marine Pharmacology in 1998: Antitumor and Cytotoxic Compounds

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Introduction

During 1998 marine antitumor pharmacology research involved research groups in Austria, Australia, Chile, England, France, Germany, Holland, Israel, Italy, Japan, Korea, New Zealand, Philippines, Russia, Spain, Switzerland and the United States. Thirty-eight papers were published in peer reviewed journals describing the antitumor and cytotoxic properties of 35 marine natural products belonging to four structural types, namely polyketides, terpenes, nitrogen-containing compounds and polysaccharides. The organisms yielding these bioactive marine compounds comprised a diverse group of marine animals, algae, fungi and bacteria. Antitumor pharmacological studies were reported for 17 marine natural products with an established mechanism of action. The Dolastins, tunicate derived-peptides with potent antitumor effect, advanced to Phase I anticancer clinical trials. *In vitro* cytotoxicity data was reported for 18 marine chemicals with undetermined mechanisms of action. This one-year overview thus provides evidence that 50 years after the discovery by Bergman and his co-workers of spongothymidine and spongouridine, there continues to be an active multinational research effort aimed at the discovery of novel antitumor agents from marine organisms.

Fifty years have passed since the seminal studies by Bergman (Bergmann and Feeney 1951; Bergmann and Burke 1955) that resulted in the discovery of spongothymidine and spongouridine from the sponge *Tethya crypta*. This finding led to the synthesis of arabinosyl cytosine (Ara-C), currently sold by the Pharmacia & Upjohn Company under the brand name Cytosar-U[R], and which presently remains the only marine-derived anticancer agent in continuous clinical use, even though there has been continuous funding for this type of research over the past several decades. Currently, the CRISP database lists 17 projects directly funded by the National Institutes of Health in the area of marine antitumor chemistry and pharmacology.

The purpose of this article is to present an overview of research published during 1998 in the field of marine antitumor pharmacology. The articles included in this paper were retrieved from the National Library of Medicine via Medline[R], Ovid Technologies, Inc.'s OVID database and MarinLit, a database dedicated to the marine natural products literature. It is possible that some relevant articles were missed, but it is the hope of the author that this number is small. Only those articles reporting on the antitumor or cytotoxic activity of marine compounds with established chemical structures were included in this review and are presented in alphabetical order in *Table 1* or *Table 2*. Those papers reporting on preclinical and/or clinical antitumor research with marine chemicals with *determined* mechanisms of action have been included in *Table 1*. All other articles describing cytotoxicity to either murine or human tumors by marine natural products with *undetermined* mechanisms of action are grouped in *Table 2*. Due to space limitations, publications on the antitumor or cytotoxic activity of extracts or structurally uncharacterized marine compounds have not been included in this brief overview.

Table 1 includes 20 reports on antitumor research involving 17 marine compounds with determined mechanisms of action that included *in vitro* and/or *in vivo* studies with human cancer cell lines. The marine chemicals Agosterol A, Jasplakinolide and Naamidine A were isolated from *Porifera* (sponges); Aplidine, Dolastin and Ecteinascidin from *Chordata* (tunicates); Eleutherobin and Sarcodictyin from *Cnidaria* (soft corals); Bryostatin from Ectoprocta (Bryozoa), 4 Phyla included in Kingdom *Animalia*. Curacin D, Dehydrothyrsiferol, Spirulan, Tolyporphin were derived from blue-green algae while Octalactin A was derived from bacteria (Kingdom *Monera*). Stypodiol was isolated from an alga from the Phylum *Phaeophyta* (Kingdom *Plantae*). Following the chemical classification proposed by Schmitz et al. (Schmitz et al., 1993), the marine natural products in *Table 1* fall into four chemical classes: polyketides (Bryostatins and Curacin D), terpenes (Agosterol A, Dehydrothyrsiferol, Eleutherobin, Sarcodictyins and Stypodiol), nitrogen-containing compounds (Aplidine, Auristastatin, Dolastin, Ecteinascidin, Jasplakinolide, Naamidine A and Tolyporphin) and polysaccharides (Spirulan). Considerable information is available for the 17 marine compounds included in *Table 1* at the mechanistic level. Distinct biochemical mechanisms have been indentified, including multidrug resistance reversal and protein kinase C binding, as well as inhibition of tubulin polimerization, protein synthesis, guanine binding, epidermal growth factor receptor, heparanase, acyl CoA:cholesterol-O-acyl transferase and the cell-cycle. Although antitumor studies involving human tumor cell lines with these 17 marine natural products were mostly of a preclinical nature (both *in vitro* and *in vivo*), a clinical anticancer trial with a synthetic Dolastin analog was reported during 1998 (Villalona-Calero et al., 1998).

