Environmental Research Institute
Te Pūtahi Rangahau Taiao
THE UNIVERSITY OF WAIKATO

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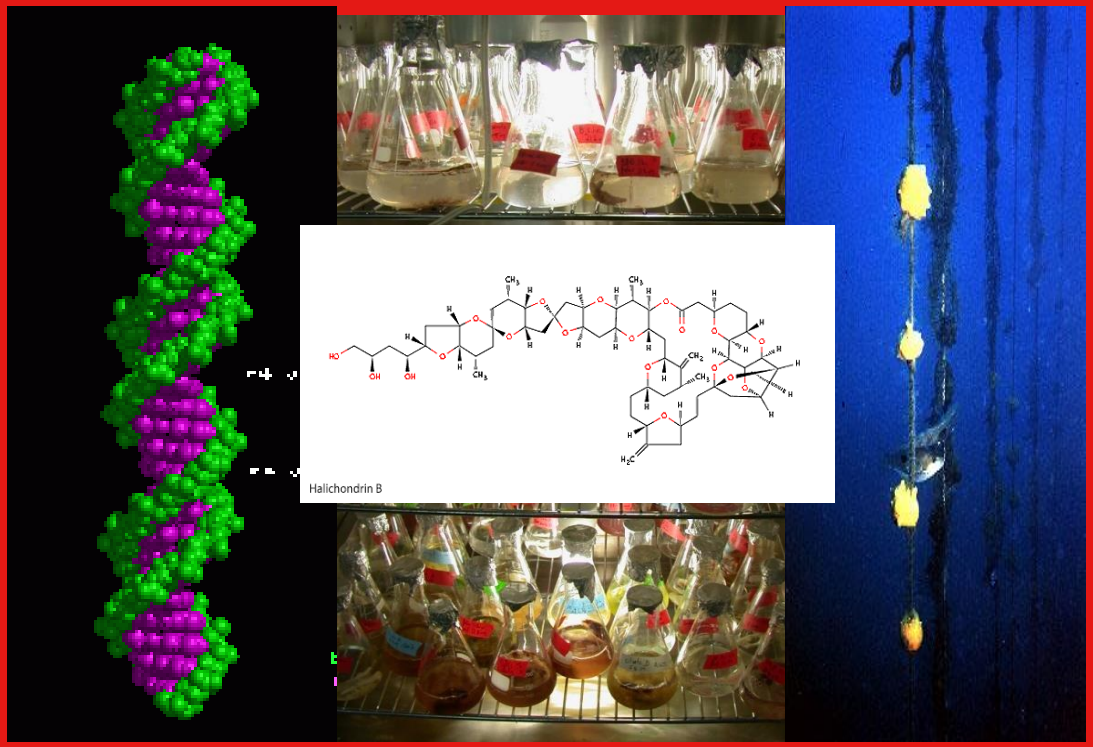
Te Whare Wānanga o Waikato

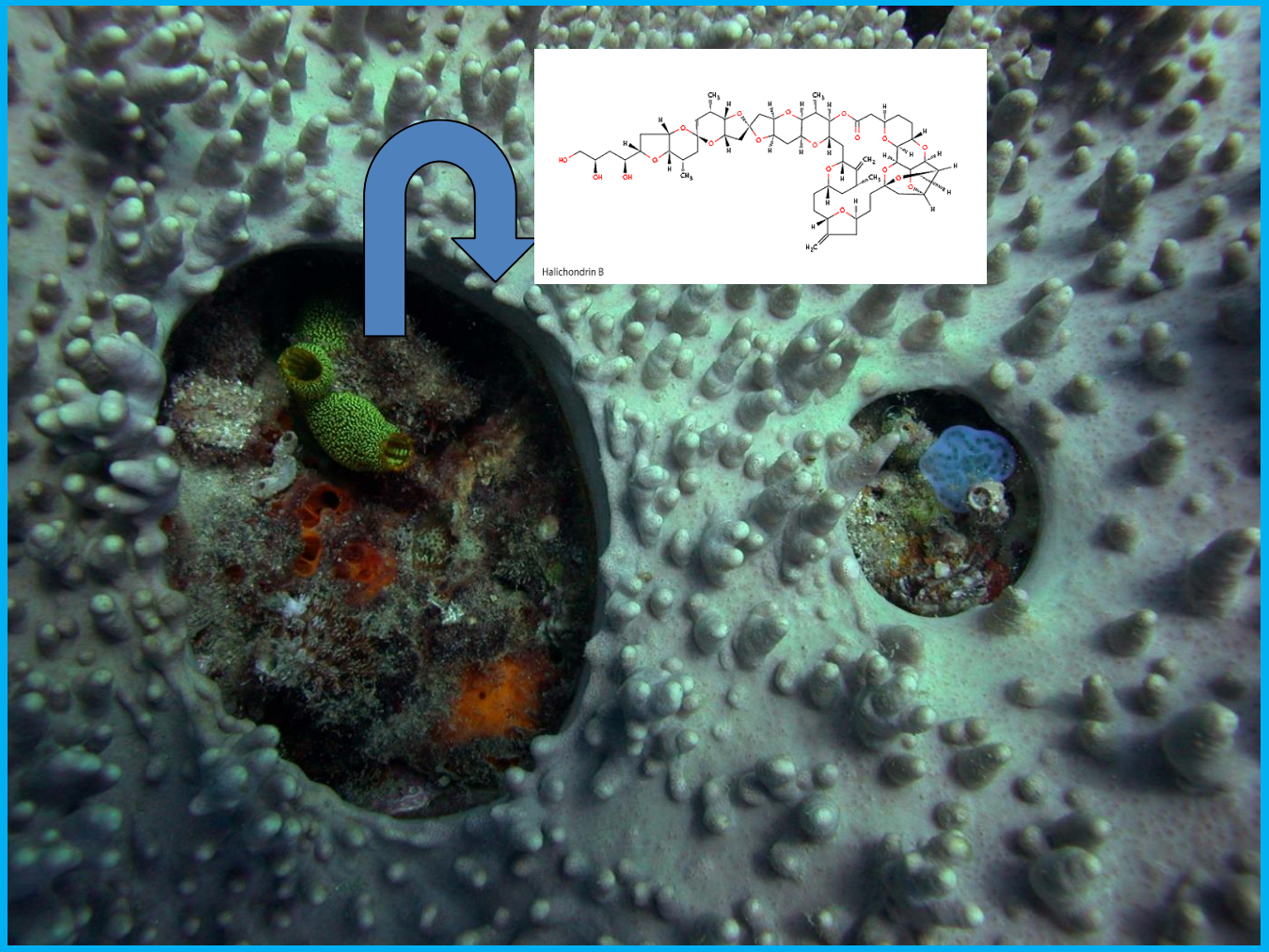
Mapping Marine Bioactives in Tairāwhiti

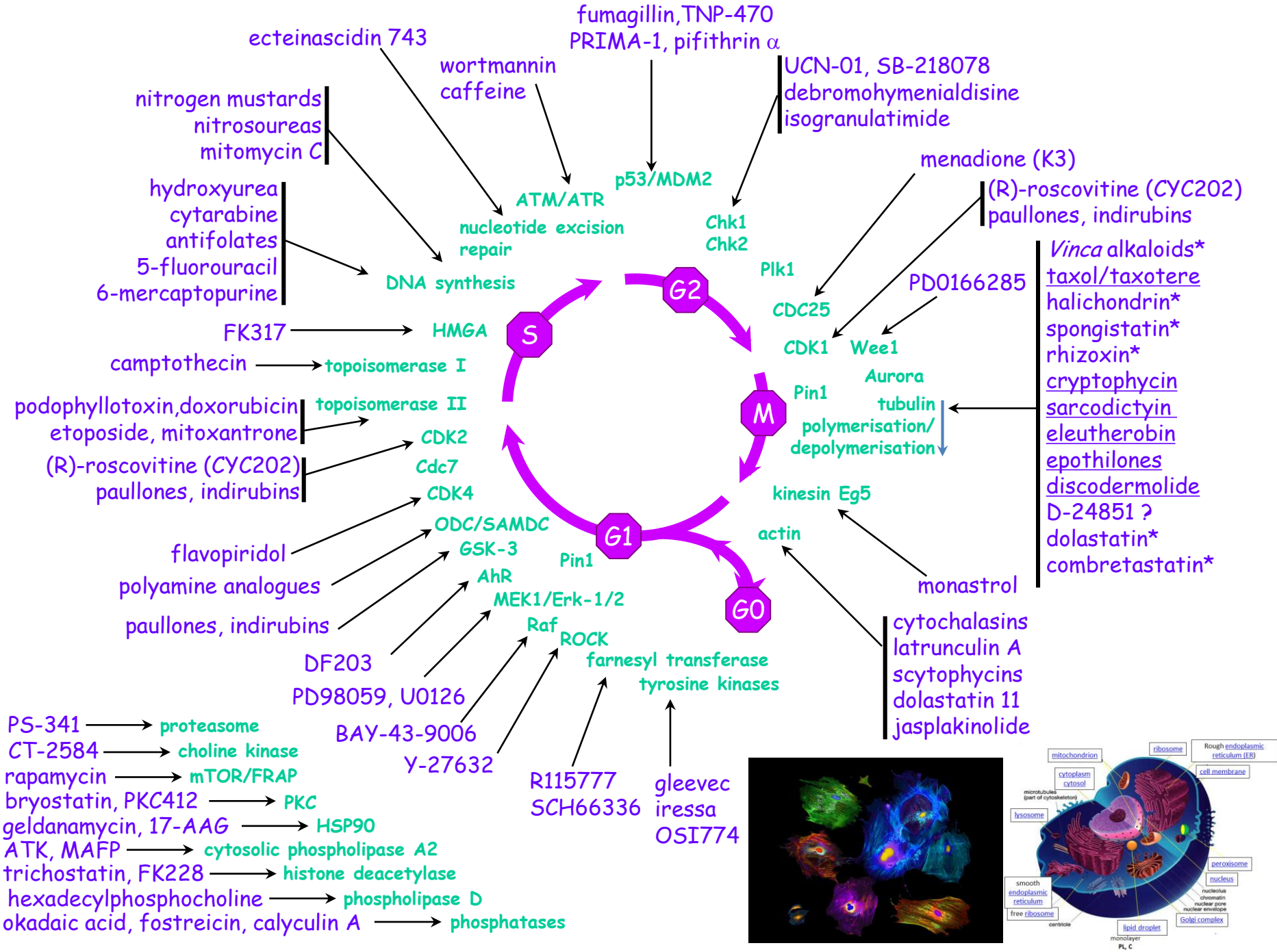
"the coast upon which the sun shines across the water"



Chemical Ecology: Why do marine compounds work?

