

INTERNATIONAL COLLABORATION IN NATURAL PRODUCTS DRUG DISCOVERY AND DEVELOPMENT

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Division of Cancer Treatment and Diagnosis
and
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NCI-Frederick

NCI: HISTORICAL PERSPECTIVE

- Established 1937.
- Mission: To provide for, foster and aid in coordinating research related to cancer.
- 1955: Cancer Chemotherapy National Service Center (CCNSC) set up.
- Procurement, screening, preclinical studies and evaluation of new chemotherapeutic agents.
- Now responsibility of Developmental Therapeutics Program.

ACHIEVEMENTS: 1955-1982

Materials screened (mainly in vivo P388 mouse leukemia):

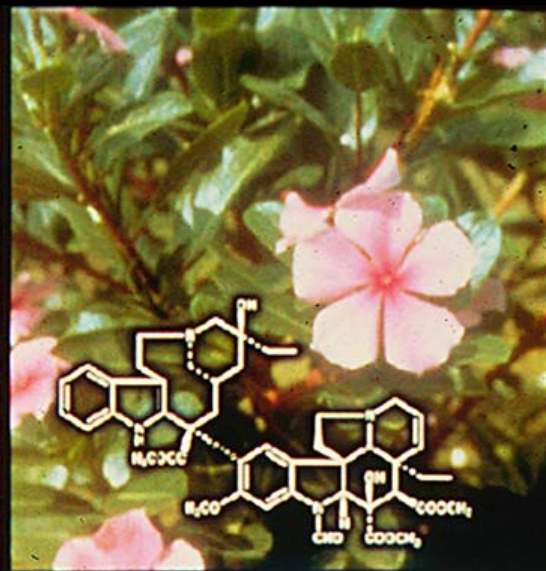
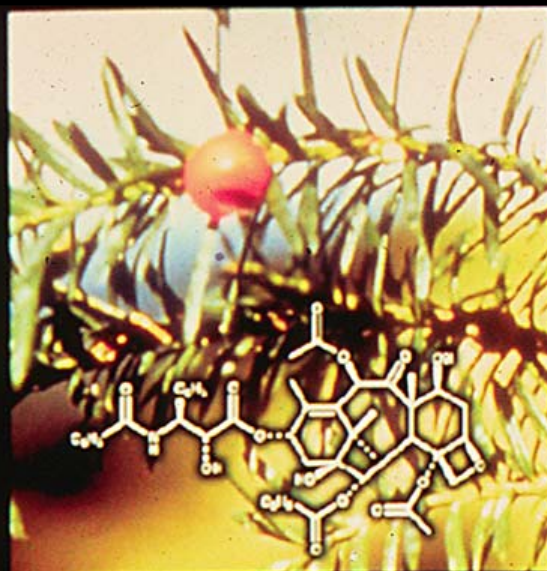
- >500K synthetic and pure natural products.
- >180K microbial extracts.
- > 114K plant extracts.
- > 16K marine organism extracts.

Major role in development of most of the available commercial and investigational agents.

Natural products: Anthracyclines (e.g., doxorubicin), bleomycins, mitomycins, taxol®[®], etoposide, camptothecins (topotecan, irinotecan), homoharringtonine, bryostatin, dolastatins (Cragg & Newman, *Cancer Investigation*, 1999, 17, 153-163).

PLANT-DERIVED ANTICANCER DRUGS IN CLINICAL USE OR DEVELOPMENT

- **Vinblastine/Vincristine:** *Catharanthus roseus*/Jamaica, Philippines (originally from Madagascar)
- **Etoposide:** *Podophyllum species*/ Eastern US, Himalayas
- **Paclitaxel/Docetaxel:** *Taxus species*/NW US, Europe
- **Topotecan/Irinotecan:** *Camptotheca acuminata*/China
- **Homoharringtonine:** *Cephalotaxus harringtonia*/China
- **Flavopiridol:** Synthetic based on rohutikine from *Dysoxylum binectariferum*/India
- **Combretastatins:** *Combretum caffrum*/S. Africa



THE MICROBIAL WORLD OF BACTERIA AND FUNGI

SOURCE OF CHEMICAL DIVERSITY

AND

WONDER DRUGS



Lentinus edodes (Berk.) Sing.



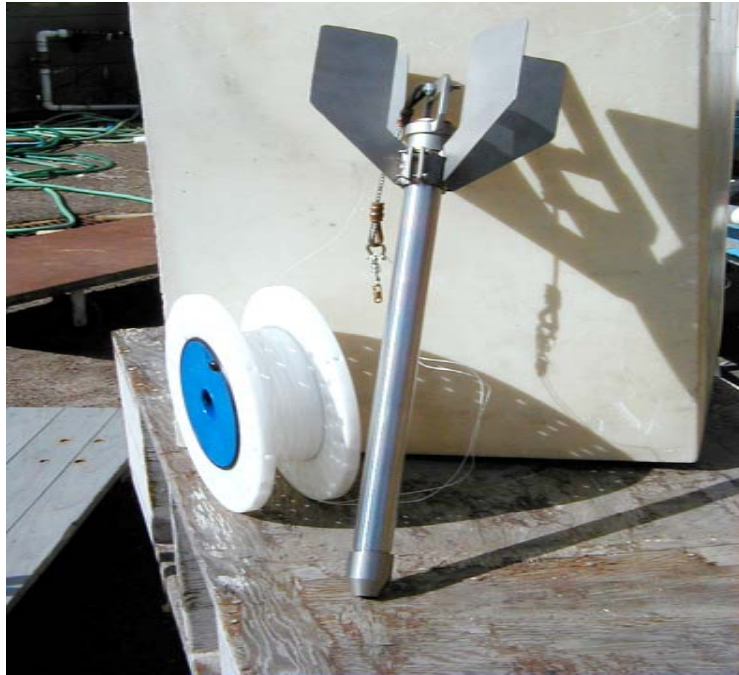
7. *Cordyceps militaris*

MICROBIAL-DERIVED ANTICANCER DRUGS IN CLINICAL USE OR DEVELOPMENT

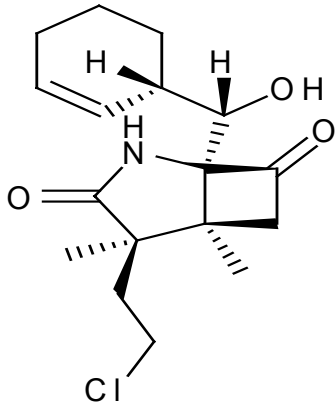
- **Anthracyclines***: Daunomycin, doxorubicin, etc. (Arcamone, Italy)
- **Glycopeptides***: Bleomycins A₂ and B₂ (Umezawa, Japan)
- **Staurosporins***: UCN-01, CEP-751, Rebeccamycin (Prudhomme, France)
- **Epothilones**: Taxol mimics from *Myxobacteria* (Höfle and Reichenbach, Germany)

* All from *Streptomyces* spp.

