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A Review on Anticancer Drug from Marine

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ABSTRACT

The marine environment is a rich source of both biological and chemical diversity. It is very much likely that marine organisms would be wonderful source of biologically active molecules The collection of the marine therapeutics includes molecules with antibiotic, antiviral, antiphrastic, analgesic and anticancer agent from bacteria, cyanobacteria, *tunica*, fungi, sponge This reviewfocuses on the latest studies and critical research in this field and evidences the immense potential ofmarine organisms as sources of bioactive peptides and other anticancer biomolecules Various anticancer compounds like Aplidine, Bryostatin-1, Didemin B, Dolastation, Ecteinascidine with diverse modes of action, such as, anti-proliferative, antioxidant, anti-microtubule havebeen isolated from marine sources. Traditional chemotherapeutic agents have a range of side effects likefatigue, gastrointestinal distress and depression of immune system which introduces the these sources have been shown to have antioxidantactivity and cytotoxic effect on several human cancers such as leukemia, lymphoma, ovarian, melanoma, breast, bladder, neuroendocrine, prostatic, colon and non-small cell lung cancer very potently.

Keywords: Marine Organisms, Bryostatin-1, Dolastation, Human Cancers

I. INTRODUCTION

Over the past few years, about 3000 new compounds like anti-tumor, anti-microtubule, anti-proliferative, photoprotective, antibiotic and anti-infective discover from various marine sources 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 synthesis7 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.

II. METHODS AND MATERIAL

Therapeutic Agents from Marine Sources

Bacteria

Marine microorganisms are a rich source of newgenes, exploitation of which is likely to lead tothe discovery of new drugs and therapeutic approaches. Only a few marine bacteria can beisolated under laboratory conditions and there is an urgent need to develop new culture techniques to isolate slow-growing bacteria and also toisolate the bacteria that are unique in production of novel natural products. (e.g.*Seudopterosins*, *Topsentins*, *Scytonemin* and *Manoalide*), anticancer agents (e.g., *Bryostatins*, *Discodermolide*, *Eleutherobin* and *Sarcodictyin*) and antibiotics (e.g.*Marinone*). Anti-Parasitic compound *Valinomycin*is isolated from*Streptomyces sp.* strains of Mediterranean

Cyanobacteria

The cyanobacteria population comprises 150genera and about 2000 species of considerablediversity. The potency of marine cyanobacteria asanticancer agents is the most explored among allmarine derived chemicals. Besides cytotoxicity in tumor cell lines, several compounds haveemerged as templates for the development of newanticancer drugs. Well studied species of marine cyanobacteria includes *Nostoc*, *Calothrix*, *Lyngbya*, *Symploca*

Fungi

Marine derived fungi provide plenty ofstructurally unique and biologically activesecondary metabolites. The Anthracenedione derivatives acting as the potent

anticancer agents screened from the mangrove endophytic fungus Halorosellinia sp. and Guignardia sp. Forexample, Cytarabine, an antileukemic drug andTrabectedin, an agent for treating soft tissuesarcoma are developed from marine fungi sources [8]. Besides, marine-derived fungi are known tobe a source of antioxidative natural products suchas Acremonin A from Acremonium sp. AndXanthonederivative from Wardomycesanomalus[9].

Sponge

Approximately 10,000 sponges have been foundworldwide [11] and most of them live in marineenvironments [12]. Marine sponges have yieldedover 70 novel compounds to date that exhibit significant inhibitory activity towards a range ofprotein kinases. A range of bioactive compoundshas been found in about 11 sponge genera. Threeof these genera (Haliclona, PetrosiaandDiscodemia) produce influential anticancer and anti-inflammatory agents [13].

SOURCE	COMPOUND	BIOACTIVITY
Bacteria	Valinomycin	Anti-Parasitic
Cyanobacteria	Calothrixin A and B	Antimalarial
Cyanobacteria	Curacao extracts	Antiproliferative
Fungi	Cephalosporins	Antibiotic
Fungi	Antioxidants	Atherosclerosis, dementia
Soft coral	Methanol extracts	Anticancer
Sponge	Kuanoniamines	Growth inhibitor
Sponge	Steroid	Inflammation, asthma
Sponge	Ara-c	Antiviral