Chemistry to stop overgrowth, fouling or pathogen attack – Potent – Gets into target cells – stops cell division = drug lead




ecteinascidin 743
fumagillin,TNP-470
PRIMA-1, pifithrin α
wortmannin
caffeine
UCN-01, SB-218078
debromohymenialdisine
isogranulatimide
nitrogen mustards
nitrosoureas
mitomycin C
menadione (K3)
p53/MDM2
ATM/ATR
nucleotide excision repair
Chk1
Chk2
(R)-roscovitine (CYC202)
paullones, indirubins
hydroxyurea
cytarabine
antifolates
5-fluorouracil
6-mercaptopurine
Plk1
PD0166285
DNA synthesis
G2
Vinca alkaloids*
taxol/taxotere
halichondrin*
spongistatin*
rhizoxin*
cryptophycin
sarcodictyin
eleutherobin
epothilones
discodermolide
D-24851 ?
dolastatin*
combretastatin*
CDC25
FK317
HMGA
S
CDK1
Wee1
camptothecin
topoisomerase I
Aurora
Pin1
M
tubulin polymerisation/ depolymerisation
podophyllotoxin,doxorubicin
etoposide, mitoxantrone
topoisomerase II
CDK2
(R)-roscovitine (CYC202)
paullones, indirubins
Cdc7
CDK4
kinesin Eg5
ODC/SAMDC
GSK-3
flavopiridol
G1
Pin1
actin
polyamine analogues
AhR
MEK1/Erk-1/2
monastrol
paullones, indirubins
Raf
ROCK
G0
DF203
farnesyl transferase
tyrosine kinases
cytochalasins
latrunculin A
scytophycins
dolastatin 11
jasplakinolide
PD98059, U0126
BAY-43-9006
Y-27632
R115777
SCH66336
gleevec
iressa
OSI774
PS-341 → proteasome
CT-2584 → choline kinase
rapamycin → mTOR/FRAP
bryostatin, PKC412 → PKC
geldanamycin, 17-AAG → HSP90
ATK, MAFP → cytosolic phospholipase A2
trichostatin, FK228 → histone deacetylase
hexadecylphosphocholine → phospholipase D
okadaic acid, fostreicin, calyculin A → phosphatases

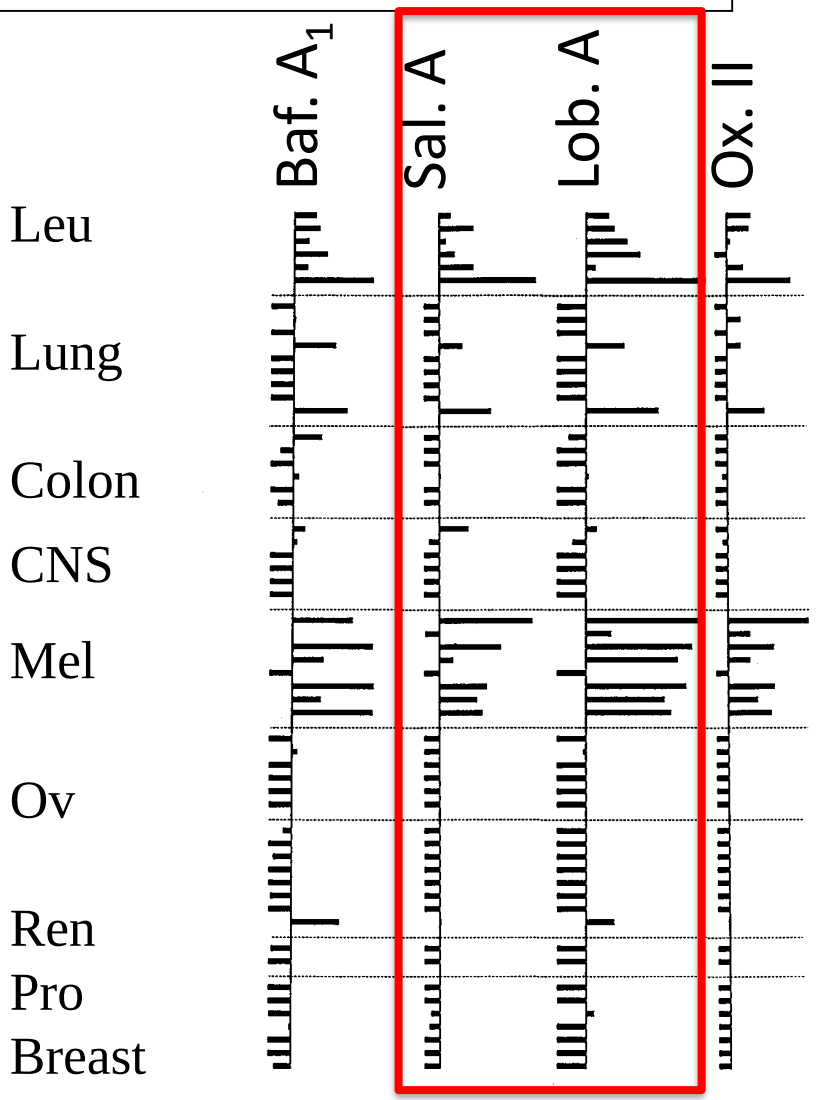
Targeted Mechanism of Action:

NCI 60 human tumour cell line

- Pattern of 60-cell selectivity is similar to that for bafilomycins and concanamycins

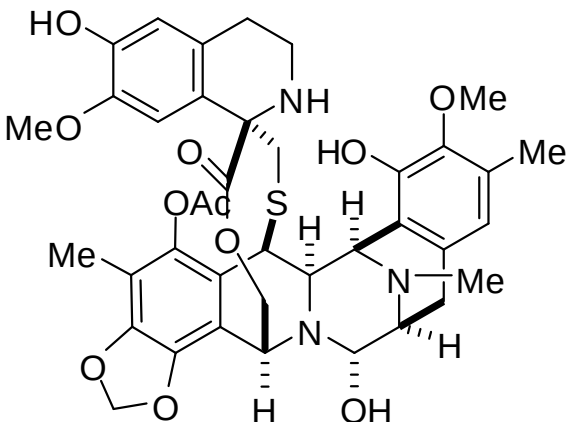
- Salicylihalamides, Lobatamides and Chondropsins inhibit *non fungal* vacuolar ATPase (V-ATPase) at low nanomolar levels

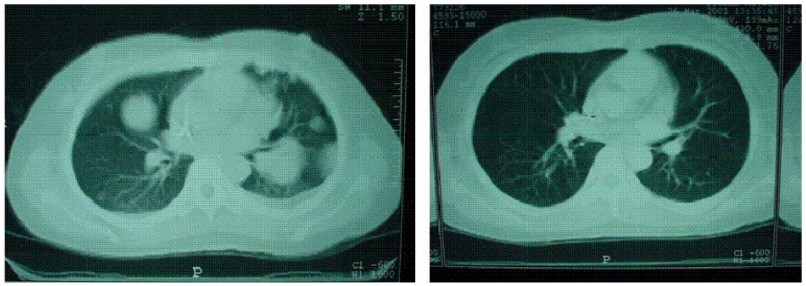
J. Pharmacol. Exp. Ther. **297**: 114, 2001.



Ecteinascidin-743
Yondelis/Trabectidin (Pharmamar)
Soft Tissue Carcinoma and Ovarian cancer

Ecteinascidia turbinata.





Marine Natural Products and Related Compounds in Clinical and Advanced Preclinical Trials

Table 1. Status of Marine-Derived Natural Products in Clinical and Preclinical Trials

name	source	status (disease)	comment
didemnin B	*Tridemnum solidum*	Phase II (cancer)	dropped middle 90s
dolastatin 10	*Dolabella auricularia*(marine microbe derived;cyanophyte)	Phase I/II (cancer)	no further trials
girolline	*Pseudaxinyssa cantharella*	Phase I (cancer)	discontinued
bengamide	*Jaspis* sp.	Phase I (cancer)	licensed Novartis
cryptophycins	*Nostoc* sp. & *Dysidea arenaria*	Phase I (cancer)	licensed to Lilly
bryostatin 1	*Bugula neritina*	Phase II (cancer)	licensed to GPC Bio
dolastatin	*Dollabella*	Phase II (cancer)	melanoma, breast,
ecteinascidin	*Ecteinascidia turbinata*	Phase II/III (cancer)	licensed to J&J
aplidine	*Aplidium albicans*	Phase II (cancer)	
E7389 (Hali B)	***Lissodendoryx* sp**	**Phase I (cancer)**	**Eisai**
discodermolide	*Discodermia dissoluta*	Phase I (cancer)	licensed to Novartis
kahalalide F	*Eylsia rufescens/Bryopsis* sp.	Phase II (cancer)	licensed to PmMar
Spisulosine	*Spisula polynyma*	Phase I (cancer)	*Rho*-GTP inhibitor
HTI-286	*Cymbastella* sp	Phase II (cancer)	licensed to Wyeth
KRN-7000	*Agelas mauritianus*	Phase I (cancer)	
squalamine	*Squalus acanthias*	Phase II (cancer)	antiangiogenic
Laulimalide	*Cacospongia mycofijiensis*	preclinical (cancer)	
Curacin A	*Lyngbya majuscula*	preclinical (cancer)	
vitilevuamide	*Didemnum cucliferum* &*Polysyncraton lithostrotum*	preclinical (cancer)	
diazonamide	*Diazona angulata*	preclinical (cancer)	
eleutherobin	***Eleutherobia* sp.**	**preclinical (cancer)**	
sarcodictyin	*Sarcodictyon roseum*	preclinical (cancer)	
peloruside A	***Mycale hentscheli***	**preclinical (cancer)**	**Just licensed**
salicylihalimide	***Haliclona* sp.**	**preclinical (cancer)**	
thiocoraline	*Micromonospora marina*	preclinical (cancer)	
variolins	***Kirkpatrickia variolosa***	**preclinical (cancer)**	
dictyodendrins	*Dictyodendrilla verongiformis*	preclinical (cancer)	licensed to Taiho
manoalide	***Luffariaella variabilis***	**Phase II**	**discontinued**
IPL-576,092	*Petrosia contignata*	Phase II	licensed to Aventis
ziconotide	***Conus magus***	**Phase III pain**	**licensed to WL**
CGX-1160 plus	***Conus geographus, catus, victoriae***	**Phase I (pain)**	