Marine sediments: Nereus Pharmaceuticals



Sediment sampler



Salinosporamide A

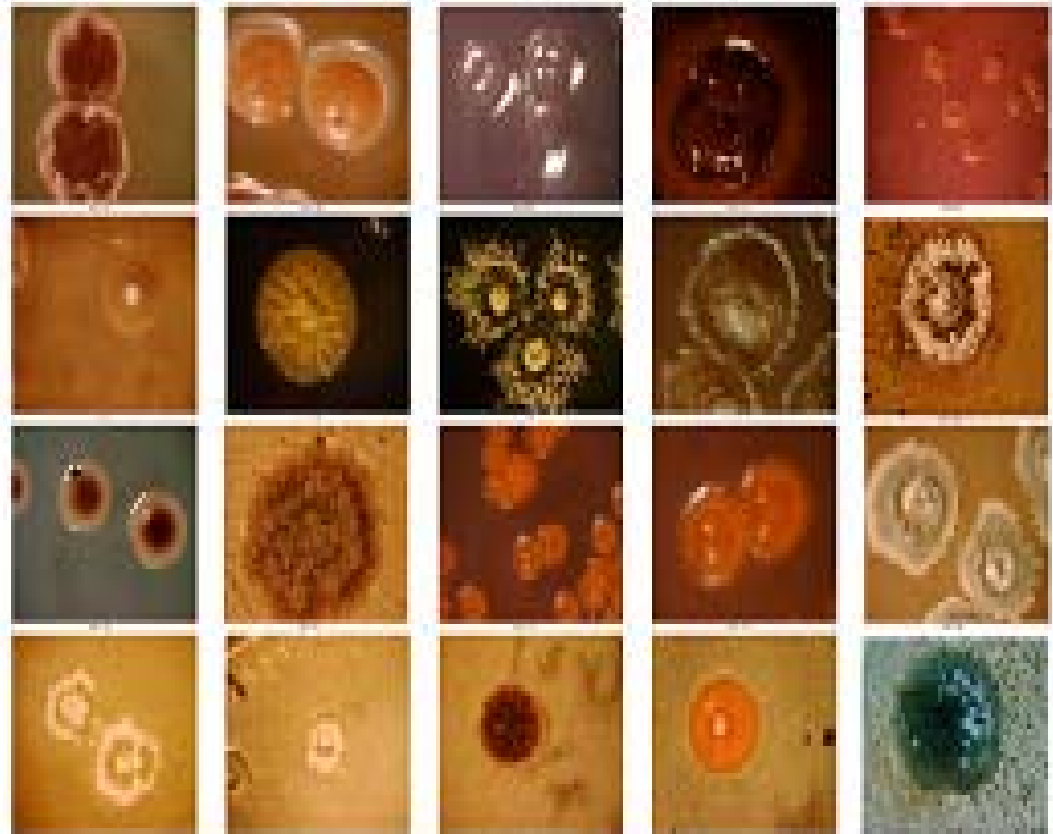
Fenical et al., *Angew. Chem. Int. Ed.*, **42**, 355-357 (2003)

Marine Microbe Culture Collection

Over 15,000 Strains

~50 % Actinomycetes; 10 New genera discovered

~50 % Fungi

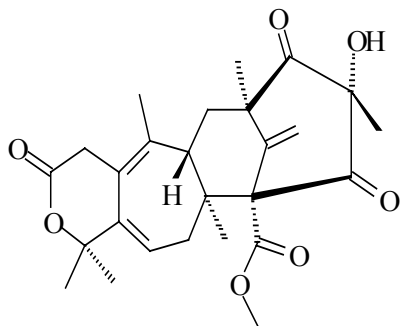


Toxic lakes and dump-sites

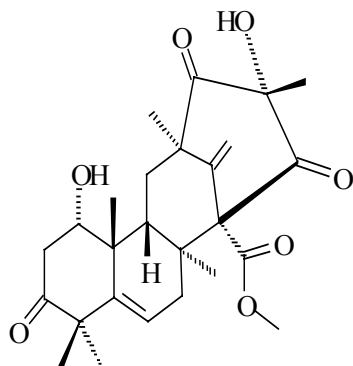


Berkeley Pit Lake - Butte, Montana

Penicillium 885-7 Structures



PM2-64F berkeleydione

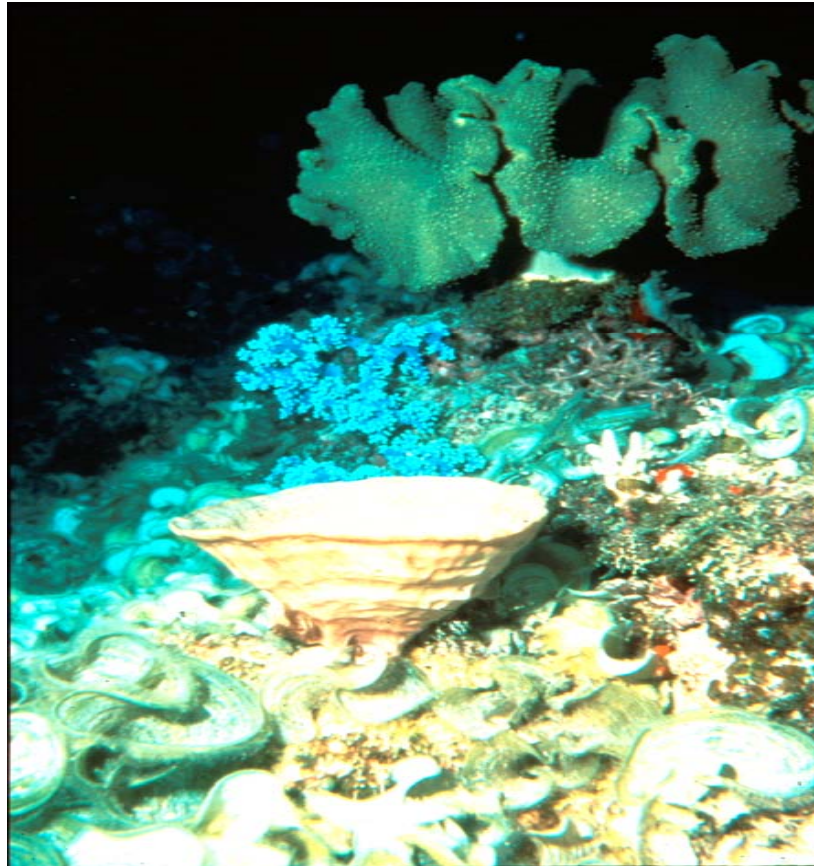


PM2-134F berkeleytrione



Andrea and Don Stierle, Montana Tech., Butte

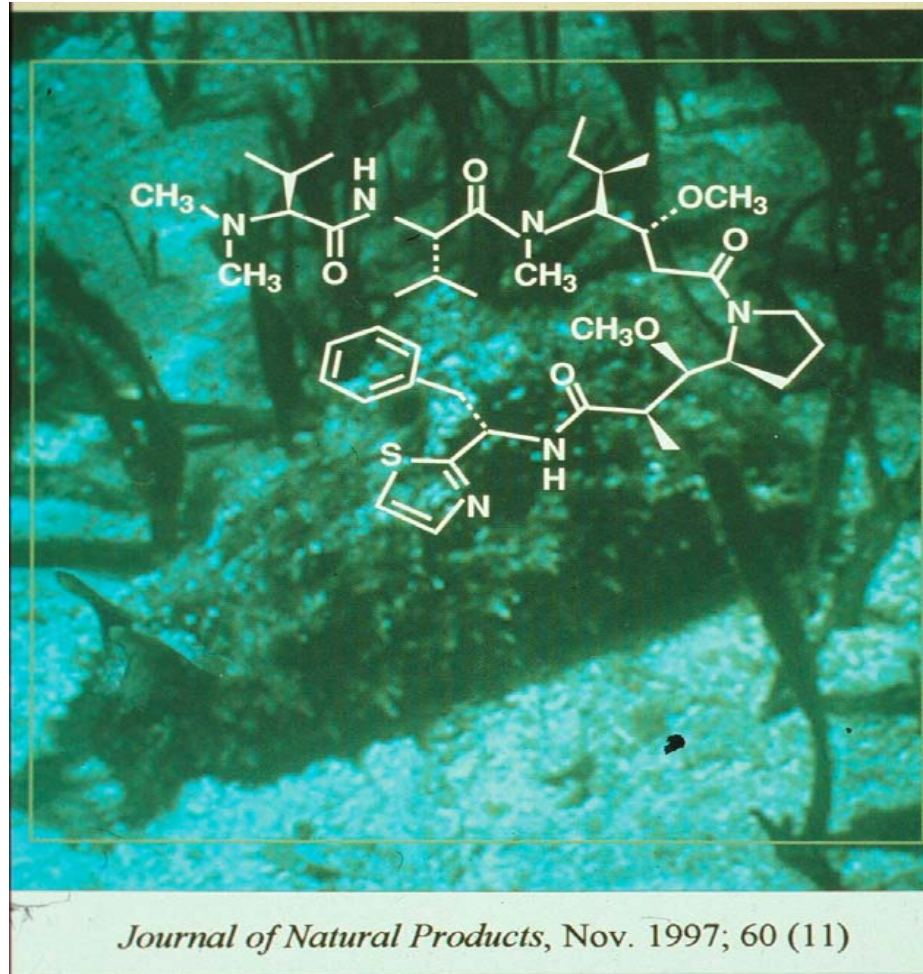
MARINE ENVIRONMENT



MARINE-DERIVED ANTICANCER AGENTS IN DEVELOPMENT

- **Aplidine:** *Aplidium albicans*/Mediterranean
- **Bengamide analog:** *Jaspis* sp./Fiji
- **Bryostatin:** *Bugula neritina*/California
- **Discodermolide:** *Discodermia dissoluta*/
Caribbean
- **Dolastatin 10:** *Dolabella auricularia*/Indian
Ocean
- **Ecteinascidin 743:** *Ecteinascidia turbinata*/Caribbean

