Sudarshan Publications

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Pharma Research

An International Peer Reviewed, Indexed Journal

10.62655/s-epub.2023.v15.i01.pp99-106

MARINE-DERIVED COMPOUNDS AS LEADS FOR ANTICANCER DRUG DISCOVERY

ANTOINE LACOMBE[1]*, CARMEN LARRANAGA[2], MICHAL WOJCIK[3]

Affiliation

[1]Department of Phytochemistry, Loire Valley Institute of Pharmacy, Saumur, France
[2]Department of Phytochemistry, Navarre Plain Institute of Pharmacy, Pamplona, Spain
[3]Department of Phytochemistry, Warmia Institute of Pharmaceutical Sciences, Olsztyn, Poland

*Corresponding author: Antoine Lacombe, a.lacombe@lvip.fr
ORCID iD: Antoine Lacombe 0000-0001-2847-8362; Carmen Larranaga 0000-0001-3065-7407; Michal Wojcik 0000-0001-2664-9092

Article info

Received date:04-08-2022
Accepted date:20-11-2022
Published date:11-02-2023
ISSN;0975-8216

Keywords:

Marine natural products, Anticancer drug discovery, Trabectedin, Eribulin, Antibody-drug conjugates

Abstract

The oceans hold a chemical diversity that has been tapped for cancer medicines only in part. This mini review summarises published work on marine-derived compounds as leads for anticancer drug discovery. It follows the path from early sponge nucleosides to approved agents such as cytarabine, trabectedin, eribulin and lurbinectedin, and to dolastatin-based antibody-drug conjugates, then considers mechanisms of action and the problems of supply, symbiont origin and development. Marine leads have repeatedly delivered potent compounds with unusual mechanisms, but the number reaching approval remains small, and supply and toxicity often limit progress. The article is a narrative review of published literature and reports no new experimental data.

1. INTRODUCTION

Natural products have long been the backbone of cancer chemotherapy. A large analysis of new drugs approved over almost four decades found that a substantial share of anticancer agents were natural products, derived from them or inspired by them [1, 2]. Most of that history comes from plants and soil microbes. The sea was explored much later, partly because collecting at depth is difficult and partly because chemists did not know what to expect. Yet marine organisms live in crowded, competitive and often sessile communities, where chemical defence is a matter of survival, and one would expect them to produce potent molecules that can interfere with cell division or signalling [3, 4]. Antibiotic and anticancer agents from soil microbes, from doxorubicin to bleomycin, built the same story on land, and the sea is a logical next place to look for comparable

chemical productivity.

The first marine-derived anticancer drug arrived quietly. Nucleosides isolated from a Caribbean sponge in the early 1950s turned out to contain arabinose in place of ribose, and a synthetic relative, cytarabine, became a mainstay of leukaemia treatment [5, 6]. For decades after that, the field produced beautiful chemistry and a sparse clinical output. Interest rose again from the 1990s as screening, structure determination and synthetic methods improved, and a series of agents moved into late-stage trials [4, 7]. Today a small group of marine-derived or marine-inspired agents is in routine clinical use, and several more are in development, which is enough to judge the field on evidence rather than promise [3, 8]. Cytarabine's route from sponge to clinic was long and largely indirect, because the clinical molecule is a synthetic stereoisomer designed after the natural nucleosides had pointed the way [5, 6].

This mini review is not a catalogue of every cytotoxic compound isolated from a sponge or an alga, a list which would be long and mostly unproductive. It asks a narrower set of questions. Which marine-derived agents have reached patients, and what do the key trials show? How do these compounds act, and what do they teach about targets? What stands between a promising isolate and a usable medicine? Answers to these questions come from reviews of the marine natural products literature, landmark isolation and structural papers, pharmacological studies and clinical trials, all cited as they arise [8, 9].

2. SOURCES AND EARLY LEADS

Marine invertebrates such as sponges, tunicates, bryozoans, molluscs and soft corals have provided most of the leading structures. Sponges have been especially productive, yielding the nucleosides that led to cytarabine and the halichondrins that led to eribulin [5, 10]. Tunicates provided the ecteinascidins, which were reported in 1990 as potent antitumour agents from the Caribbean species *Ecteinascidia turbinata* [11]. Molluscs supplied the dolastatins, first isolated from the sea hare *Dolabella auricularia* [12]. Reviews of the pipeline show that the invertebrate sources dominate the early literature, while microorganisms associated with them or living free in marine sediments have become more prominent in recent years [7, 9, 13]. Many of these animals are soft-bodied and lack physical defences, so chemistry does the protective work, a pattern often used to explain why they have turned out to be rich sources [3, 4].