BRYOSTATIN-1

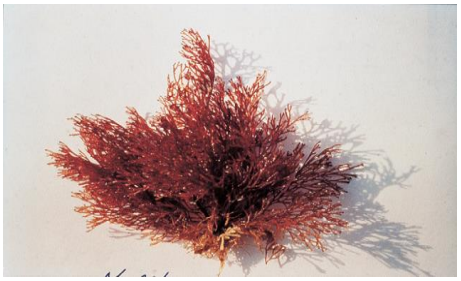
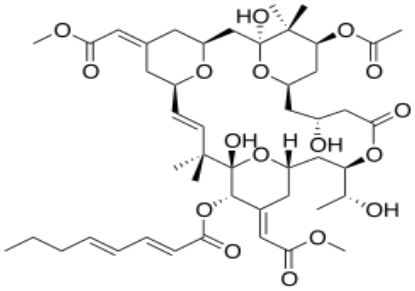


Figure 1. The Bryozoan Bugula neritina

Source organism: *Bugula neritina* (Bryozon)

Bryostatin-1 is a macrocyclic natural lactone isolated from the marine Bryozoan, *Bugulaneritina*(Fig.1). It has shown both antitumour as well as immunomodulatory effects [1,2]. It is a potentactivator of the protein kinase C (PKC) family, lacking tumour-promoting activity and with antagonisticeffects on tumour-promoting phorbol esters. This effect isprobably related to down-regulation ofPKC or by specific isoform activation. It alsostimulates cytokine production, bone marrow progenitorcells and neutrophils [3,4]. In vitro, bryostatin-1 has cytotoxic activity against various leukaemia and solid tumour cell lines. It has also in vivo antitumouractivity in various murine models, including leukemia, lymphoma, ovarian cancer and melanoma. It was shown to enhance the antitumour effects of various anticancer agents, suchas vincristine, cytosine arabinoside, cisplatin, melphalan,paclitaxel and others.



Bryostatin-1

These effects may beschedule-dependent [1,2,5].This agent was studied in phase I trials at different infusion schedules. The recommended doses for phase II trials were 25-35 M-g/m2 when administered over one hour for three of every four weeks; 25 u.g/m2 given as a weekly 24 hour infusion. Myalgia was the DLT in all trials. Other toxicities werejoint aches and a transient decrease in platelet counts [6,7]. Notably, partial responses were reported inpatients with melanoma, ovarian cancer and. Phase II trials of bryostatin-1 are being conductedat various infusion regimens in a large number of tumour types in both solid and haematological malignancies.In addition, phase I trials of brystatin-1in combination with other agents, such as cisplatin,paclitaxel, fludarabine, vincristine, cytosine arabinoside and 2-CDA are also being conducted.

APLIDINE

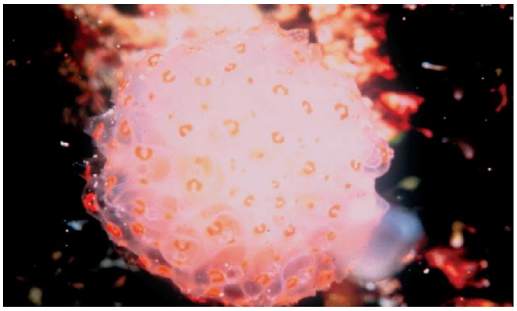
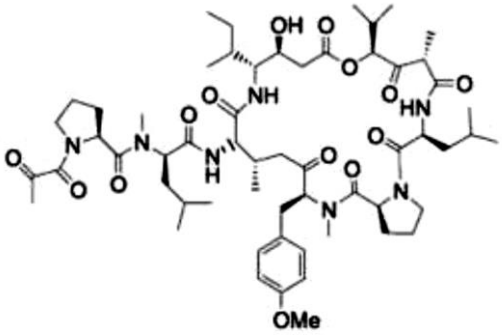


Figure 2. The tunicate Aplidium albicans

Source Organism*: Aplidium albicans* (tunicate)

Aplidine was obtained from a Mediterranean colonial tunicate, *Aplidiumalbicans*. It has a pyruvylgroup replacing the lactyl group in DB and its synthesis has been achieved. It appears more active than DB in preclinical models and apparently not cardiotoxic.Aplidine entered clinical trials in 1999 both in Europe and in the US under the sponsorship of the Spanish company Pharma Mar. It is appearedthat these cancer cells are sensitive to lowconcentrations of this compound. *Aplidine*'s mode of action involves several pathways; that's why *Aplidine*is described as multifactorial apoptosis inducer. The compound induces rapid cell cycle arrest at G1-G2 and inhibition of protein synthesis, thus introduce apoptosis ofcancer cells [9] *Aplidine*also inhibits the expression of the vascular endothelial growth factor gene, having antiangiogenic effects [10].However, *Aplidine*is appeared as more active than *Didemnin*in preclinical models and so far has not shown evidence of life threateningneuromascular toxicity [8,9,4].