“You are what you eat”



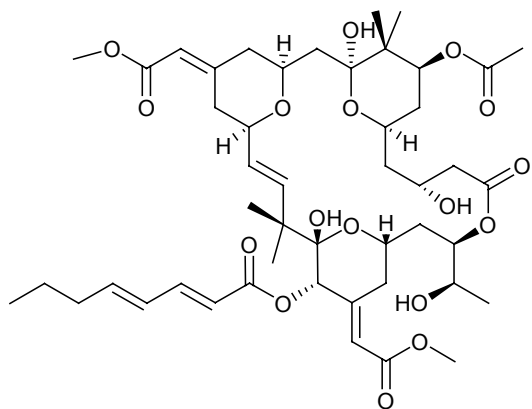
Dolabella auricularia

Dolastatins come from a *Symploca* species that they graze on

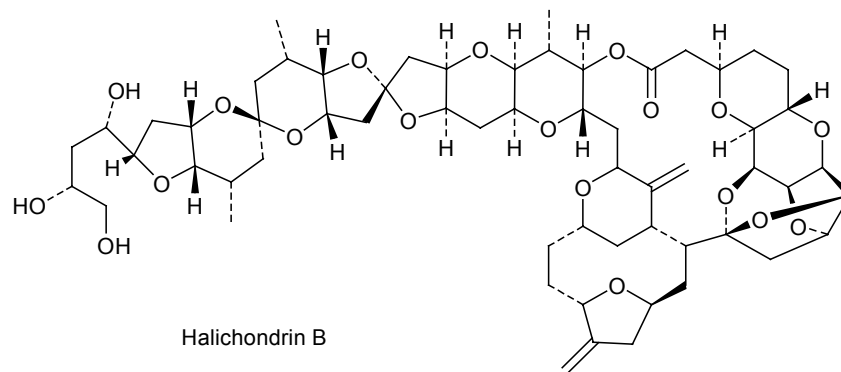
MARINE-DERIVED ANTICANCER AGENTS IN DEVELOPMENT

- **Eleutherobin: *Eleutherobia* sp./Western Australia**
- **Halichondrin B analog: *Lissodendoryx* sp./New Zealand**
- **Hemiasterlin analog: *Cymbastella* sp./Papua New Guinea**
- **Isogranulatimide: *Didemnum granulatum*/Brazil**
- **Kahalahide F: *Elysia rubefescens*/Hawaii**
- **Squalamine: *Squalus acanthius*/Atlantic**

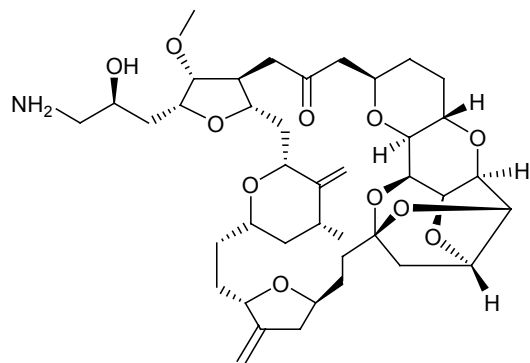
MARINE-DERIVED ANTICANCER AGENTS



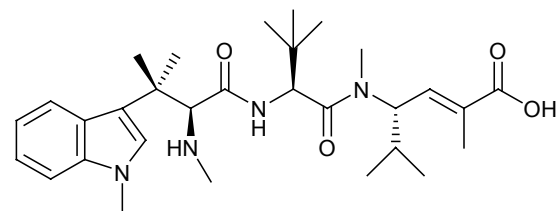
Bryostatin 1



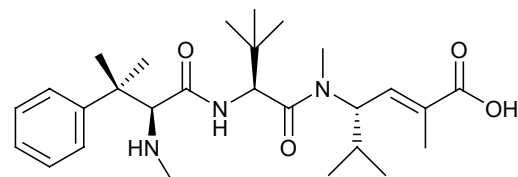
Halichondrin B



E7389 / NSC 707389



Hemiasterlin



HTI-286 / SPA 110

Halichondrin B

**Collaboration in Large-Scale Collections
and Aquaculture of Source Sponge,
Lissodendoryx species,
and Isolation of Compound**