A recurring puzzle is that the amounts obtained from the organism are tiny. Dolastatin 10 was isolated from many tonnes of sea hare to give a fraction of a gram, and the original ecteinascidin yields were similarly low [11, 12]. The compounds are present at levels that suit a defence role in the animal but not a pharmaceutical supply chain. Clinical development therefore required either total synthesis, semisynthesis from an abundant precursor, culture of the true producer, or a simplified analogue that retains activity. Each of these routes has been used successfully for at least one marine drug, and the choice depends heavily on the complexity of the molecule [4, 14, 15]. Practical consequences follow for trial planning: a compound that cannot be supplied in gram quantities will not reach a phase 1 study, however attractive its cell data look [4, 14].

The suspicion that microbes, not animals, make many of these compounds has grown over two decades. In the sponge *Theonella swinhoei*, an antitumour polyketide was shown to be produced by an uncultivated bacterial symbiont, based on gene cluster analysis of the metagenome [16]. A similar approach for the tunicate that yields trabectedin pointed to a bacterial consortium as the likely producer [17]. These findings have practical meaning. If the producer is a microbe, then in principle it can be cultured, or its biosynthetic genes can be transferred into a host that is easier to grow, and the problem of supply could be solved without harvesting wild animals [16, 17, 18]. Metagenomic methods allow the producing gene cluster to be located without growing the organism, which was previously a barrier for uncultivated symbionts [16, 17].

Collection and identification introduce quieter sources of difficulty. The chemistry of a sponge or tunicate can vary with depth,

season, geography and the microbial community it carries, so a compound found in a sample from one site may be absent from another sample of the apparently same species [3, 4]. Misidentification of the source organism has also caused confusion in the literature. For this reason, voucher specimens, careful taxonomic work and reproducible isolation protocols matter more than they seem to when a promising extract is first found. Without them, a lead can be lost simply because the next collection does not contain it [4, 18].

3. AGENTS IN CLINICAL USE

The principal marine-derived and marine-inspired anticancer agents and their evidence base are summarised in table 1, and fig. 1 groups the entries as approved drugs, conjugates, clinical candidates and supply topics. Cytarabine, the oldest, is a nucleoside analogue that is phosphorylated in cells and incorporated into DNA, where it blocks chain elongation, and its principal role is in acute myeloid leukaemia [5, 6]. Trabectedin is a tetrahydroisoquinoline alkaloid that binds in the minor groove of DNA and interferes with transcription and DNA repair. A randomised phase 2 study in patients with liposarcoma or leiomyosarcoma after anthracycline and ifosfamide showed that the dosing schedule changed outcome, and the drug was later approved for advanced soft tissue sarcoma [19]. Its structure is complex, so supply depends on semisynthesis [14]. Dose, schedule and indication are not detailed here, since they are available from prescribing information and the cited trials.

Eribulin shows how a natural product lead can be simplified without losing activity. Halichondrin B, from the sponge *Halichondria okadai*, was found to be a powerful inhibitor of cell division, but it is a huge polyether macrolide and only trace quantities were available from the sponge [10]. Synthetic work identified a much smaller macrocyclic ketone fragment that kept most of the activity, and this analogue became eribulin [15]. In a randomised phase 3 study in heavily pretreated metastatic breast cancer, eribulin gave a modest median survival gain of about two and a half months compared with physician's choice of treatment, which was enough for approval [20]. Part of the appeal of such an analogue is that synthesis lets medicinal chemists vary the structure, which is generally impossible when the molecule must be extracted from an animal [4, 15].