Aplidine

The dose limiting toxicity with the protracted schedule is muscular with a remarkable lack ofhaematological toxicity in spite of the cytotoxicity noted at low concentrations in leukemic blasts explanted from patients [11,12]. Consistent evidence of activity has been noted in pretreatedneuroendocrine tumors [13] and other tumor types. Phase II studies are now ongoing with an every other week schedule giving APL as a protracted or 3 hours intravenous infusion at a dose of 5mg/m2.

DOLASTATINS

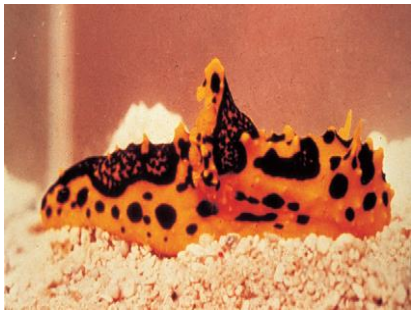
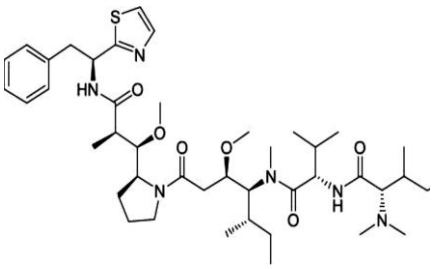


Figure 3. Dolabellaauricularia

Source Organism: Dolabellaauricular

The dolastatins are cytotoxic peptides, which can be cyclic or linear, derived from the sea hare, *Dolabellaauricularia*, amollusc from the Indian Ocean. Dolastatin10 and 15 are small peptides that were shown to interact with tubulin. Dolastatinwas selected for initial clinical development because of its more favourable preclinical profile. It is extremely potent in vitro and it was shown to inhibit microtubule assembly, tubulin-dependent guanosinetriphosphate (GTP) binding and inhibit vincristine and vinblastine binding to tubulin. It causes cells toaccumulate in metaphase arrest and is modulated by the MDR gene product [14,15].Dolastatinhas in vitro activity against several human leukaemia, lymphoma and solid tumour cell lines.



Dolastatins

It has documented antitumour activity in various human solid tumour models, such as LOX#IMVI melanoma,

OVCAR-3 ovarian carcinoma and NCI-H522 NSCLC cell lines. In animal toxicology studies, myelo suppression was the dose-limiting toxicity. This agent is highly bound to plasma proteins and pharmacokinetic studies in animals showed a rapid degradation probably by hepatic metabolism [16,17].This agent entered phase I trials as an i.v. bolus injection every 3 weeks. The maximum tolerated dose (MTD) was 300 mg/m2 for heavily pretreated patients, while 400 mg/m2 appears to be the MTD for minimally pre-treated patients. The dose-limiting toxicity (DLT) was myelo suppression, and local irritation and phlebitis, and mild peripheral neuropathy were also observed. Phase II trials are being initiated in breast, colon, lung, ovarian and prostate cancer, as well as lymphomas and leukaemias [18, 19].side effects observed were peripheral sensory neuropathies, pain, swelling, and erythematic at the injection site. Complexity and low yield of chemical synthesis of *Dolastatins* together with low water solubility

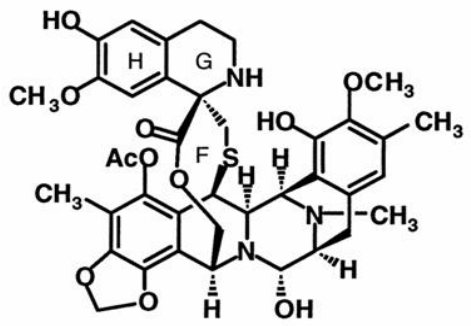
- **ECTEINASCIDINS(ETS)**

Figure 4. The tunicate Ecteinascidiaturbinata

Source Organism: Ecteinascidiaturbinata

The ecteinascidins (Ets) are derived from the Caribbean tunicate Ecteinascidiaturbinata. Following a period of supply problems, enough amounts of this compound could be obtained from aquaculture and synthesis. The derivative Ecteinascidin 743 (ET 743) showed promising activity in murine and human tumour models, and is currently in early clinical development. It is a tetrahydro isoquinoline alkaloid that alkylates selectively guanine N2 from the DNA minor groove, and this alkylation is reversed by DNA denaturation. Therefore, it differs from other DNA alkylating agents so far used in the clinic.