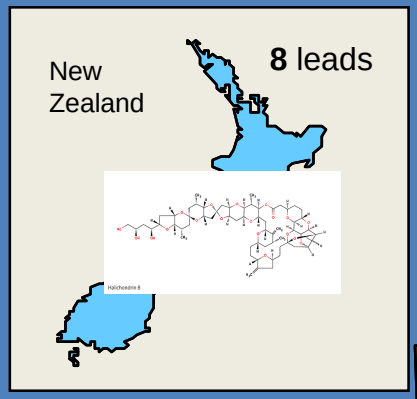
David J. Newman* , Gordon M. Cragg, Chris N Battershill 2010
Natural Products Branch, Developmental Therapeutics Program, NCI-Frederick, P.O. Box B, Frederick, Maryland 21702
see also Fortman and Sherman CC 2005

@ 30% from or have affinities with Australasian/Antarctic fauna

New Zealand and Australia NCI leads 1986-1992

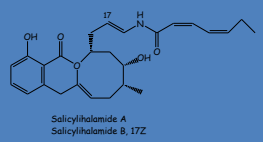
PreClinical Development:
Peloruside A
Variolins (Antarctic)

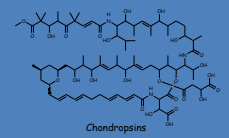
Eleutherobin
Lobotamide A
Chondropsins
Salicylihalamide A

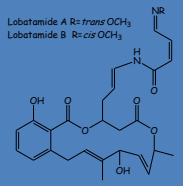


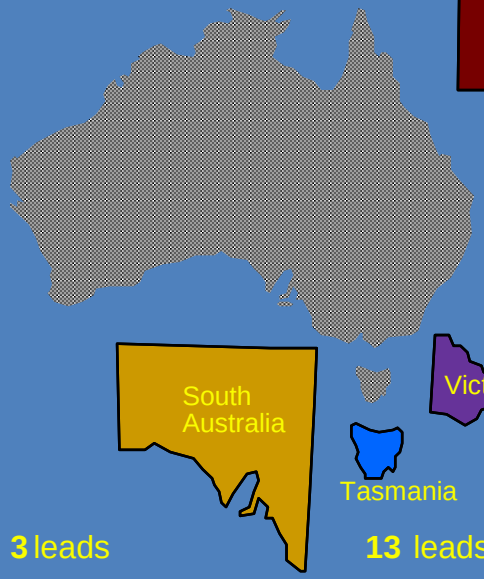
Halaven® eribulin

Eisai







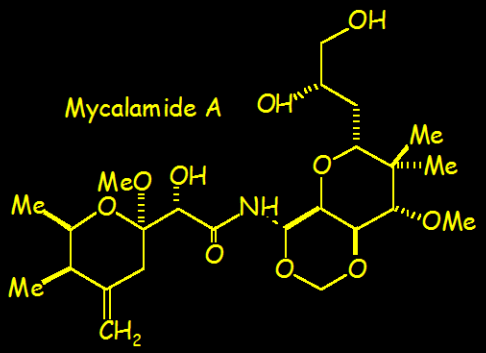


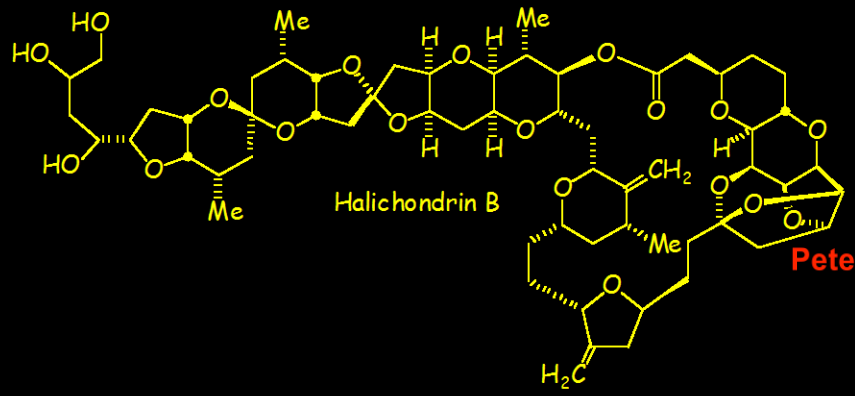
National Cancer Institute

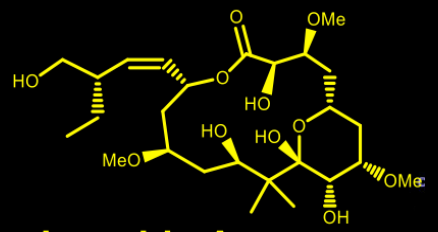
UC University of Canterbury
Te Whare Wānanga o Waitaha
Christchurch New Zealand

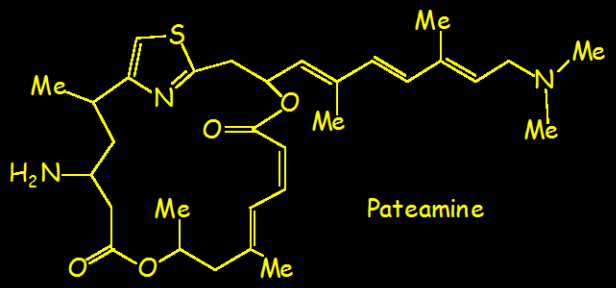
Australian Government
Australian Institute of Marine Science