The laboratories that reported the articles listed in Table 1 were located in the USA (14 papers), Spain (4 papers), Japan and France (2 papers each), while Germany, Austria, Switzerland, Italy, the Netherlands and Chile contributed one paper each.

In a similar manner, Table 2, lists 18 marine natural products with potential antitumor activity because they demonstrated activity in cytotoxicity assays. However, in contrast to the compounds listed in Table 1, no detailed mechanism of action studies have been completed so far with any of these compounds, with the exception of cytotoxicity tests against panels of human or murine tumor cell lines. The marine natural products Agelastin, Bolinaquinone, Crellastatin, Gymnastatin, Haliclonacyclamine, Scalarane and Sesterstatin were isolated from Porifera (sponges) ; Lobatamide, Comoramide and Mayotamide from Chordata (tunicates); Capnellene and Sarcophine from Cnidaria (soft corals); Asteriidoside, Frondoside and a lectin from Echinodermata (seastar and cucumber, respectively); Cephalostatin from the Annelida (worm), 5 Phyla included in Kingdom Animalia. Cryptoxanthin was isolated from an alga from Phylum Phaeophyta (Kingdom Plantae) while Aspergillamide was derived from marine fungi (Kingdom Fungi). Once more, following the chemical classification proposed by Schmitz et al. (Schmitz et al., 1993), these 18 marine natural products can be assigned to three chemical classes: polyketides (Lobatamides), terpenes (Asteriidosides, Bolinaquinone, Capnellenes, Cephalostatin, Crellastatin, Cryptoxanthin, Frondoside, Sarcophine, Scalarane, Sesterstatin) and nitrogen-containing compounds (Agelastatins, Aspergillamides, Comoramides, Mayotamides, Gymnastatins, Haliclonacyclamines, Lectin). The cytotoxic marine compounds listed in Table 2 were reported by investigators in the USA (7 papers), France (3 papers) , Australia, Italy, Korea and Japan (2 papers each), while Israel, the Phillipines, Russia and the U.K. contributed one paper each.

In conclusion, this brief overview leads the author to concur with a recent review by D'Incalci (D'Incalci 1998) that there is "… some hope for marine natural products…" as human anticancer agents. Two specially significant examples are the Dolastins, that advanced to Phase I clinical trials in patients with advanced solid malignancies (colorectal, lung, melanoma, breast , kidney, jejunum) (Villalona-Calero et al., 1998) and the Ecteinascidins, shown to be active against human breast, non-small-cell lung, ovarian cancer and melanoma xenografts (Izbicka et al., 1998; Valoti et al., 1998). Furthermore, although a number of novel cytotoxic marine compounds have been reported during 1998, additional studies are clearly required to complete their pharmacological characterization. Thus the 1998 anticancer research literature provides convincing evidence that 50 years after the discovery by Bergman and his co- workers of spongothymidine and spongouridine, there continues to be a sustained multinational effort aimed at the discovery of novel antitumor agents derived from marine organisms.

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Table 1: 1998 Antitumor pharmacology of marine natural products with determined mechanisms of action.