Table 1: Principal marine-derived leads and agents in anticancer drug discovery

Compound|source	Reported feature or evidence	Ref.
Cytarabine sponge nucleoside lead	Synthetic analogue of sponge nucleosides; mainstay in acute myeloid leukaemia	[5, 6]
Trabectedin tunicate alkaloid	Binds the DNA minor groove; active in soft tissue sarcoma; supplied semisynthetically	[11, 14, 19]
Eribulin halichondrin B analogue	Suppresses microtubule growth; modest survival gain in heavily pretreated breast cancer	[10, 15, 20]
Lurbinectedin trabectedin analogue	Active in relapsed small-cell lung cancer in a single-arm phase 2 basket trial	[21]
Brentuximab vedotin dolastatin-derived payload	High response rates in relapsed CD30-positive lymphomas	[22, 23]
Polatuzumab vedotin dolastatin-derived payload	Activity in relapsed diffuse large B-cell lymphoma	[24]
Dolastatin 10 sea hare, cyanobacterial origin	Potent tubulin inhibitor; limited as a free drug but a basis for conjugate payloads	[12, 25, 26]
Marizomib marine actinomycete	Irreversible proteasome inhibitor; phase 1 evaluation in relapsed myeloma	[27, 28, 29]
Plitidepsin tunicate depsipeptide	Strong antimyeloma activity in vitro and in vivo	[30]
Symbiont origin sponge and tunicate compounds	Several compounds likely made by microbial partners, supporting culture or heterologous expression	[16, 17]
Supply routes low natural yield	Semisynthesis, total synthesis and analogue design each solved supply for particular molecules	[4, 14, 18]

Lurbinectedin is a synthetic analogue of the trabectedin family. In a single-arm phase 2 basket trial in relapsed small-cell lung cancer it produced a meaningful response rate with

manageable toxicity, mostly myelosuppression, and it received accelerated approval on that basis [21]. It illustrates a point made often by medicinal chemists, namely that an approved marine natural product acts as a template for further optimisation, so the full return from a lead includes its descendants. Plitidepsin, derived from another tunicate, has shown strong antimyeloma activity in preclinical models and has been studied in combination regimens, though its regulatory path has been less straightforward than that of the agents above [2, 30]. Both trabectedin and lurbinectedin cause neutropenia and raised liver enzymes in many patients, so monitoring is a routine part of care [19, 21].

The most commercially successful use of marine chemistry may be as the payload in antibody-drug conjugates. Dolastatin 10 is extremely cytotoxic and binds the vinca domain of tubulin, but as a free drug it did not provide enough clinical benefit at tolerable doses [12, 25]. Synthetic derivatives of the dolastatins, linked to antibodies that recognise tumour-associated antigens, deliver the toxin selectively to cells. Brentuximab vedotin, which targets CD30, produced high response rates in relapsed Hodgkin lymphoma and anaplastic large cell lymphoma, and polatuzumab vedotin later showed activity in relapsed diffuse large B-cell lymphoma [22, 23, 24]. The commercial importance of these conjugates is considerable, and reviews of conjugate design discuss how linker and payload choice shape safety [26]. Conjugate technology also changes the dose conversation, since the payload is delivered attached to an antibody, giving a far lower systemic exposure than the free toxin would require [22, 26].

Practical use of these agents is shaped by their toxicity as much as by their efficacy. Trabectedin commonly causes neutropenia, nausea, fatigue and raised liver enzymes, and because it can damage tissue if it leaks from a vein it is usually given through a central line over several hours [19, 21]. Eribulin is associated with neutropenia and peripheral neuropathy, so blood counts and nerve symptoms are tracked from cycle to cycle [20]. High-dose cytarabine can cause cerebellar toxicity in older patients and those with reduced kidney function, which is why dose adjustment is standard [6]. None of this lessens the value of the drugs, but it is a reminder that potency and selectivity are separate properties.