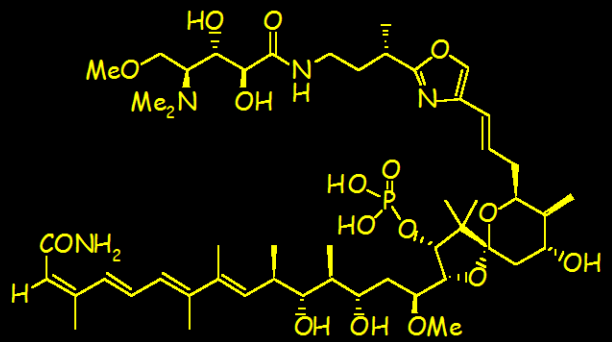
Some Bioactive NZ Marine Metabolites

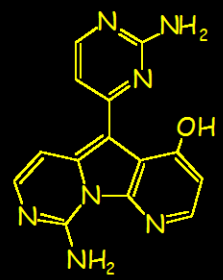


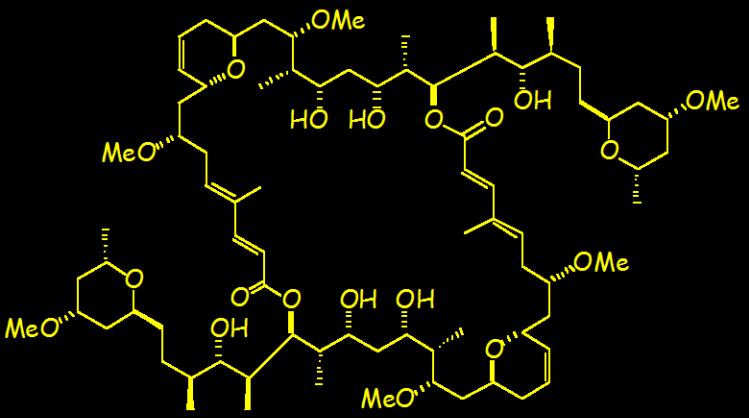


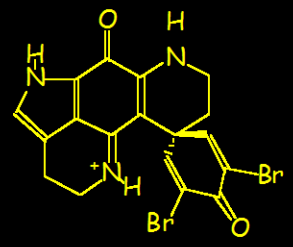


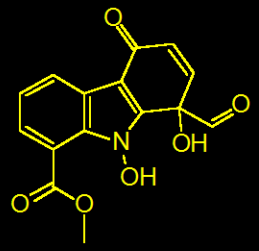












SUPPLY

- **Quantities Required**

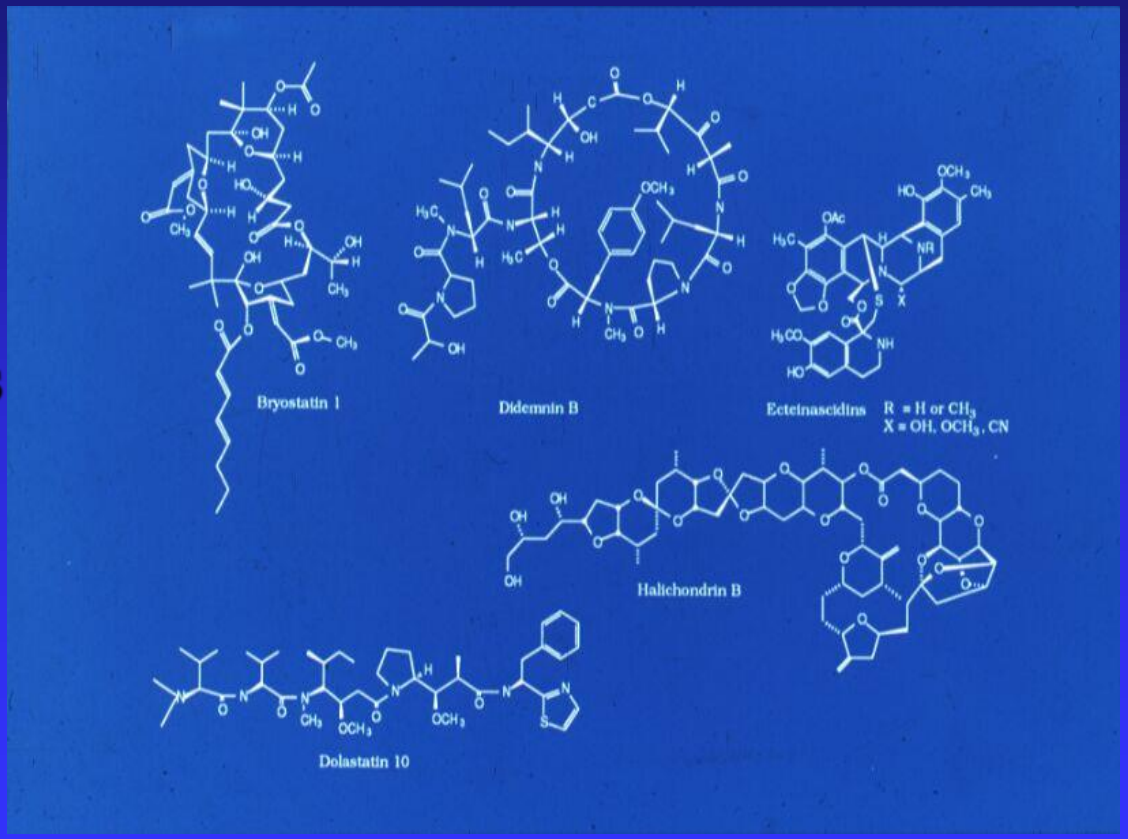
  - **1kg wet weight *Lissodendoryx* = 400ug Halichondrin B**
  - **450kg acorn worms = 1mg cephalostatin**
  - **1600 kg sea hares = 10mg dolastatin**
  - **2400 kg sponge = <1mg spongistatin**
  - **847 kg moray eel livers = .35mg ciguatoxin**
  - **22 tonnes of *Bugula neritina* for bryostatin I**
  - **1kg wet weight *Dysidea* = 3g Avarol**

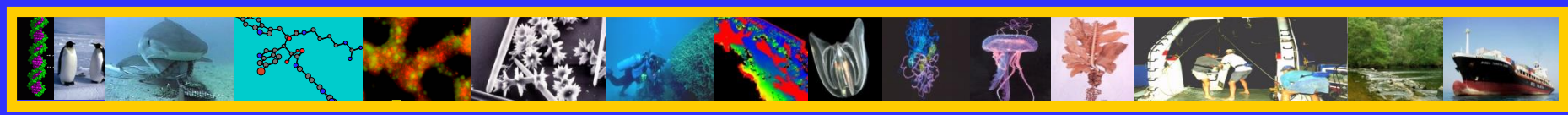
(Garson, 1994; Munro et al, 1998; Sipkema et al, 2005)

Supply options

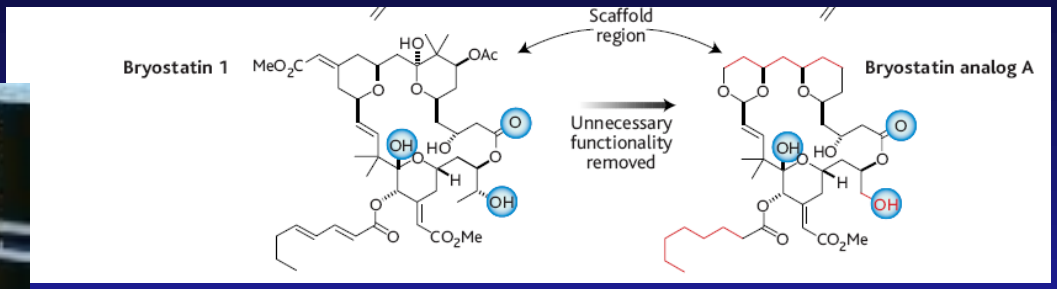
Guarantee sufficient and sustainable quantities

- wild harvest
- chemical synthesis
- aquaculture
- cell culture
- genomic splicing
- culture of symbionts



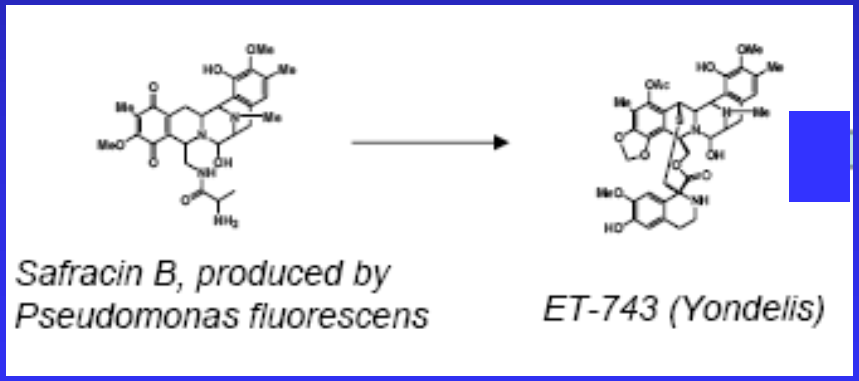


Aquaculture of drug leads



Taken from Paterson and Anderson, Science 21 October 2005

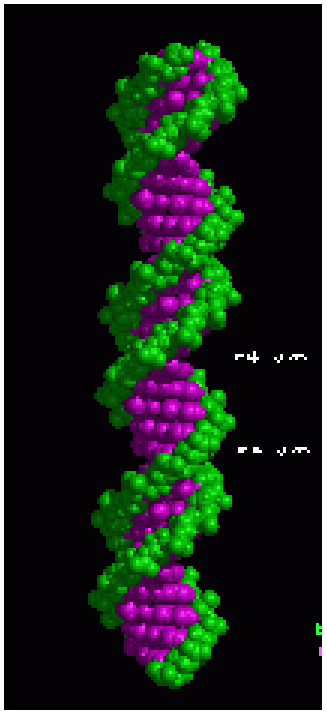
Bryostatin Analogue A
Total Synthesis



Yondelis (ET-743)
Hemi-Synthesis

Phar ma Mar
Soft Tissue Carcinoma active
Licensed Europe
September 2007

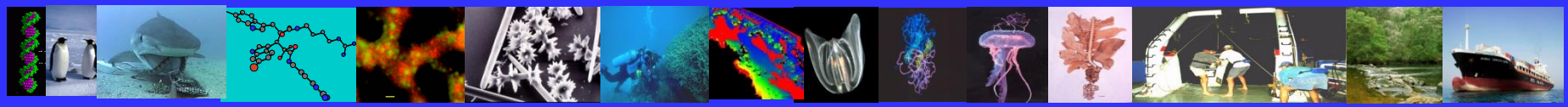
Supply Side Opportunity



Resupply from harvest, aquaculture, fermentation, gene expression or synthesis, attuned to the stage of development and scale needed

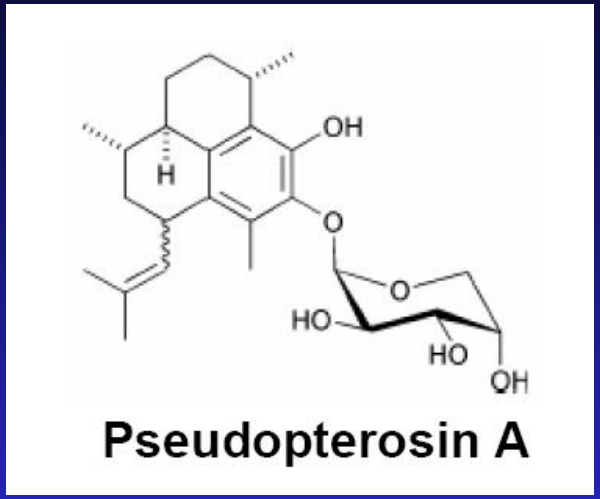
The natural non-drugs

- Functional foods ($US5b+/yr)
- Food additives ($US6b+/yr)
- Cosmetic’s, sunscreen’s ($US 7b+/yr)