**University of Canterbury
and**

**New Zealand National Institute of
Water and Atmospheric Research (NIWA)**

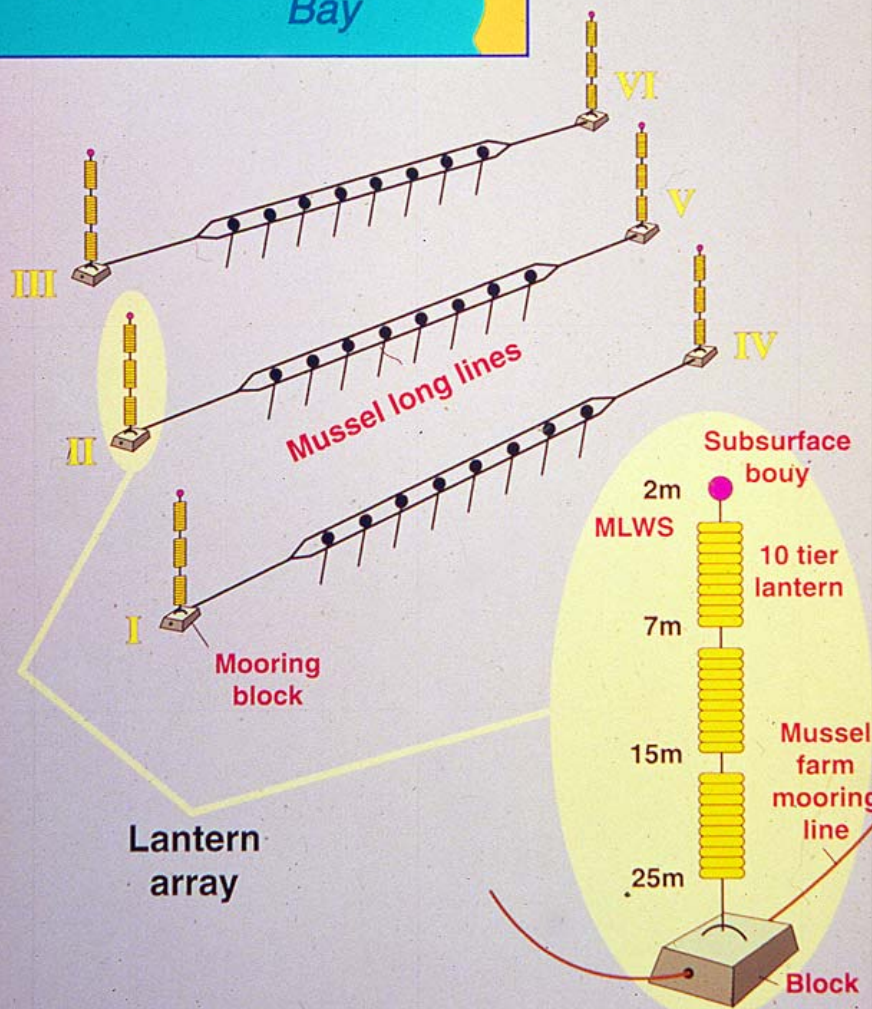


92 K07-01

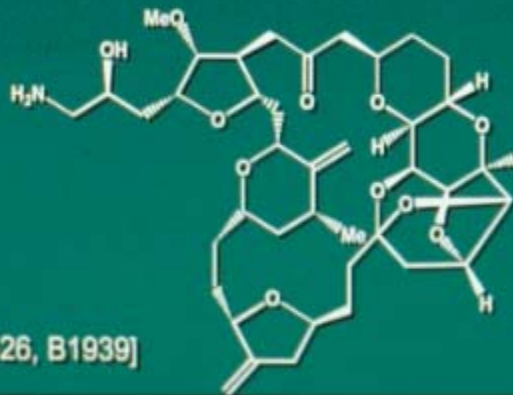
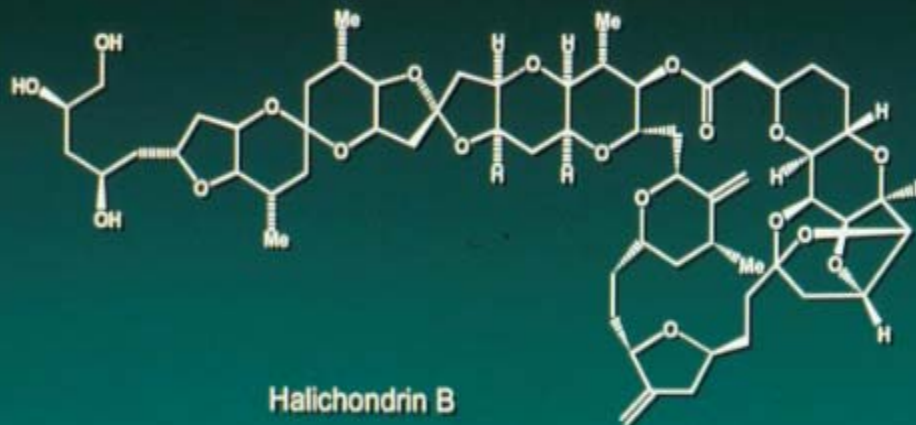




Experimental Set-up



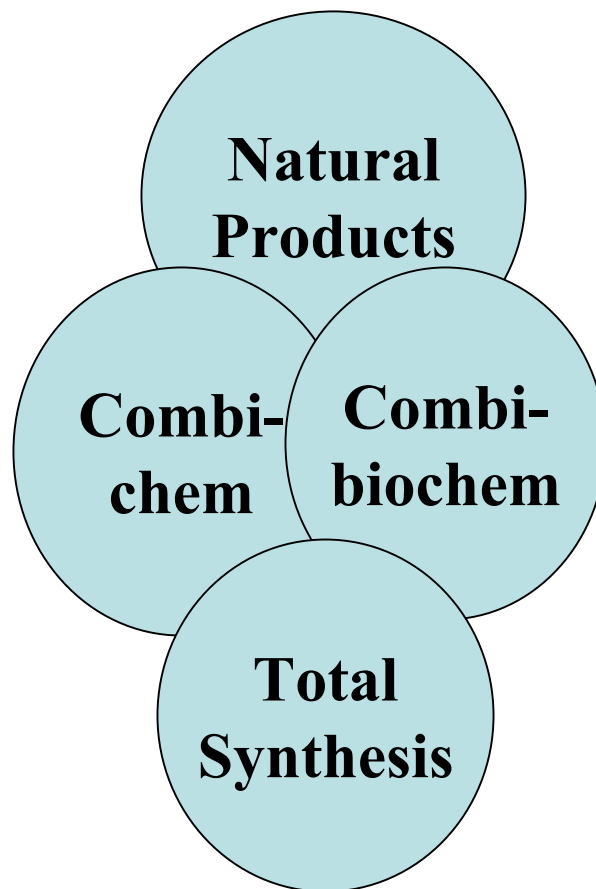
Halichondrins: Natural and Synthetic Modifications



Total Synthesis of Halichondrin B: Kishi et al., JACS, 1992, **114**, 3162-3164

Multidisciplinary Collaboration

Modified from Dr. David Kingston, VPI



Antitumor Agents from Natural Products, Cragg, Kingston and Newman, eds.,
Auerbach Publications Chapman & Hall CRC Press, Taylor & Francis Group, 2005

INTERNATIONAL COLLABORATION

- **Prior informed consent/permits from Source Country Government and stakeholders.**
- **Collaboration with Source Country Organizations.**
- **Training and technology transfer.**
- **Protection of environment and sustainable development.**
- **Plans for benefit-sharing**

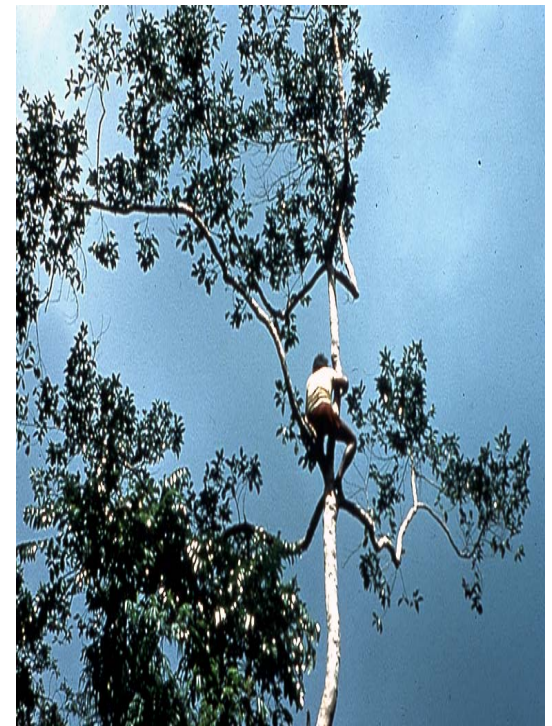


Dr. D. Soejarto
U. Illinois at Chicago

NCI NATURAL PRODUCTS ACQUISITIONS: 1986-

Plant Collections

Africa and Madagascar: Missouri Botanical Garden.
Central/S. America (1986-96): New York Botanical Garden.
South East Asia: Univ. of Illinois at Chicago.
U. S. Territories: Morton Arboretum (1996-2001).
World Botanical Associates (2001-)



Dr. D. Soejarto
U. Illinois at Chicago



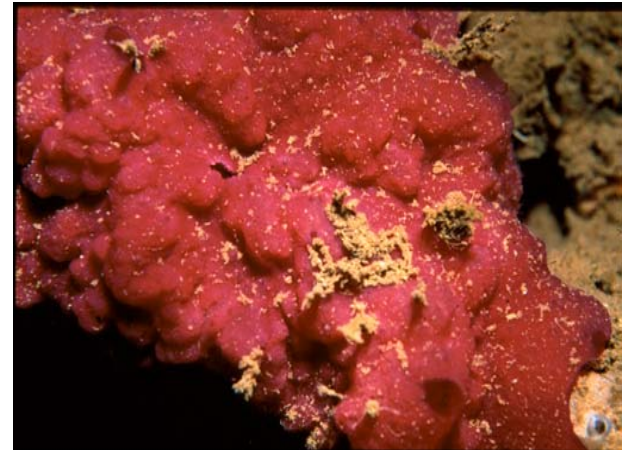
NCI NATURAL PRODUCTS ACQUISITIONS: 1986-

Marine Organisms

Indo-Pacific & Caribbean (1986-92): SeaPharm, Inc., Harbor Branch Oceanographic Institute, Australian Institute of Marine Science.

Indo-Pacific (1992-2002): Coral Reef Research Foundation (CRRF).

Worldwide (2002-): CRRF





NCI LETTER OF COLLECTION

Agreements with Source Countries commit NCI to:

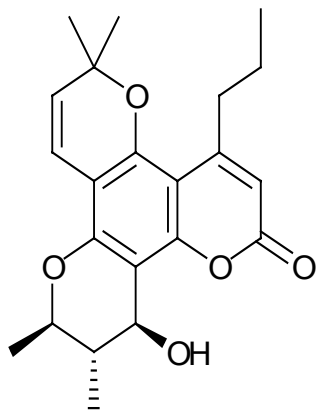
- Conservation of Source Country genetic resources
- Collaboration with Source Country Organizations
- Training and Technology Transfer
- Return of test results on confidential basis
- Protection of Source Country rights including any IP
- Collaboration in development of approved candidate drugs
- Benefit-sharing in event of licensing of drugs
- Use of Source Country resources for production of drugs

LOC AGREEMENT HOLDERS

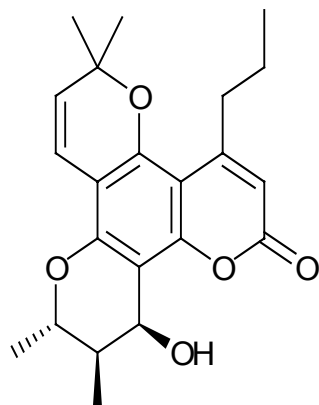
- Australia, Bangladesh, Cambodia, Ecuador, Gabon, Ghana, Laos, Madagascar, Palau, Papua New Guinea, Philippines, Sarawak (Malaysia), Tanzania, Vietnam.
- First agreement signed with CNARP Madagascar: 1990.
- Other collaborating countries without official agreements but fully aware of the terms of the LOC. NCI fully committed to terms of the LOC:

Bahrain, Belize, Bolivia, Cameroon, Central African Rep., Colombia, Dominica, Dominican Rep., Federated States of Micronesia, Guatemala, Guyana, Honduras, Indonesia, Malaysia, Maldives, Marshall Islands, Martinique, Nepal, Paraguay, Peru, St. Lucia, Thailand, Tonga.