Compound Reference	Organism[1]	Chemistry	MMOA[2]	Country[3]
Agosterol A (Aoki et al., 1998)	sponge	terpene	MDR reversal	JAPN
Aplidine (Depenbrock *et al.*, 1998)	tunicate	depsipeptide	prot. synth. inhibit.	GER, SPA, USA
Auristastatin (Mohammad *et al.*, 1998)	synthet.	peptide	tubulin pol. inhibit.	USA
Bryostatins (Wender *et al.*, 1998)	bryozoa	macrolide	PKC binding	USA
Curacin D (Marquez *et al.*, 1998)	alga	polyketide	tubulin pol. inhibit.	USA
Dehydrothyrsiferol (Pec *et al.*, 1998)	alga	terpene	S-phase inhibit.	ATRIA, USA
Dolastin 10 (Poncet *et al.*, 1998)	synthet.	peptide	tubulin pol. inhibit.	FRA
Dolastin 10 (Turner *et al.*, 1998)	tunicate	peptide	tubulin pol. inhibit.	USA
Dolastin analog (Villalona-Calero *et al.*, 1998)	synthet.	peptide	tubulin pol. inhibit.	USA
Ecteinascidin (Ghielmini *et al.*, 1998)	tunicate	quinoline	Guanine binding	SWI, SPA
Ecteinascidin (Izbicka *et al.*, 1998)	tunicate	quinoline	Guanine binding	SPA, USA
Ecteinascidin (Valoti *et al.*, 1998)	tunicate	quinoline	Guanine binding	ITA, SPA, NETH
Eleutherobin (Long *et al.*, 1998)	coral	terpene	tubul. pol. prom.	USA
Jasplakinolide (Takeuchi *et al.*, 1998)	sponge	peptide	tubul. pol. prom.	USA
Naamidine A (Copp *et al.*, 1998)	sponge	imidazole	EGF inhibition	USA
Octalactin A (Perchellet *et al.*, 1998)	bacteria	polyketide	tubulin pol. inhibit.	USA
Sarcodictyins (Nicolaou *et al.*, 1998)	coral	terpene	tubul. pol. prom.	USA
Spirulan (Mishima *et al.*, 1998)	alga	polysaccharide	heparanase inhibit.	JPAN
Stypodiol (Depix *et al.*, 1998)	alga	terpenoid	tubul. pol. prom.	Chile
Tolyporphin (Morliere *et al.*, 1998)	alga	pyrrol	ACAT inhibit.	FRA, USA, NZ

(1) synthet.:synthetic

(2) MMOA: molecular mechanism of action ; ACAT inh: acyl CoA:cholesterol-O-acyl transferase inhibition; EGF: epidermal growth factor; inhibit.: inhibition ; MDR, multidrug resistance; pol.: polymerization; PKC: protein kinase C; prot. synth.: protein synthesis; tub. pol. prom.: tubulin polymerization promotion

(3) ATRIA: Austria, FRA: France, GER: Germany, ITA: Italy, JAPN: Japan, NETH: Netherlands, NZ: New Zealand, SPA:Spain, SWI: Switzerland.

Table 2: 1998 Antitumor pharmacology of marine natural products with undetermined mechanism of action

Compound Reference	Organism	Chemistry	Cell line[2]	Country[3]
Agelastatins (Anderson *et al.*, 1998)	sponge	alkaloid	N.R.	USA
Aspergillamides (Toske *et al.*, 1998)	fungus	peptide	HU	USA
Asteriidosides (De Marino *et al.*, 1998)	starfish	sterol	HU	ITAL, FRA
Bolinaquinone (de Guzman *et al.*, 1998)	sponge	terpene	HU	USA, PHIL
Capnellenes (Morris *et al.*, 1998)	coral	terpene	HU	UK
Cephalostatins (Pettit *et al.*, 1998)	worm	sterol	HU, MU	USA
Comora & Mayotamides (Rudi *et al.*, 1998)	tunicate	peptides	HU	ISR, FRA
Crellastatin (D'Auria *et al.*, 1998)	sponge	sterol	HU	ITAL, FRA
Cryptoxanthin (Park *et al.*, 1998)	alga	terpene	N.R.	KOR
Frondoside (Avilov *et al.*, 1998)	cucumber	terpene	HU, MU	RUS, SPA
Gymnastatins (Amagata *et al.*, 1998)	fungus	(1)	MU	JAPN
Haliclonacyclamines (Clark *et al.*, 1998)	sponge	alkaloid	MU	AUS
Lectin (Shon *et al.*, 1998)	seastar	protein	MU, HU	KOR
Lobatamides (McKee *et al.*, 1998)	tunicate	macrolide	HU	AUS, USA
Sarcophine (El Sayed *et al.*, 1998)	coral	terpene	MU	USA
Scalarane (Tsuchiya *et al.*, 1998)	sponge	terpene	MU, HU	JAPN
Sesterstatins (Pettit *et al.*, 1998)	sponge	terpene	MU	USA

(1) Nitrogen-containing compound, tyrosine-based metabolite

(2) N.R: not reported, HU:human, MU:murine

(3) AUS: Australia, FRA: France, ITAL: Italy, KOR: Korea, ISR: Israel, JAPN: Japan, PHIL: Philippines, RUS: Russia, SPA: Spain, UK: United Kingdom.

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