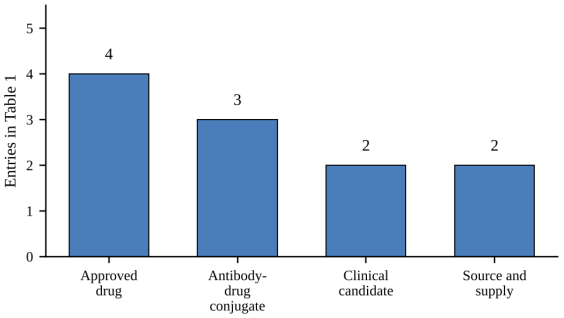


Fig. 1: Number of entries in table 1 by development status or topic

4. MECHANISMS OF ACTION

A notable feature of the group is how many of its members attack microtubules. Dolastatin 10 and the halichondrins both interfere with tubulin, and each does so in a way that differs from taxanes and vinca alkaloids [10, 12, 25]. Microtubules are dynamic polymers, and drugs that stabilise or destabilise them block mitosis, so cells arrest and die [31, 32]. Eribulin is unusual because it suppresses microtubule growth without affecting shortening and seems to bind the plus ends, which gives it a mechanism of its own among the antimitotics [20, 32]. The fact that marine sources contributed several microtubule binders suggests that evolution has repeatedly converged on this target for chemical defence [31, 32]. Binding sites differ between classes, and competition experiments in tubulin assays have been used to map where each agent sits [25, 32].

The second group of mechanisms involves DNA. Trabectedin is a clear example, as its binding in the minor groove bends the helix toward the major groove and interferes with transcription factor binding and the transcription-coupled repair pathway, so that cells with certain repair backgrounds are particularly sensitive [11, 19]. Cytarabine works through a different DNA-linked route, as the triphosphate of the drug competes with the natural nucleotide and halts replication in rapidly dividing cells [5, 6]. These actions explain both the clinical value of the agents in

specific tumours and their predictable toxicities, such as myelosuppression, which are an unavoidable consequence of attacking cell division [6, 19]. Cells deficient in particular repair genes appear more sensitive to the DNA-binding alkaloids, a lead that has been explored for patient selection [19].

Proteasome inhibition forms a third group. The proteasome degrades regulatory proteins, and cancer cells that depend on rapid protein turnover, such as myeloma cells that secrete large quantities of immunoglobulin, are especially sensitive to its blockade [27, 28]. Salinosporamide A binds covalently and irreversibly to the catalytic threonine of the proteasome, which distinguishes it from the reversible boronate inhibitors in clinical use [27, 28]. This example shows that the sea can supply chemical solutions to targets already validated by other classes of drug, as well as new targets, and that a different binding mode can offer a different spectrum of activity [28, 29]. Dependence on the proteasome also explains why myeloma has been such a productive disease for this class of agent [28, 29].

Resistance deserves attention because it determines how long any of these agents stays useful. For the microtubule-binding drugs, the principal reported mechanisms are increased efflux through transporters such as P-glycoprotein, altered expression of tubulin isotypes and mutations that change drug binding [31, 32]. Auristatin payloads are also exposed to efflux, which is one reason why tumours that stop responding to a conjugate may carry high transporter expression, besides loss of the target antigen [22, 26]. Compounds acting on DNA face a different set of escape routes, including altered repair capacity [19]. Understanding these routes in advance guides combination design, for example pairing agents that are not cross-resistant, and the marine literature gives several useful examples to build on [20, 32].

5. DEVELOPMENT CHALLENGES

Supply remains the problem that gives marine drug discovery its distinct character. The story of trabectedin is the best illustration. Wild harvest could not meet the needs of clinical trials, aquaculture of the tunicate was costly and uncertain, and total synthesis was elegant but long. The practical solution was a semisynthetic process starting from a related bacterial metabolite made by fermentation, which converted a supply crisis into a manufacturing process [14]. Not every compound has such a precursor. Complex structures without a convenient starting point may require long total syntheses, and the cost of goods then restricts how far development can go [4, 18]. Tunicate farming has been attempted for several species, but yields and consistency have so far been inadequate for pharmaceutical use [14, 18].

Compounds that are extremely potent present their own difficulties. Cytotoxins that kill cells at nanomolar or lower concentrations leave little room between effective and toxic exposure, and dose-limiting toxicities often arise before therapeutic benefit is secure. Several marine candidates failed in trials because the therapeutic window was too narrow, or because pharmacokinetic properties, such as rapid clearance or poor solubility, made delivery difficult [7, 33]. The success of antibody-drug conjugates can be read partly as a response to this problem: targeted delivery widens the window for compounds too toxic to be given systemically [22, 26]. Formulation of lipophilic compounds adds further cost and risk, particularly when intravenous administration requires solubilising excipients [7, 33].