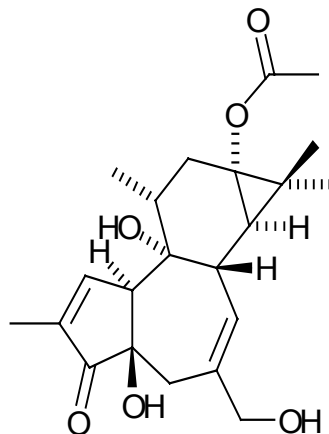
PLANT-DERIVED ANTI-HIV AGENTS



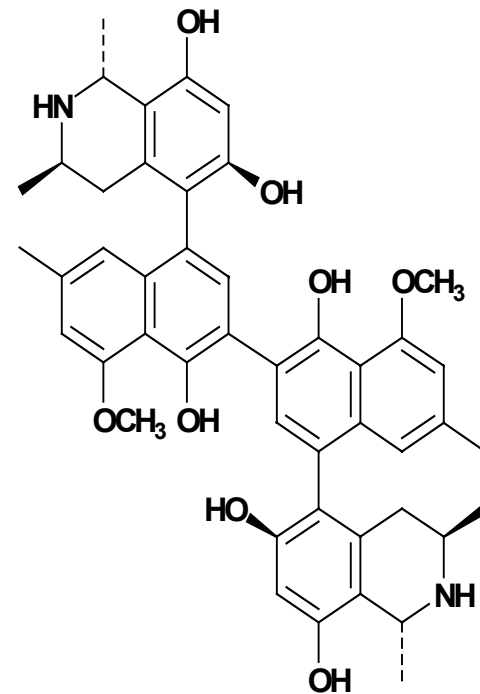
(+) - Calanolide A



(-) - Calanolide B



Prostratin



Michellamine B

MICHELLAMINE B

Potential Anti-AIDS Agent

Discovery and Development

- 1987: Collected liana *Ancistrocladus korupensis* leaves. Korup National Park, Mundemba, S. West Cameroon. Dr. Duncan Thomas (MBG) and Mr. Ndembe (Forestry Dept.).
- New species (Thomas & Gereau, Novon, 1993, 3, 494-498).
- 1989: Michellamine B isolated. Active against a range of HIV-1 and HIV-2 strains (Boyd et al., J. Med. Chem, 1994, 37, 1740-45).
- Sufficient isolated from fallen leaves for preclinical development.

***A. KORUPENSIS* CULTIVATION STUDIES**

- 1993: Contract for cultivation feasibility study awarded.
- All studies performed in Korup region involving local population.
- Extensive botanical and analytical survey:
 - Distribution: One liana per hectare.
 - Dried leaf analysis (N=>1,000): Up to 4% (w/w) MB.
- Nursery established at Mundemba. Cuttings of high-yielding plants propagated.
- MB content of 1,5 year old seedlings: 0.07-0.73%

MICHELLAMINE B COLLABORATION: CAMEROON



DEVELOPMENT OF MICHELLAMINE B

- Formulation as diacetate salt.
- Toxicology: Rodents, dogs, primates.
- Toxic dose level close to anticipated effective antiviral dose (narrow therapeutic index).
- Development suspended.
- Possibility of lead development.
- Novel antimalarial agents, the korupensamines, add further promise for *A. korupensis*.

CALANOLIDES DISCOVERY

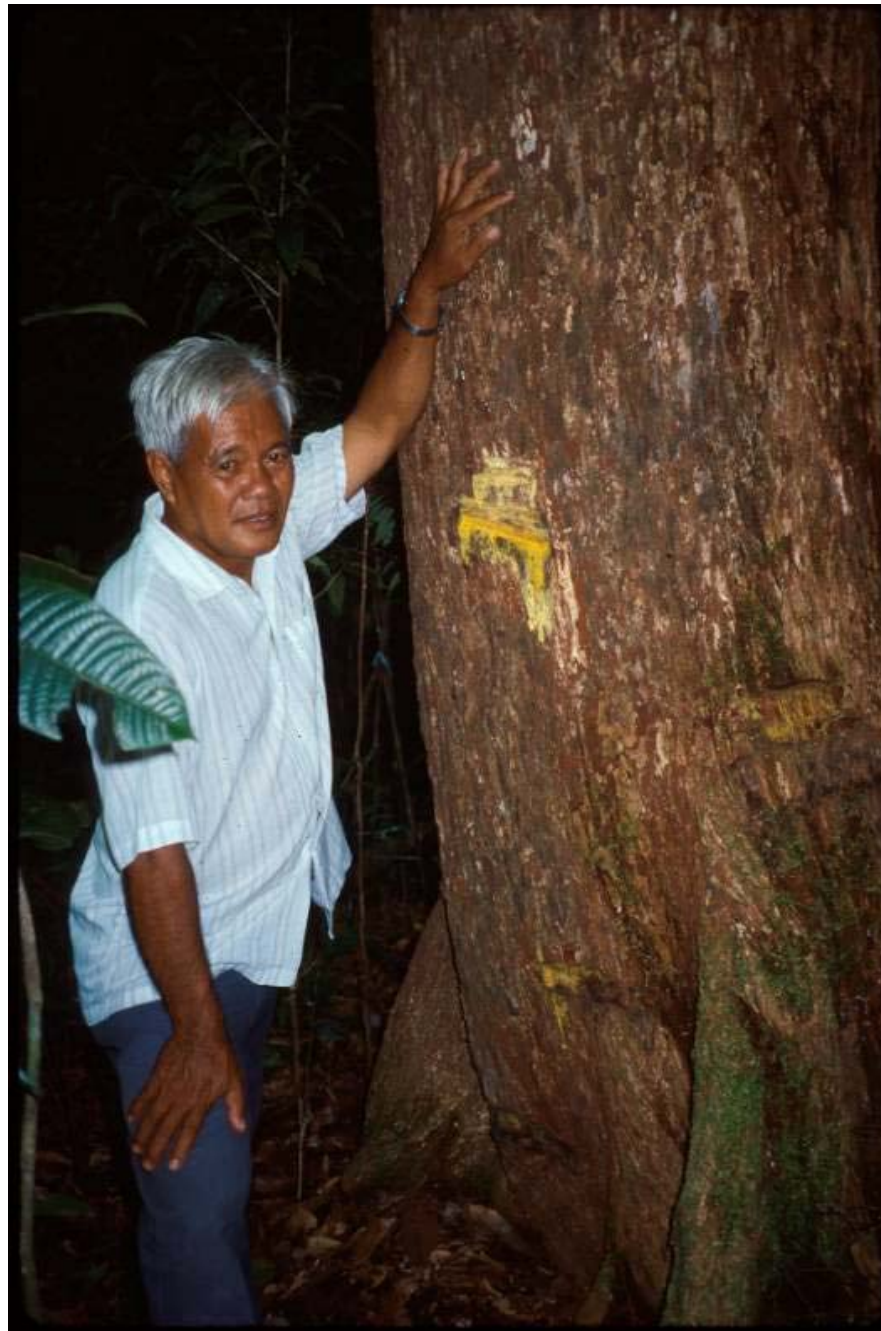
- 1987: Collection *Calophyllum lanigerum*; Leaves/twigs.
Dr. John Burley, Arnold Arboretum, Harvard Univ.
Mr. Bernard Lee, Sarawak State Forestry Department.
- In vitro anti-HIV activity observed for organic extract.
- 1990: (+)- Calanolide A and (-)-Calanolide B isolated.
- Active against resistant mutants of HIV-1 and 181 mutant reverse transcriptase.