Pseudopterosins

Pseudopterogorgia elisabethae

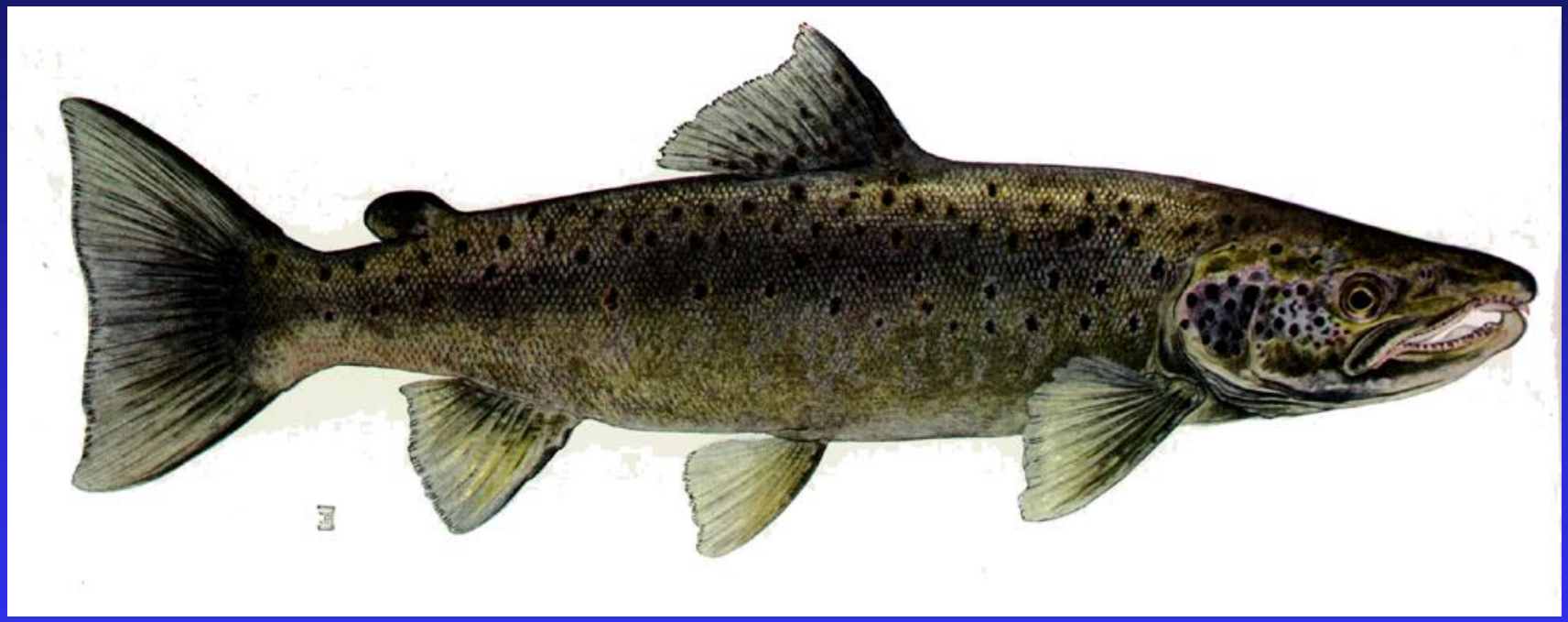


Anti-inflammatory added to skin care lotions

- $7 b US/yr
- Patented by University of California (1989)
- Resilience® Estee Lauder
- Wild harvest in Bahamas, also cultured

http://www.iflos.org/uploads/Fernando_de_la_Calle_-_MGR_PP.pdf

Animal Feeds, Fuel and Biologicals



Agriculture Applications of Marine Products

Sponge metabolites insecticidal against Lepidopteran pests:

- upto 95% growth inhibition of fifth instar larvae

Marine Natural Products with herbicidal and fungicidal activities:

- Novel chemistry
- Biodegradable
- No resistance to marine compounds

Marine Biotechnology:
Agricultural and Industrial Applications

Algal Biochar, Cosmetics, Food and Agri-Feeds

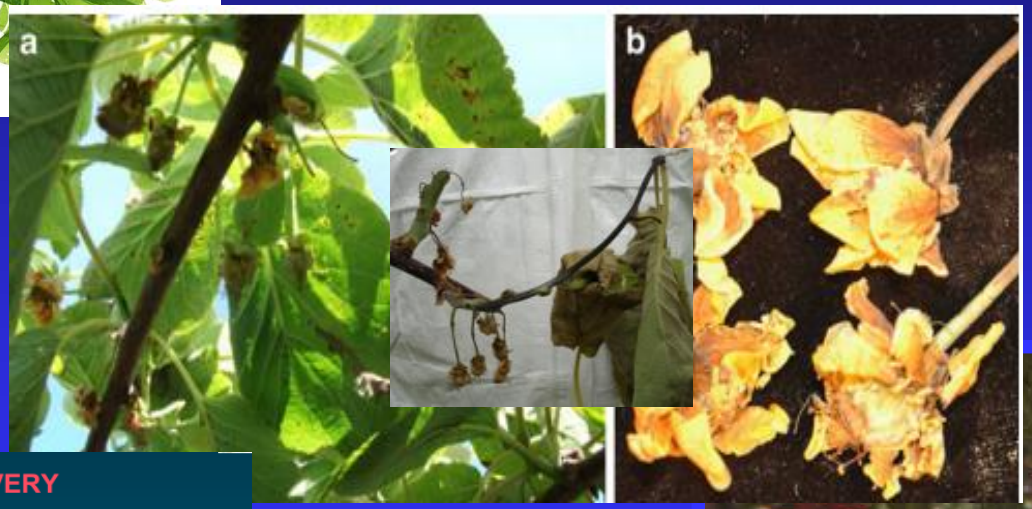
International By-Products Conference 187
April 1990, Anchorage, Alaska

USE OF MARINE BY-PRODUCTS ON AGRICULTURAL CROPS

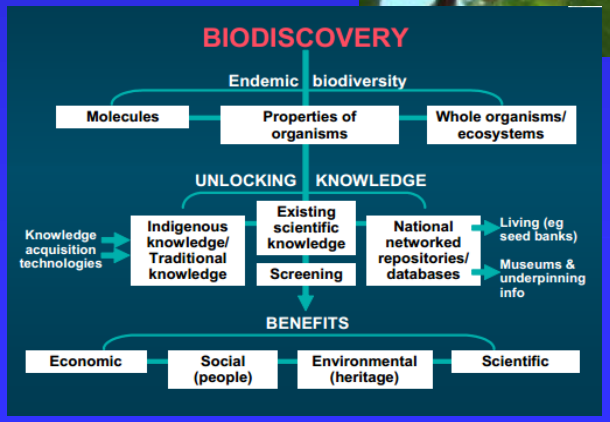
Bruce Wyatt
University of California Cooperative Extension
Santa Rosa, California

Glenn McGourty

Applied Biosciences



Ashleigh Browne,
MSc Student



Novel Agrichemicals – New Zealand

- *Pseudomonas syringae pv. Actinidiae* (Psa-V) have affected over 50% of kiwi fruit orchards world wide
- Cost to the $1b+ industry was over $500m, NZ alone
- Based on biomedicinal leads for other *Pseudomonas* pathogens (invoking a Quorum Sensing Modifying mode of action), leads have been discovered or the Kiwi Fruit Industry from Marine sources…

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THE UNIVERSITY OF WAIKATO

Plant & Food RESEARCH
RANGAHAU AHUMĀRA KAI

Zespri Kiwifruit

BIOMARINE BUSINESS CONVENTION

30-31 OCTOBER 2014

CASCAIS, PORTUGAL

Marine Bio-Resources… For a New Blue Economy

BIOTECH • FOOD & NUTRITION • HEALTH & PHARMA • COSMETICS • ENV^{T} & CLEANTECH

BioMarine

30-31 OCTOBER 2014
CASCAIS, PORTUGAL

3. GROWTH POTENTIAL

GLOBAL TRENDS

THE MARKET FOR BIOMARINE ECONOMY
IS WORTH $176 BILLION

BUT...

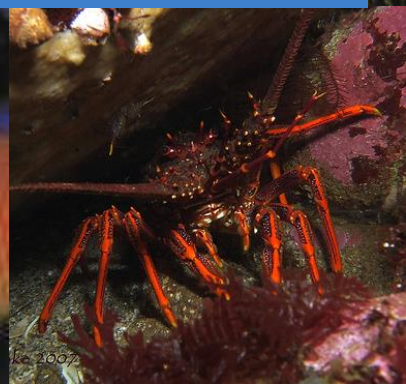
	Estimate for 2020
Marine biotechnologies represent only 8% of the total biotech market	15%
Marine bioplastic is less than 1% of the total biomaterial market	10%
Marine bio energies represent 1.5 % of the energy market	3%
Marine renewable energies are less than 8% of the energy market	17%
Aquaculture represents 12% of the global protein market	35%
Blue chemistry represents only 6% of the chemicals market	15%
Marine cosmetics account only for 13% of the cosmetics market	30%
Marine nutraceuticals represent 32 % of the nutraceuticals market	50%
Marine ingredients represent 38% of natural compounds market	55%



Tairāwhiti Potential

- Mixture of neritic, and offshore species
- Mixture of cool temperate to sub tropical species
- Never examined for medicinal leads…….