Recent mechanistic data demonstrates that ET-743 induces a broad inhibition of activated transcription with no effect on the constitutive transcription [20,21,22]: ET-743 inhibits the activation of the multidrug resistant pathway [23] that is considered to be the main mechanism of primary and acquired resistance of cancer cells to natural drugs such doxorubicin and taxanes. ET-743 is the only known anticancer entity for which there is an inverse correlation between the DNA repair efficiency and the sensitivity/resistance pattern [24,25]; such evidence offered a rationale to Marine Drugs **2004**, 2 18implement combinations studies with platin salts [26] and to seek for correlations in patients between the DNA efficiency and the response to ET-743 [27]An extensive phase I program assessing different schedules of administration was completed[28,29,30]: The dose limiting toxicities were bone marrow toxicity and fatigue. As predicted inthe preclinical toxicology, transaminitis is noted in the majority of the patients but such a drug induced effect is transient/reversible and non cumulative and therefore does not represent a limiting factor for long-term therapy.



Ecteinascidins

Consistent evidence of antitumor activity in patients bearing resistant disease was reported in the phase I program. In fact, objective remissions in breast cancer, melanoma and mesothelioma were observed together with a consistent evidence of antitumor activity in patients with advanced resistant sarcoma. Such evidence was the starting point for a fast track pivotal phase II program in patients with advanced soft tissue sarcoma resistant or relapsed to conventional therapies. Long-term results from such studies have clearly confirmed a significant therapeutic impact in this disease setting [36,

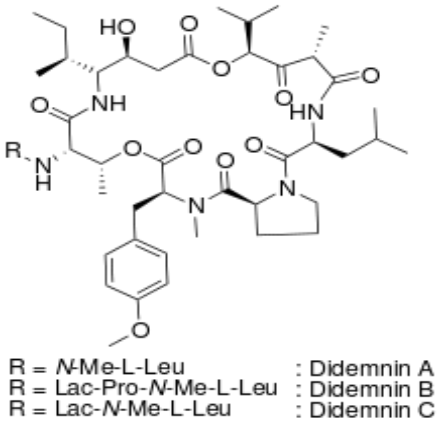
37, 38, 39, and 40]. In these studies ET-743 has been given as a 24 hours intravenous infusion every 3 weeks at a dose of 1.5 mg/m2.

DIDEMNIN B

Figure 5. Tridemnum Solidum

Source Organism: Tridemnum Solidum

Different types of tunicates and ascidia are inhabitants of sea floor. They produce complex antitumor compounds that are estimated as more effective than any other cancer medicine now in use. One of these potent compounds is Didemnin which was isolated first from Caribbean tunicate Tridemnum solidum[41]. But later has also been extracted from other species of the same genus [42]. Among various Didemnin, Didemnin B has the most potent antitumor and antiproliferative activity against human prostatic cancer cell lines [41]. DidemninB is the first marine peptide to enter into clinical trial as a potent anticancer drug [43]. This is acyclic depsipeptide which exerts antitumor activity via protein synthesis inhibition [44].However, high toxicity, poor solubility and short life span led to the discontinuation of clinical trials of Didemnin B [43].