Calophyllum teysmannii var. *inophylloide*. Sustainable source of potential anti-AIDS drug, calanolide B. Discovery from tree in Sarawak, Malaysia, promoted conservation and replanting of seedlings in clearcut regions, and led to establishment of the Sarawak Biodiversity Center for in-country research on drug discovery from local biodiversity



D.D. Soejarto, University of Illinois at Chicago



CALANOLIDES DEVELOPMENT

- **1995: Calanolides licensed to Medichem Research Inc.**
- **Synthesis of (+)-calanolide A supported by NCI SBIR grant**
- **Negotiation with Sarawak State Govt. required by LOC**
1996: Joint venture company, Sarawak Medichem
Pharmaceuticals formed
- **Phase I trials of Calanolide-A completed/well tolerated**
- **Phase II trials planned**
- **Calanolide B in preclinical development**

PROSTRATIN

- Dr. Paul Cox entered into a Covenant with healers of Western Samoan village of Falealupo
- Covenant signed with village chiefs and orators with concurrence of Prime Minister and Parliament.
- Use of *Homalanthus nutans* by healers recorded by Dr. Cox.
- \$480,000 provided for schools, clinics, water supplies, trails, aerial walkways, etc.
- Endowment established for preservation of forest.

Samoan Traditional Healer in Village of Falealupo



PROSTRATIN

- **Licensed by NIH to the AIDS ReSearch Alliance of America.**
- **Agreement with Government of Samoa.**
- **Milestone payments on completion of Phase I, II and III clinical trials.**
- **Royalties totaling 20% of net revenues.**



Distribution of Extracts

- Active extracts distributed to qualified investigators worldwide through Active Repository Program (ARP) for study as a source of novel anti-cancer agents.
- “Inactive” extracts distributed to qualified investigators worldwide via Open Repository Program (ORP) for testing in screens related to all human diseases.
- Access to APR and OPR subject to signing a Material Transfer Agreement protecting the rights of all parties, particularly those of Source Countries.

NCI MEMORANDUM OF UNDERSTANDING

- Agreements with qualified Source Country Organizations.
- SCO performs collections, extractions, prescreening and bioassay-guided fractionation in-country at own expense.
- NCI assists SCO to establish screening facility through provision of training and cell lines at NCI expense.
- NCI provides free secondary *in vitro* and *in vivo* testing with no IPR claims.
- SCO applies for appropriate patent coverage.
- NCI collaborates in development of SCO drugs meeting NCI selection criteria – at NCI expense

NCI MEMORANDUM OF UNDERSTANDING

MOUs have been signed with organizations in the following countries:

Australia, Bangladesh, Brazil (5), China (3), Costa Rica, Fiji, Iceland, Korea, Mexico, New Zealand, Nicaragua, Pakistan, Papua New Guinea, Panama, South Africa (2), Zimbabwe

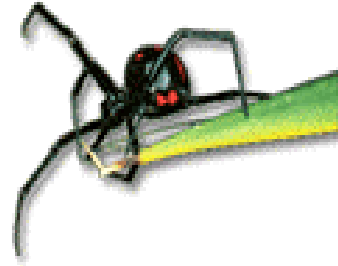
First MOUs in 1994



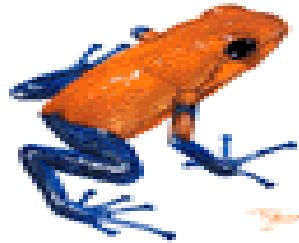
National Biodiversity Institute COSTA RICA



COSTA RICA – BIODIVERSITY – INBIO – BIOPROSPECTING - CONSERVATION



Fuente: INBio.
© Derechos Reservados.



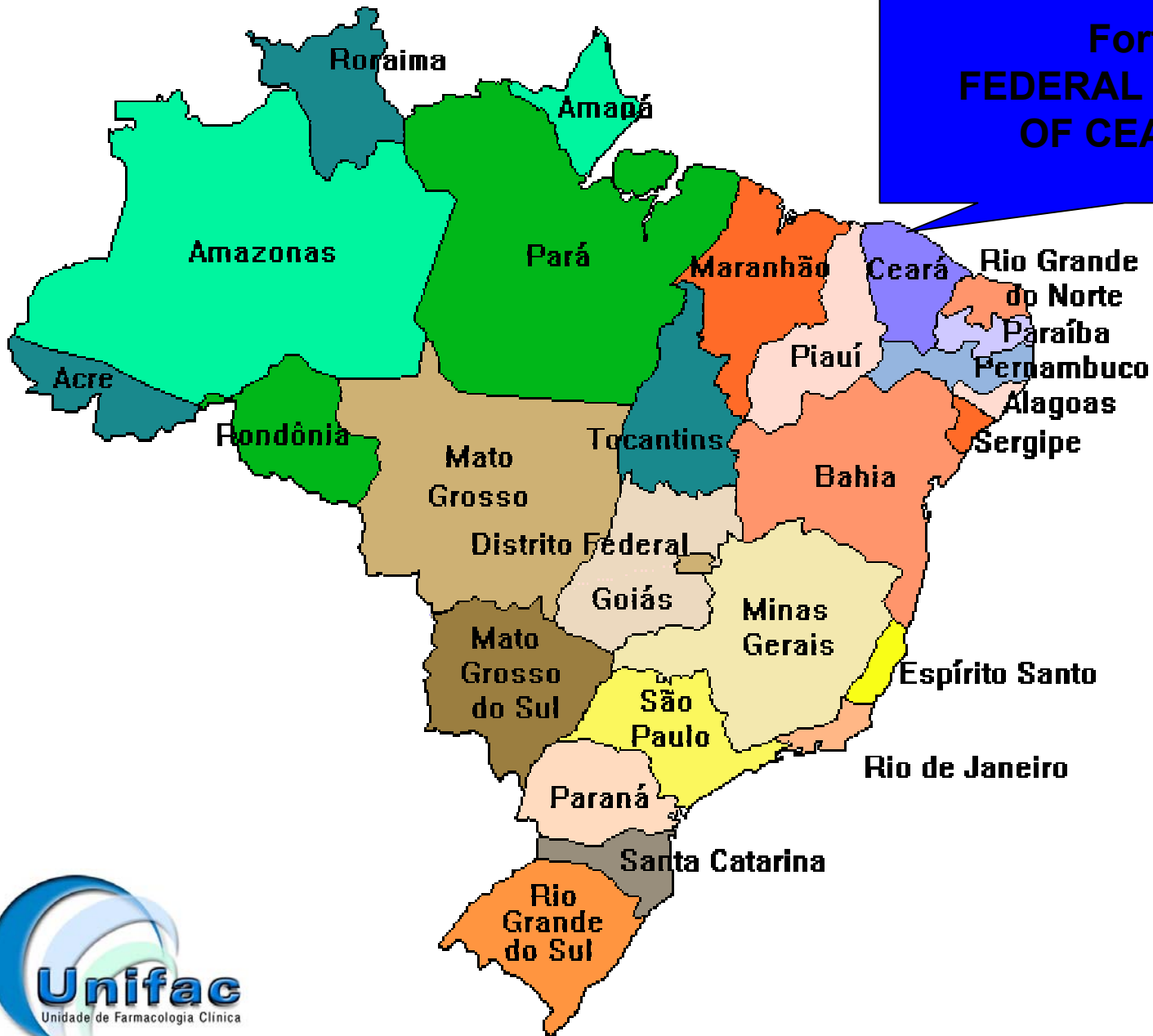


Studies on Anticancer Drug Discovery and Development from Brazilian Biodiversity

Laboratory of Experimental Oncology– LOE
Clinical Pharmacology Unit - UNIFAC
Department of Physiology and Pharmacology
Federal University of Ceará
www.loe.ufc.br