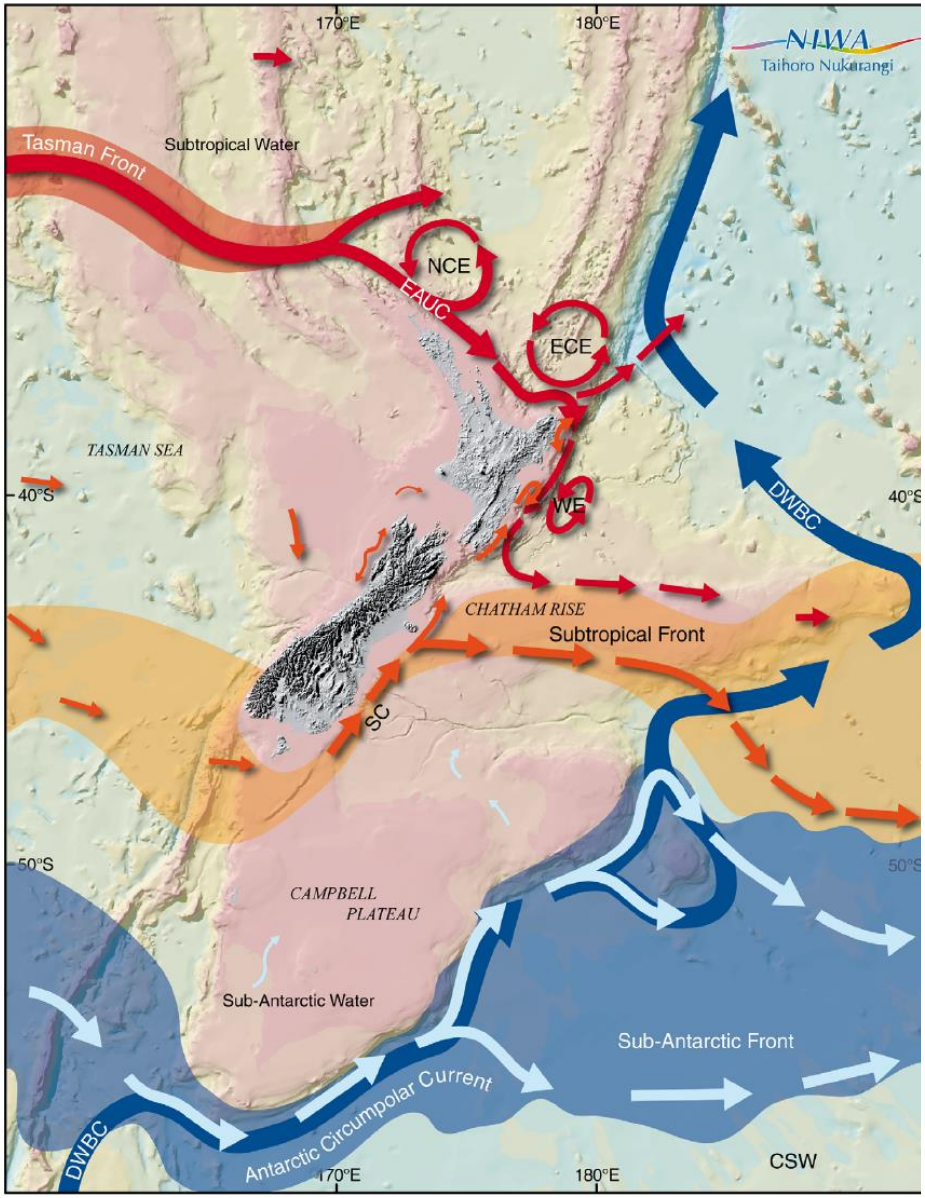
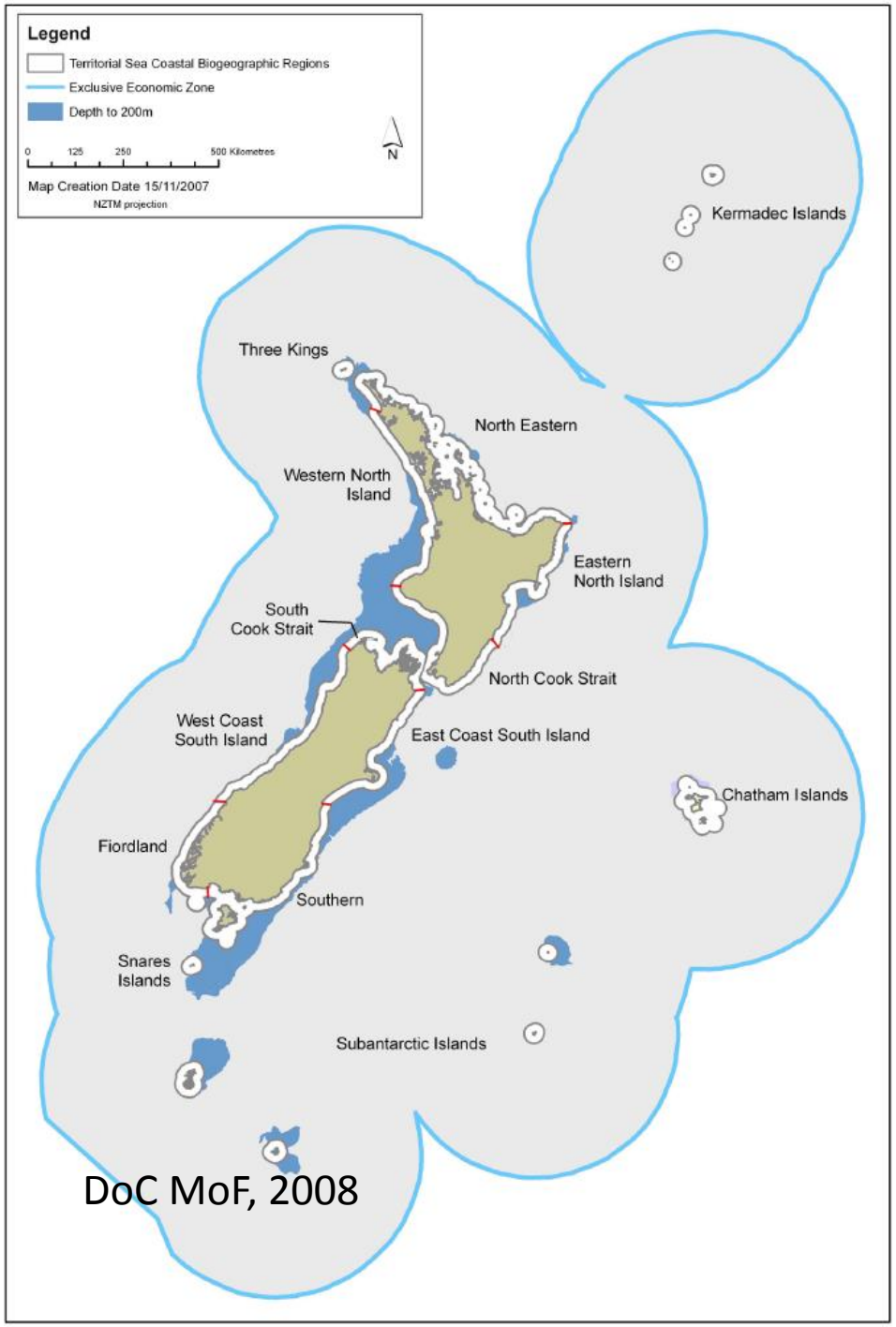


Figure 2. Circulation in the New Zealand region, showing the major fronts and eddy features. EAUC, East Auckland Current; ECC, Cape Current; NCC, North Cape Current; SC, Southland Current; WE, Wairarapa Eddy; DWBC, Deep Western Boundary Current.
doi:10.1371/journal.pone.0010905.g002



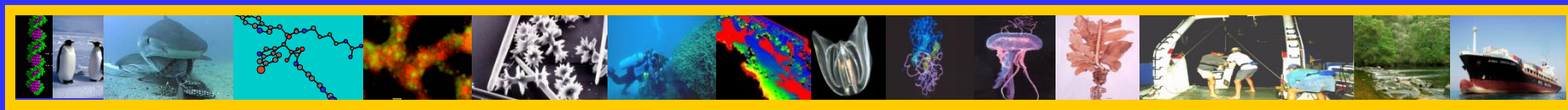
DoC MoF, 2008

The Loss of Marine Biodiversity

Sediment, Invasions, Pollution

against the backdrop of a

Changing Climate



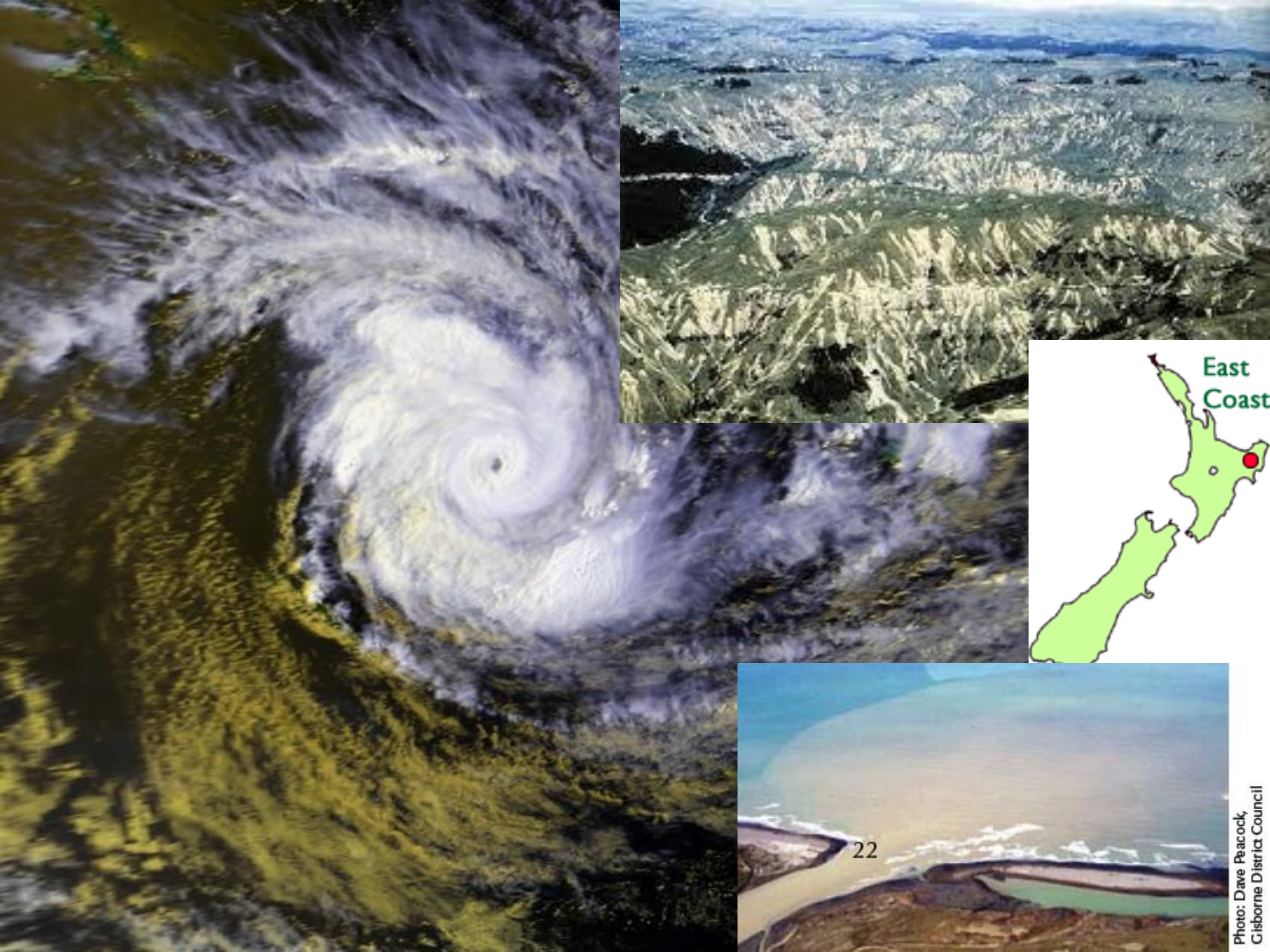


Photo: Dave Peacock, Gisborne District Council

Muddy rivers:

Cyclone Bola: 1mt/day
Waiapaoa: 15mt/yr
Waiapu: 35mt/yr

= 140m m^2 @25cm depth of soil
Or 80 dairy farms/yr

International Partnerships in waiting

PHARMASEA

中国科学院烟台海岸带研究所
YANTAI INSTITUTE OF COASTAL ZONE RESEARCH, CAS
2006

NATIONAL CANCER INSTITUTE

MAURICE WILKINS CENTRE
FOR MOLECULAR BIODISCOVERY

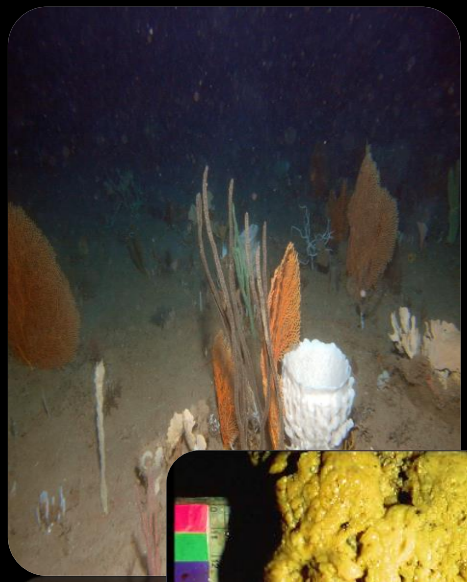
SOUTH CHINA SEA INSTITUTE OF OCEANOLOGY
中国科学院南海海洋研究所

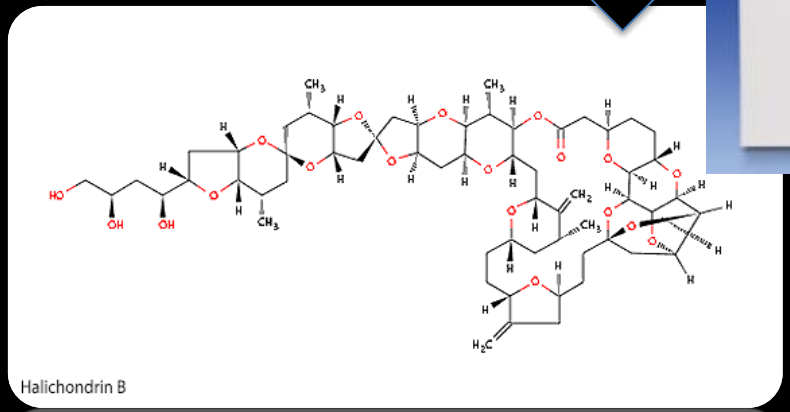
SCRIPPS INSTITUTION OF OCEANOGRAPHY
UCSD

SIMM

So, what does a sponge, a crab and cancer have in common?

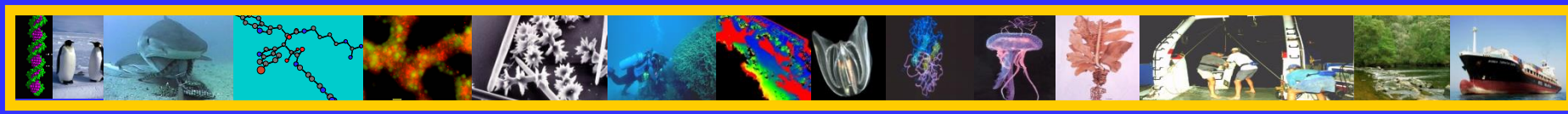
Smart lead discovery using nature!

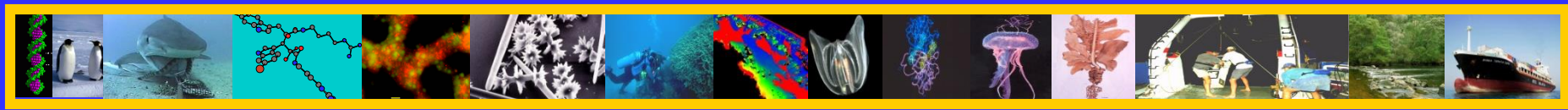


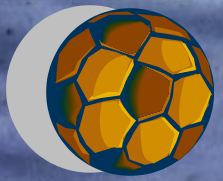
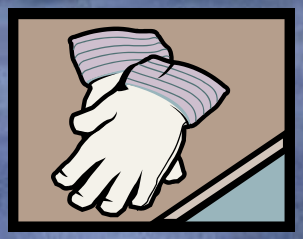


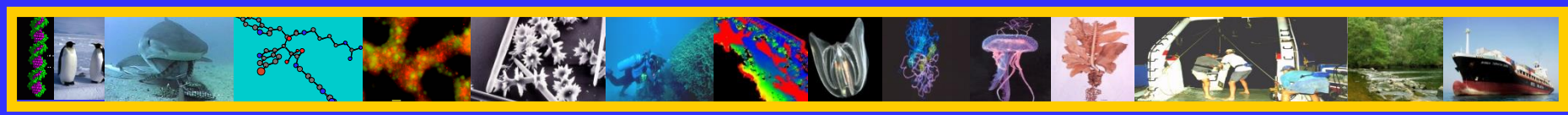
Acknowledgements

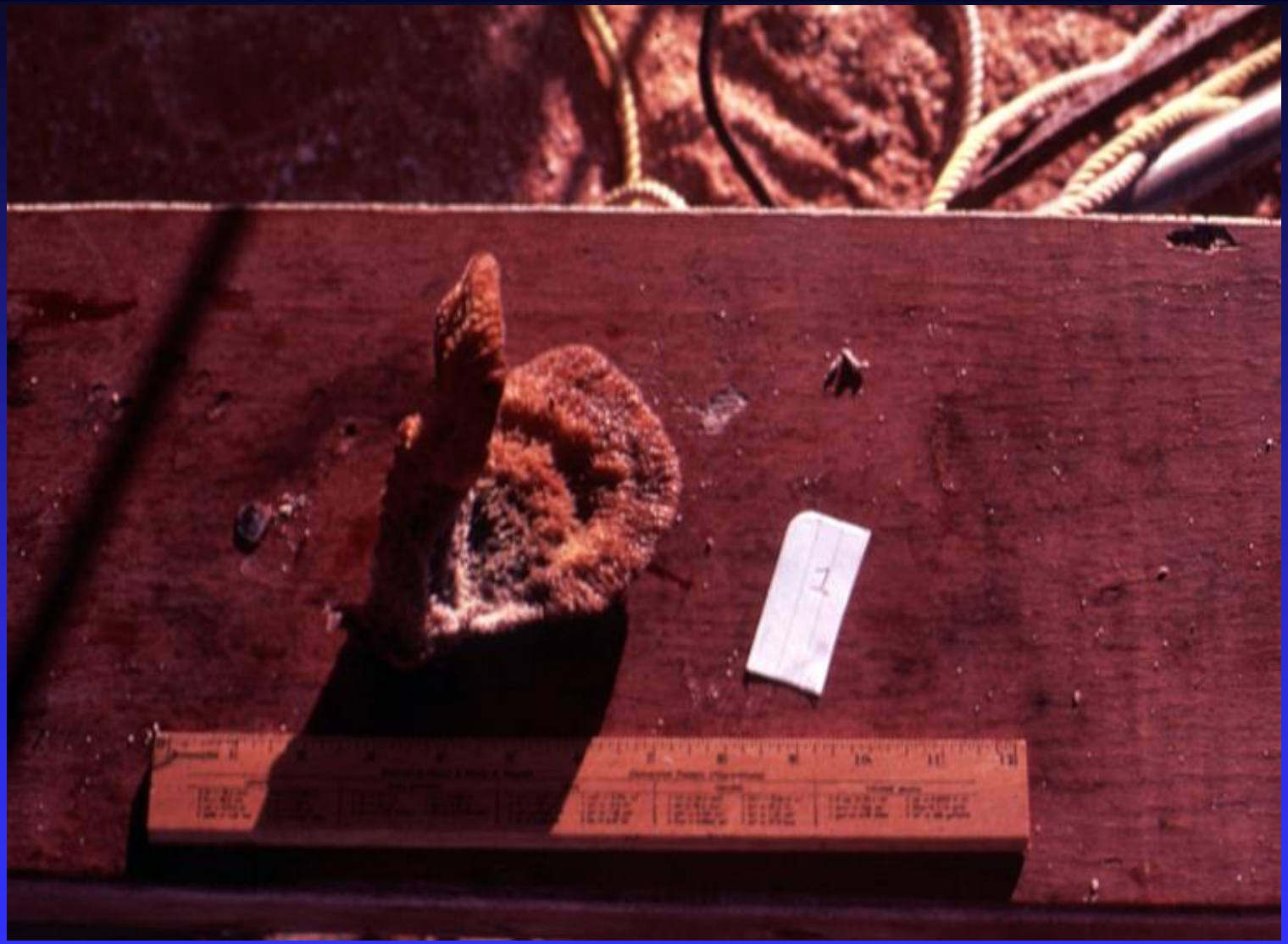
- Hikurangi Enterprises
- Tangata Whenua, Tairāwhiti
- National Cancer Institute
- University of Canterbury
- Australian Institute of Marine Science