Didemnin

It has shown impressive antitumour activity in human tumour models in vitro as well as in tumours growing in athymic mice.10 In initial clinical trials, patients with various solid tumours or non-Hodgkin lymphoma were given a short intravenous infusion of didemnin B every 3 weeks, and antitumour effects were observed. However, severe neuromuscular and cardiotoxic effects led to the discontinuation of clinical trials.11,12

III. CONCLUSION

The marine environment is a rich source of both biological and chemical diversity. It is very much likely that marine organisms would be a wonderful source of biologically active molecules .The collection of the marine therapeutics includes molecules with antibiotic, antiviral, antiphrastic, analgesic and anticancer agent from bacteria, cyanobacteria, *tunica*, fungi, sponge .This review focuses on the latest studies and critical research in this field and evidences the immense potential of marine organisms as sources of bioactive peptides and other anticancer biomolecules Various anticancer compounds like Aplidine, Bryostatin-1, Didemin B, Dolastation, Ecteinascidine with diverse modes of action, such as, anti-proliferative, antioxidant, anti-microtubule have been isolated from marine sources. Traditional chemotherapeutic agents have a range of side effects like fatigue, gastrointestinal distress and depression of immune system which introduces the these sources have been shown to have antioxidant activity and cytotoxic effect on several human cancers such as leukemia, lymphoma, overian, melanoma, breast, bladder, neuroendocrine, prostatic, colon and non-smallcell lung cancer very potently..

IV. REFERENCES

[1]. Wender PA, Hinkle KW, Koehler MF, Lippa B. The rational design of potential chemotherapeutic agents: synthesis of bryostatin analogues. Med *Res Rev 1999; 19(5): 388-407.*

[2]. Wall NR, Mohammed RM, Nabha SM, et al. Modulation of Ciap-1 by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in human early pre-B acute lymphoblastic leukemia cell line REH. *Biochem Biophys Res Commun 1999; 266: 76-80.*

[3]. Trenn G, Pettit GR, Takayama H, et al. Immunomodulating properties of a novel series of protein kinase C activators. The bryostatins. *J Immunol 1988; 140: 433—439.*

[4]. Hornung RL, Pearson JW, Beckwith M, Longo DL. Preclinical evaluation of bryostatin as an anticancer agent against several murine tumor cell lines: in vitro and in vivo activity.*Cancer Res 1992; 52(1): 101-107.*

[5]. Varterasian ML, Mohammad RM, Eilender DS, et al. Phase I study of bryostatin-1 in patients with relapsed non-Hodgkin's lymphoma and chronic lymphocytic leukemia. *J Clin Oncol 1998; 16(1): 56-62.*

[6]. Basu A, Lazo JS. Sensitization of human cervical carcinoma cells to cis diamminedichloroplatinum(II) by bryostatin 1. *Cancer Res 1992; 52(11): 3119-3129.*

[7]. Jayson GC, Crowther D, Prendiville J, et al. A phase I trial of bryostatin 1 in patients with advanced malignancies using a 24 hour intravenous infusion. *Br J Cancer 1995; 72: 461-468.*

[8]. Prendiville J, Crowther D, Thatcher N, et al. A phase I study of intravenous bryostatin 1 in patients with advanced cancer. *Br J Cancer 1993; 68: 418-424.*

[9]. Faivre, S.; Chieze, S.; Delbaldo, C.; Ady-Vago, N.; Guzman, C.; Lopez-Lazaro, L.; Lozahic, S.; Jimeno, J.; Pico, F.; Armand, J.; *et al.* Phase I and pharmacokinetic study of aplidine, a new marine cyclodepsipeptide in patients with advanced malignancies. *J. Clin. Oncol. 2005, 23, 7871–7880.*

[10]. Garcia-Fernandez, L.F. *et al.* (2002) Aplidin™ induces the mitochondrial apoptotic pathway via oxidative stress-mediated JNK and p38 activation and protein kinase Cδ. *Oncogene 21, 7533–7544.*

[11]. Broggini, M.; Marchini, S.V.; Galliera, E.; Borsotti, P.; Taraboletti, G.; Erba, E.; Sironi, M.; Jimeno, J.; Faircloth, G.T.; Giavazzi, R.; *et al.* Aplidine, a new anticancer agent of marine origin, inhibits vascular endothelial growth factor (VEGF) secretion and blocks VEGF-VEGFR-1 (flt-1) autocrine loop in human leukemia cells MOLT-4. *Leukemia 2003, 17, 52–59.*

[12]. Armand, J.-V.; Ady-Vago, N.; Faivre, S. Phase I and Pharmacokinetic Study of Aplidine (apl) Given as a 24-Hour Continuous Infusion Every Other Week (q2w) in Patients (pts) with Solid Tumor (st) and Lymphoma (NHL). In *Proceedingof 2001 ASCO Annual Meeting*; American Society of Clinical Oncology: San Francisco, CA, USA,2001.