**Fortaleza
FEDERAL UNIVERSITY
OF CEARA - UFC**

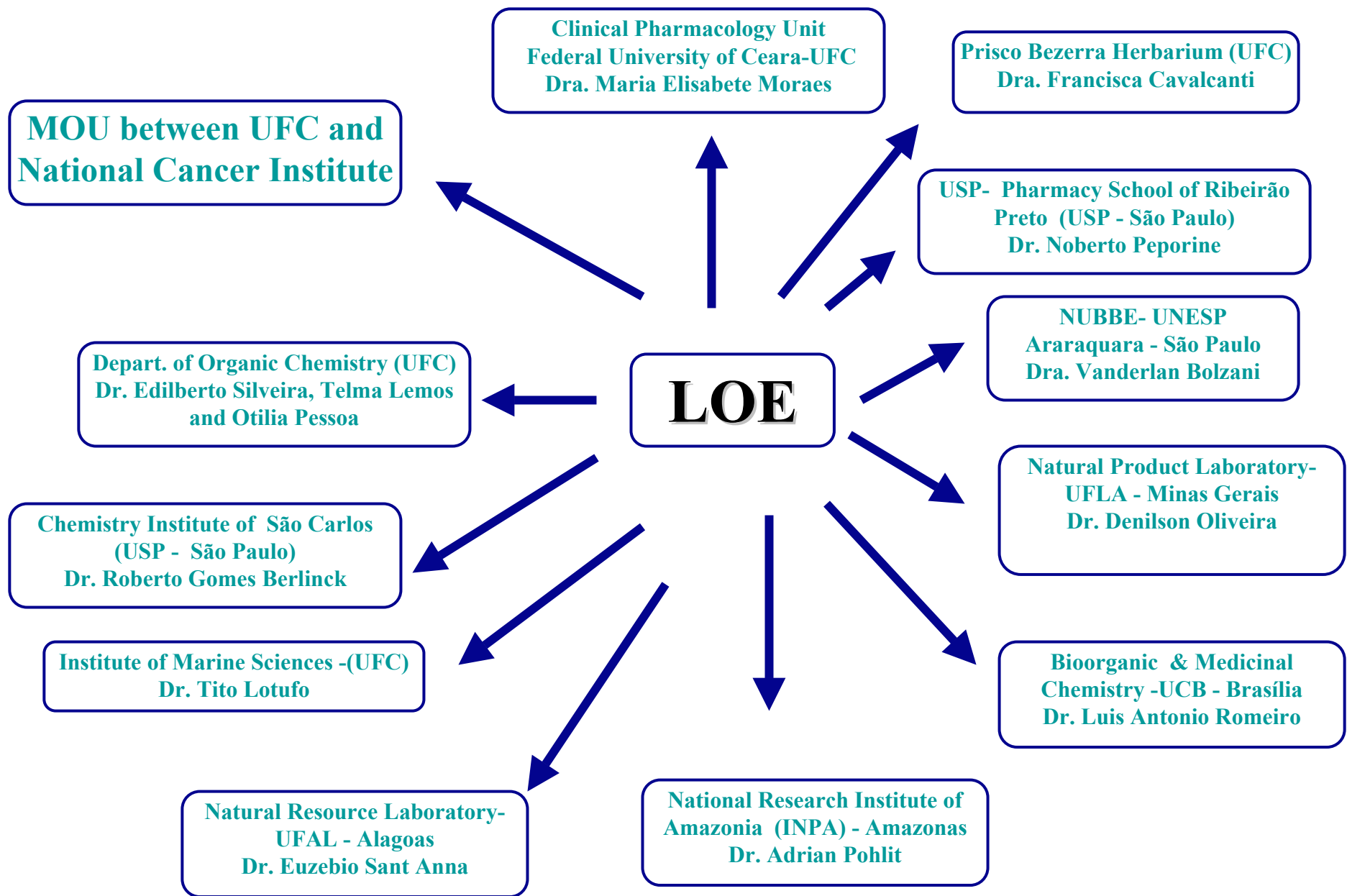


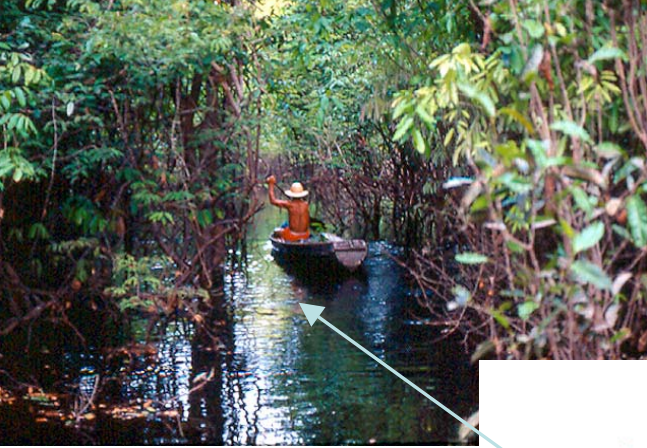




Research area of interest:

The discovery and development of new anticancer compounds from Brazilian biodiversity, including plants, marine organisms and fungi.



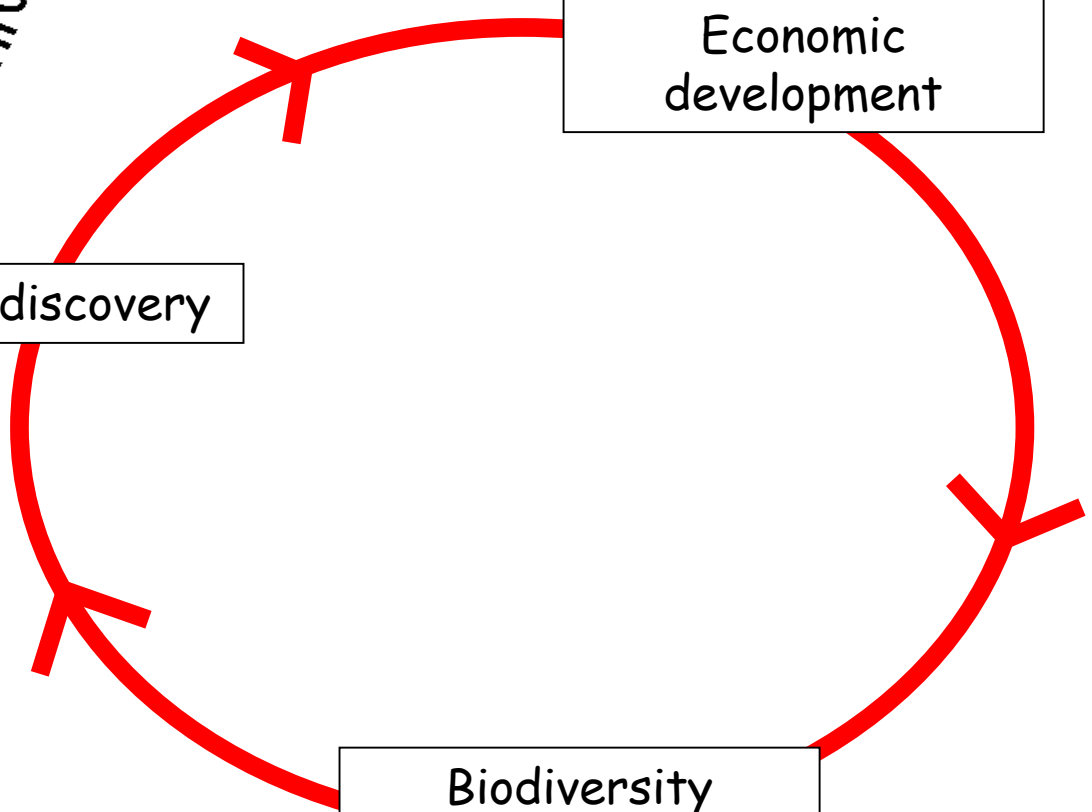




Drug discovery

Economic development

Biodiversity conservation



INTERNATIONAL COOPERATIVE BIODIVERSITY GROUP PROGRAM: 2003

New ICBG U01 Awards



- Vietnam/Laos
- Madagascar
- Panama
- Uzbekistan/
Kyrgyzstan
- Papua New
Guinea

Planning Grants



Costa Rica
Jamaica
Jordan
Fiji
Samoa
Madagascar
Philippines



**Argentina Bolivia Brasil Chile
Colombia Costa Rica Cuba
Ecuador El Salvador España España
Guatemala Honduras México
Nicaragua Panamá Paraguay Perú
Portugal República Dominicana
Uruguay Venezuela**