A further obstacle is the sheer length of the discovery chain, from collection and taxonomic identification through extraction, dereplication, structure determination, bioassay and scale-up. Dereplication, the process of recognising known compounds early, has improved with mass spectrometry and databases, which saves effort spent on rediscovery [4, 18]. Legal and ethical questions about access to biological material and sharing of benefits also constrain collection, particularly in the waters of developing countries, and sound practice requires formal agreements with the country of origin. These administrative issues rarely feature in pharmacological papers but have shaped which projects are practical [3, 18]. In practice a project often loses a year or more at the dereplication and scale-up stages before

any animal study is possible [4, 18].

Regulatory and trial design considerations also set boundaries. Many marine-derived agents were developed for rare tumours, such as soft tissue sarcomas and relapsed lymphomas, where large randomised trials are difficult and single-arm or small randomised studies may support approval under accelerated pathways [19, 21, 23]. This helps access for patients with few options, but it leaves open questions about long-term benefit, and confirmatory evidence has to be collected after approval. Developers of marine leads should plan for this from the start, choosing indications in which a clear clinical signal can be recognised in a modest number of patients, and collecting biomarker data that can later support patient selection [7, 33].

6. LIMITATIONS AND FUTURE DIRECTIONS

The evidence reviewed here has some limitations. Reports of cytotoxicity in cell lines greatly outnumber reports of in vivo efficacy, and cell line potency alone predicts little about clinical benefit [7, 8]. Clinical evidence for most marine-derived agents comes from small phase 1 and 2 studies, often single-arm, and only a few drugs have survived randomised phase 3 testing [19, 20, 21]. Comparisons between agents are rarely possible. Reviews also differ in what they count as marine-derived, since semisynthetic and synthetic descendants of marine leads may or may not be included, which makes headline numbers hard to compare from one source to another [1, 3, 9]. Randomised comparisons between marine agents and standard care are especially scarce [19, 20].

Looking ahead, three developments seem most likely to matter. Genome mining of marine microbes and symbiont metagenomes should reveal many new biosynthetic gene clusters that were silent under laboratory conditions, and heterologous expression offers a way to produce them in tractable hosts [16, 17, 18]. Second, antibody-drug conjugates and other targeted delivery systems may allow marine cytotoxins that were set aside because of toxicity to be reconsidered [22, 24, 26]. Third, deep-sea and extreme habitats remain barely sampled and may provide structural classes unlike those known so far [34]. These possibilities should be pursued with realistic expectations, since the history shows many leads and few drugs [7, 8]. Careful reporting of every stage reached by each lead would make the real success rate of the field visible to funders and researchers [7, 8].

7. CONCLUSION

Marine organisms have given oncology a small but real set of medicines and a larger set of instructive leads. Cytarabine, trabectedin, eribulin and lurbinectedin, together with dolastatin-derived conjugates, show that marine chemistry can yield potent agents with distinct mechanisms, as table 1 and fig. 1 summarise [5, 19, 20, 21, 22]. Microtubule, DNA and proteasome targets dominate, which suggests that defence chemistry tends to hit the most vulnerable cellular machinery [28, 31, 32]. Their record also shows that patience is needed, because decades separated several isolations from first approvals [10, 11, 14].

The obstacles are well known: low natural supply, narrow therapeutic windows and long, costly discovery chains. Practical solutions have emerged from semisynthesis, simplified analogues, microbial culture and targeted delivery, and they will probably carry forward the next generation of leads [14, 15, 16, 26]. Readers should expect progress to be steady and slow, and should read claims of a new marine anticancer compound with attention to the stage of evidence reached, not only to the potency reported in culture [7, 8, 33]. Collaboration between chemists, microbiologists and clinicians, with early attention to supply, will decide how many leads are finally realised [4, 18].

8. ABBREVIATIONS

ADC-Antibody-drug conjugate, DNA-Deoxyribonucleic acid, CD30-Cluster of differentiation 30, MMAE-Monomethyl auristatin E, AML-Acute myeloid leukaemia, SCLC-Small-cell lung cancer, DLBCL-Diffuse large B-cell lymphoma, MM-Multiple myeloma, FDA-Food and Drug Administration, EMA-European Medicines Agency

9. FUNDING

Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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