[13]. Bai, R., Friedman, S. J., Pettit, G. R. & Hamel, E. Dolastatin-15, a potent antimitotic depsipeptide derived from *Dolabella auricularia*: interaction with tubulin and effects on cellular microtubules. *Biochem. Pharmacol. 43, 2637–2645 (1992).*

[14]. García-Rocha, M.; Bonay, P.; Avila, J. The antitumoral compound Kahalalide F acts on celllysosomes. *Cancer Lett.* 1996, *99, 43–50.*

[15]. Faircloth, G.T.; Smith, B.; Grant, W. Selective antitumor activity of Kahalalide F, a marine derived cyclic depsipeptide. *Proc. Am. Assoc.Cancer Res. 2001, 42, 1140*

[16]. Pettit GR, et al. The isolation and structure of a remarkable marine animal amineoplastic constituent: Dolastatin 10. *J Am Chem Sec 1987; 109: 6883-6885.*

[17]. Bai R, Pettit GR, Hamel E. Dolastatin 10, a powerful cytostatic peptide derived from a marine animal. Inhibition of tubulin polymerization mediated through the vinca alkaloid binding domain. *Biochem Pharmacol 1990; 39(12): 1941-1949*

[18]. Pathak S, Multani AS, Ozen M, et al. Dolastatin-10 induces polyploidy, telomeric associations and apoptosis in a murine melanoma cell line. *Oncol Rep 1998; 5(2): 373-376.*

[19]. Maki A, Mohammad R, Raza S, et al. Effect of dolastatin 10 on human non-Hodgkin lymphoma cell lines. *Anticancer Drugs 1996; 7(3): 344-350.*

[20]. Anticancer agent: a phase I clinical, pharmacological and pharmacodynamic study of dolastatin 10 (NSC 376128) in patients with advanced solid tumors. *Clin Cancer Res 2000; 6: 1293-130.*

[21]. McElroy EA, Pitot HC, Erlichman C, et al. Phase I trial of dolastatin-10 in patients with advanced solid tumors. Proc Am Soc Clin Oncol 1997; abstr. #782.

[22]. Minuzzo M, Marchini S, Broggini M, Faircloth G, D'incalci M And Mantovani R: Interference of transcriptional activation by the anti-neoplastic drug ET-743. *Proc.Natl.Acad.Sci.USA.* ***2000,*** *97: 6780-6784*

[23]. Jin S, Gorfajn B, Faircloth G And Scotto K: Ecteinascidin 743, a transcription-targeted chemotherapeutic that inhibits MDR1 activation. *Proc.Natl.Acad.Sci.USA.* ***2000,*** *97, 6775-6779.*

[24]. Friedman D, Hu Z, Kolb EA, Gorfajn B And Scotto KW: Ecteinascidin-743 inhibits activated but not constitutive transcription. *Cancer Res*. **2002**, 62, 3377-3381.

[25]. Kanzaki A, Takebayashi Y, Ren XQ, Akiyama S., Bates S., Pommier Y., : Overcoming multidrug drug resistance in P-glycoprotein/MDR1-overexpressing

cell lines by ecteinascidin 743. *Mol Cancer Ther. **2002**, 1, 1327-1334.*

[26]. Damia G; Silvestri S; Carrassa L; Filiberti L; Faircloth G T; Liberi G; Foiani M; D'Incalci M:Unique pattern of ET-743 activity in different cellular systems with defined deficiencies in DNA-repair pathways. *Int J Cancer. **2001,** 92, 583-588.*

[27]. Takebayashi Y; Pourquier P; Zimonjic D B; Nakayama K; Emmert S; Ueda T; Urasaki Y; Kanzaki A; Akiyama S I; Popescu N; Kraemer K H; Pommier Y: Antiproliferative activity of ecteinascidin 743 is dependent upon transcription-coupled nucleotide-excision repair. *Nat Med.* **2001,** 7, 961-966. 30 D'incalci M, Colombo T, Ubezio P., Nicoletti I., Giavazzi R., Erba E., Ferrarese L., Meco D.,Riccardi R., Sessa C., Cavallini E., Jimeno J., Faircloth G: The combination of yondelis and cisplatin is synergistic against human tumor xenografts. *Eur J Cancer. **2003,** 39, 1920-1926.*