LISTA DE ÁREAS TEMÁTICAS Y SUBPROGRAMAS

1. AGROALIMENTACIÓN

II.-ACUICULTURA XI.-TRATAMIENTO Y CONSERVACION DE ALIMENTOS XIX.-TECNOLOGÍAS AGROPECUARIAS

2. SALUD

III.-BIOTECNOLOGIA X.-QUIMICA FINA FARMACEUTICA

3. PROMOCIÓN DEL DESARROLLO INDUSTRIAL

IV.-BIOMASA COMO FUENTE DE PRODUCTOS QUIMICOS Y ENERGIA V.-CATALIZADORES Y ADSORBENTES PARA EL MEDIO AMBIENTE Y CALIDAD DE VIDA VIII.-TECNOLOGIA DE MATERIALES XV.-CORROSION E IMPACTO AMBIENTAL SOBRE MATERIALES

4. DESARROLLO SOSTENIBLE

VI.-NUEVAS FUENTES Y CONSERVACION DE LA ENERGIA (EXCLUIDA BIOMASA) XII.-DIVERSIDAD BIOLÓGICA XIII.-TECNOLOGIA MINERAL XIV.-TECNOLOGIA DE VIVIENDAS DE INTERES SOCIAL XVII.-APROVECHAMIENTO Y GESTIÓN DE RECURSOS HÍDRICOS XVIII.-TECNOLOGÍAS DE PREVISIÓN Y EVALUACIÓN DE DESASTRES NATURALES

5. TECNOLOGÍAS DE LA INFORMACIÓN Y LAS COMUNICACIONES

VII.-ELECTRONICA E INFORMATICA APLICADAS IX.-MICROELECTRONICA

6. CIENCIA Y SOCIEDAD XVI.-GESTION DE LA INVESTIGACION Y EL DESARROLLO TECNOLÓGICO

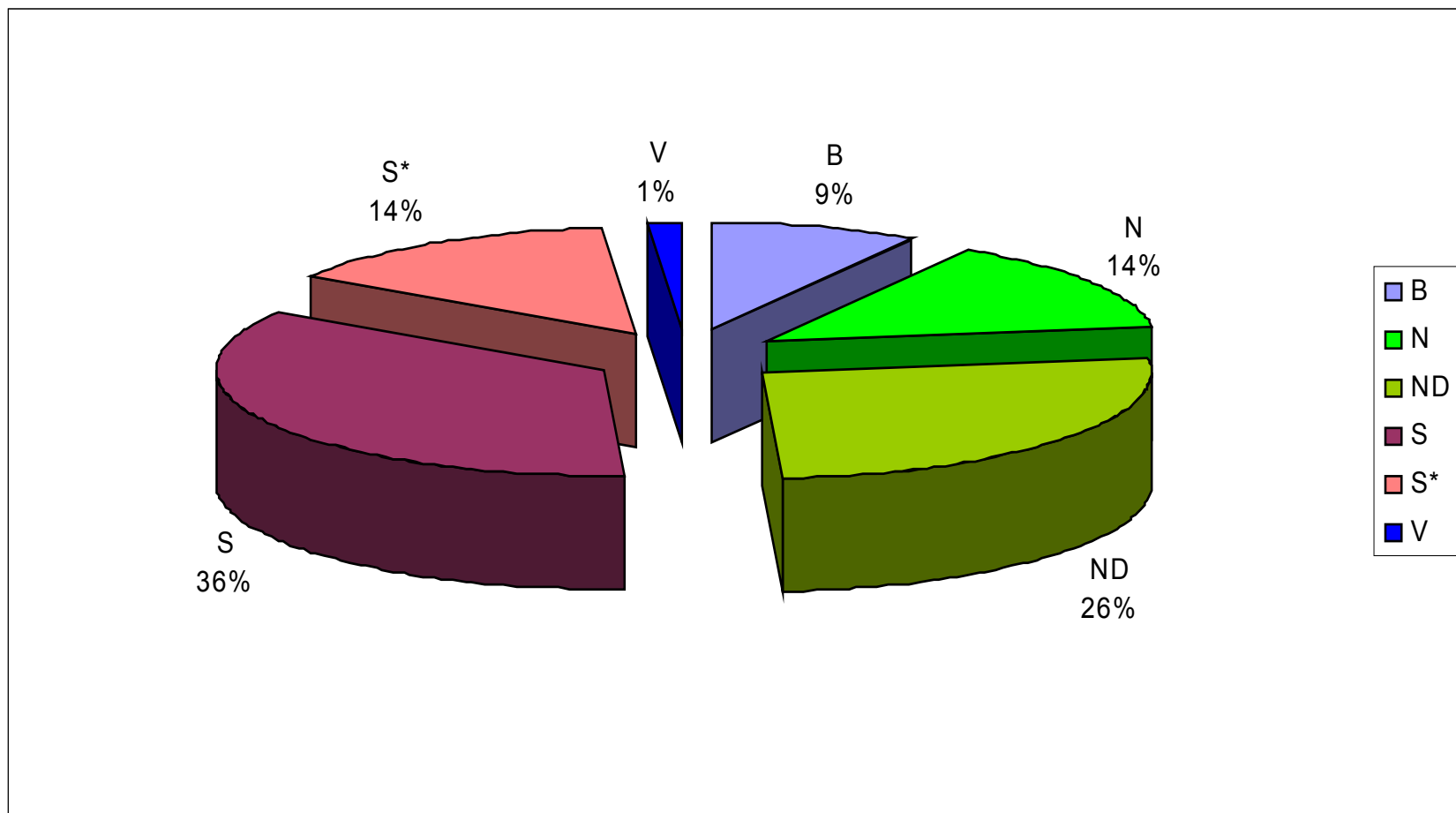
AFASSA: Africa Asia and South America

- Co-ordinates activities of networks involved in natural product research in Africa, Asia and South America.
- Founded at Intercontinental Symposium on Natural Products Research in Montevideo in December, 1999.
- Chairmanship of Dr Federico Dajas, Clemente Estable Institute, Montevideo University, Uruguay

NAPRECA SYMPOSIUM
ADDIS ABABA 2003



Drug Sources

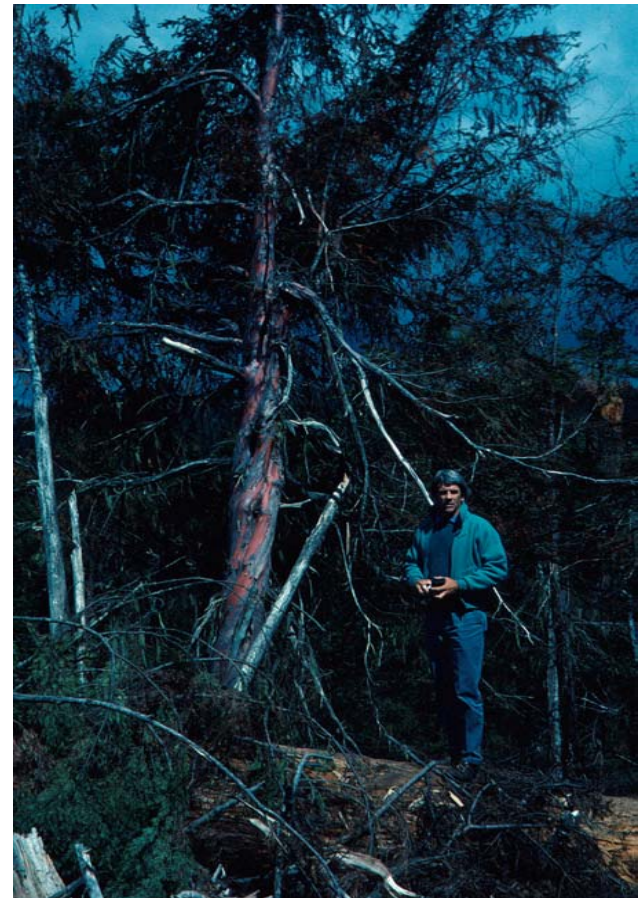


Newman *et al.*, *J. Nat. Prod.* 66:1022 (2003)



WHAT ARE WE LOSING!

CLEAR-CUTTING AND SLASH AND BURN DESTROYS NOT ONLY THE TREES AND MACRO-FAUNA BUT MUCH OF THE ASSOCIATED MICRO-FAUNA AND MICROBIAL LIFE – AN INVALUABLE AND IRREPLACABLE RESOURCE.





THANK YOU
<http://dtp.nci.nih.gov>