[28]. Sarries C., Haura E., Roig B. Pharmacogenomic strategies for developing customized chemotherapy in non-small cell lung cancer. *Pharmacogenomics. **2002**, 3(6), 763-780.*

[29]. Taamma A, Misset JL, Riofrio M, Guzman C, Brain E, Lopez Lazaro L, Rosing H, Jimeno J, Cvitkovic E.: Phase I and pharmacokinetic study of ecteinascidin-743, a new marine compound, administered as a 24-hour continuous infusion in patients with solid tumors. *J Clin Oncol. **2001,** 19, 1256-1265.*

[30]. Ryan DP, Supko JG, Eder JP, Seiden M, Demetri G, Lynch TJ, Fischman AJ, Davis J, Jimeno J, Clark JW: Phase I and pharmacokinetic study of ecteinascidin 743 administered as a 72-hour continuous intravenous infusion in patients with solid malignancies. *Clin Cancer Res. **2001,** 7, 231-242.*

[31]. Villalona-Calero MA, Eckhardt SG, Weiss G, Hidalgo M, Beijnen JH, van Kesteren C, Rosing H, Campbell E, Kraynak M, Lopez-Lazaro L, Guzman C, Von Hoff DD, Jimeno J, Rowinsky EK.: A phase I and pharmacokinetic study of ecteinascidin-743 on a daily x 5 schedule in patients with solid malignancies. *Clin Cancer Res. **2002,** 8, 75-85.*

[32]. Twelves C., Hoekman K., Bowman A., Vermorken J.B., Anthoney A., Smyth J., Van Kesteren C., Beijnen J.H., Uiters J., Wanders J., Gomez J., Guzmán C., Jimeno J., Hanauske A..: Phase I and pharmacokinetic study of Yondelis (Ecteinascidin 743; ET-743) administered as an infusion over 1h or 3h every 21 days in patients with solid tumors. *Eur J Cancer. **2003,** 39, 1842-1851.*

[33]. Delaloge S, Yovine A, Taamma A, Riofrio M, Brain E, Raymond E, Cottu P, Goldwasser F,Jimeno J, Misset JL, Marty M, Cvitkovic E. Ecteinascidin-743: a marine-derived compound inadvanced, pretreated sarcoma patients-preliminary evidence of activity. *J Clin Oncol. **2001**,19(5), 1248-1255.*

[34]. Demetri G., Manola J., Harmon D., Maki R., Seiden R., Supko J., Ryan D., Puchlaski T., Goss G., Merriam P., Waxman A., Slater S., Potter A., Quigley T., Lopez T., Sancho MA., Guzman C., Jimeno J., Garcia Carbonero R. Ecteinascidin-743 (ET-743) induces durable responses and promising 1-year survival rates in soft tissue sarcomas (STS): Final results of Phase II and Pharmacokinetic studies in the U.S.A American Society of Clinical Oncology, San Francisco, *CA, May 12 –15,.**2001.** Procc. 352a. Abstract 1406.*

[35]. Le Cesne A., Blay J.,. Judson I, Van Oosterom A, Verweij J, Radford J, Lorigan P, Rodenhuis S, Donato De Paola E, Van Glabbeke M., Jimeno J., Nielsen O. ET-743 is an active drug in adult soft-tissue sarcoma: a STBSG-EORTC Phase II trial. American Society of Clinical Oncology,

[36]. The Annual Meeting . San Francisco, CA, May 12 – 15, **2001.** Procc. 353a. Abstract 1407.

[37]. Yovine A., Riofrio M., Brain E., Blay JY., Kahatt C., Delaloge S., Beautier L., Cottu P., Jimeno J., Cvitkovic E., Misset JL. Ecteinascidin-743 given as a 24 hour (H) intravenous continuos infusion (IVCI) every 3 weeks: results of a Phase II trial in patients (PTS) with pretreated soft tissue sarcomas (PSTS). American Society of Clinical Oncology. 37th Annual Meeting . *San Francisco, CA, May 12 – 15, **2001**. Proc. 363a. Abstract 1449.*

[38]. Jimeno J., Maki R., Casali P., Faircloth G., Martinez N., Nieto A., Cañigueral S. Therapeutic impact of ET-743 (Yondelis®, Trabectidin) a new marine derived compound in Sarcoma.Current Opinion in Orthopedics. Submitted September **2003**.solid tumors. *Eur J Cancer*. **2003,** 39, 1842-1851