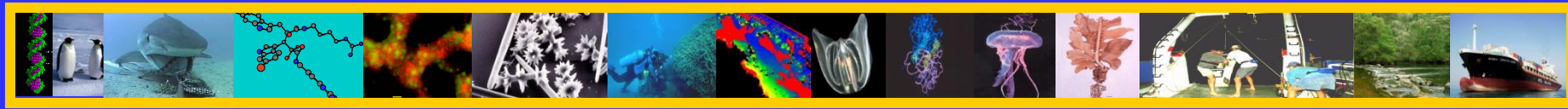




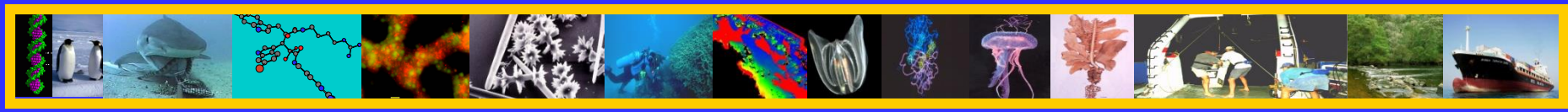
- Play 
- Protection 
- Getting High 
- Biomedicinal benefits 



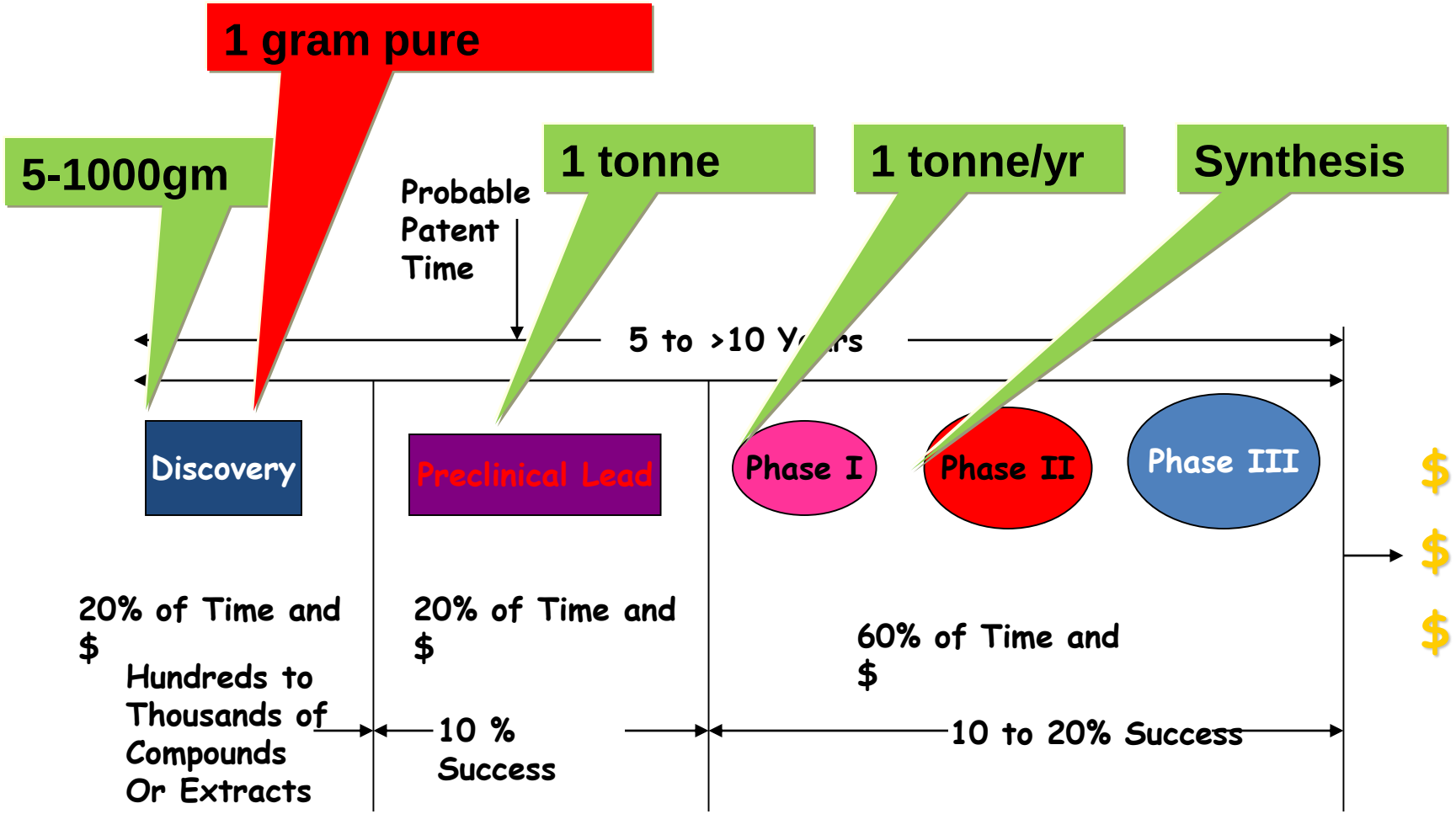




Kia ora!

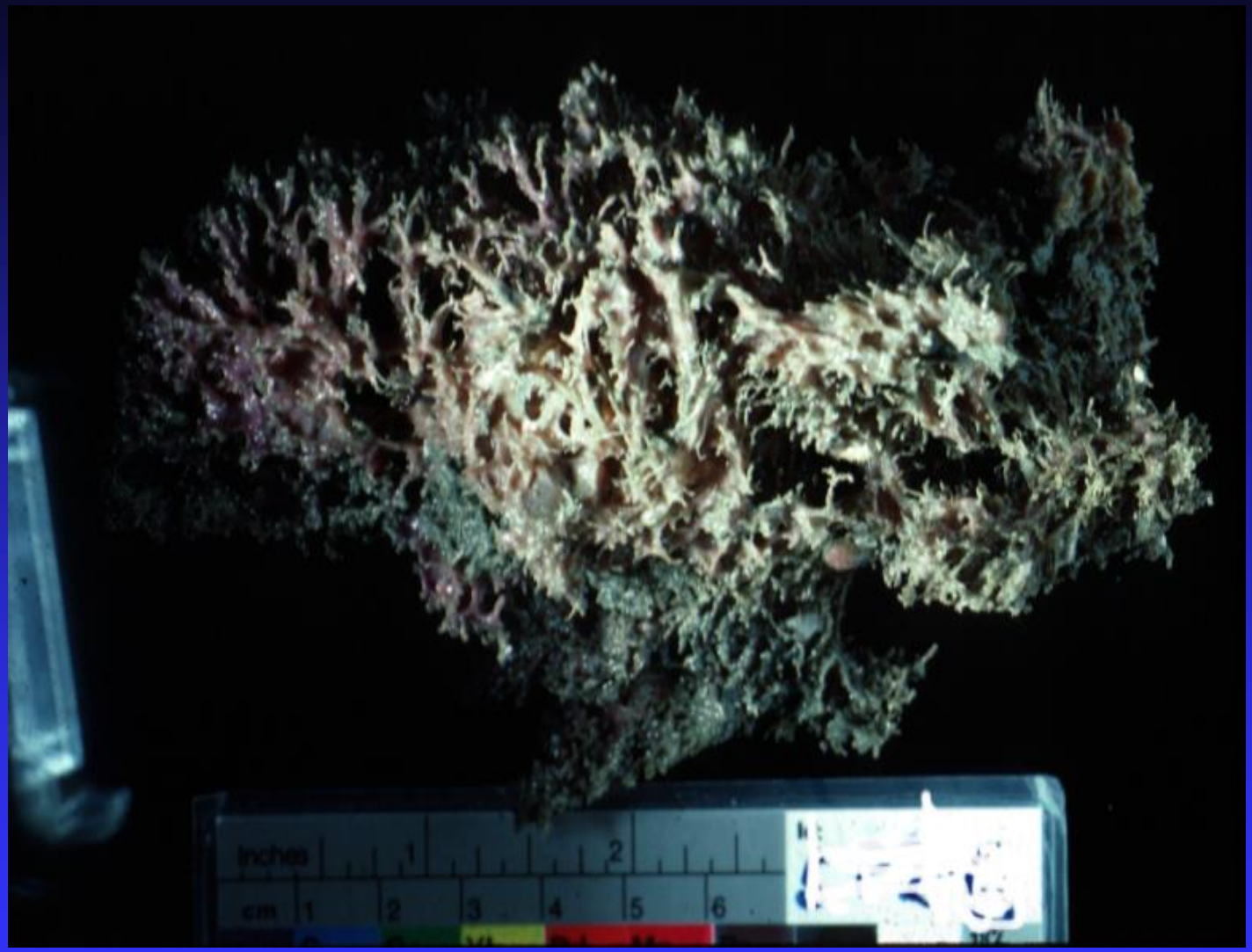


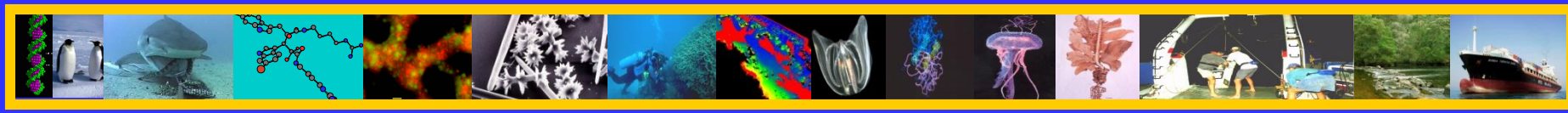
Phases of Drug Development

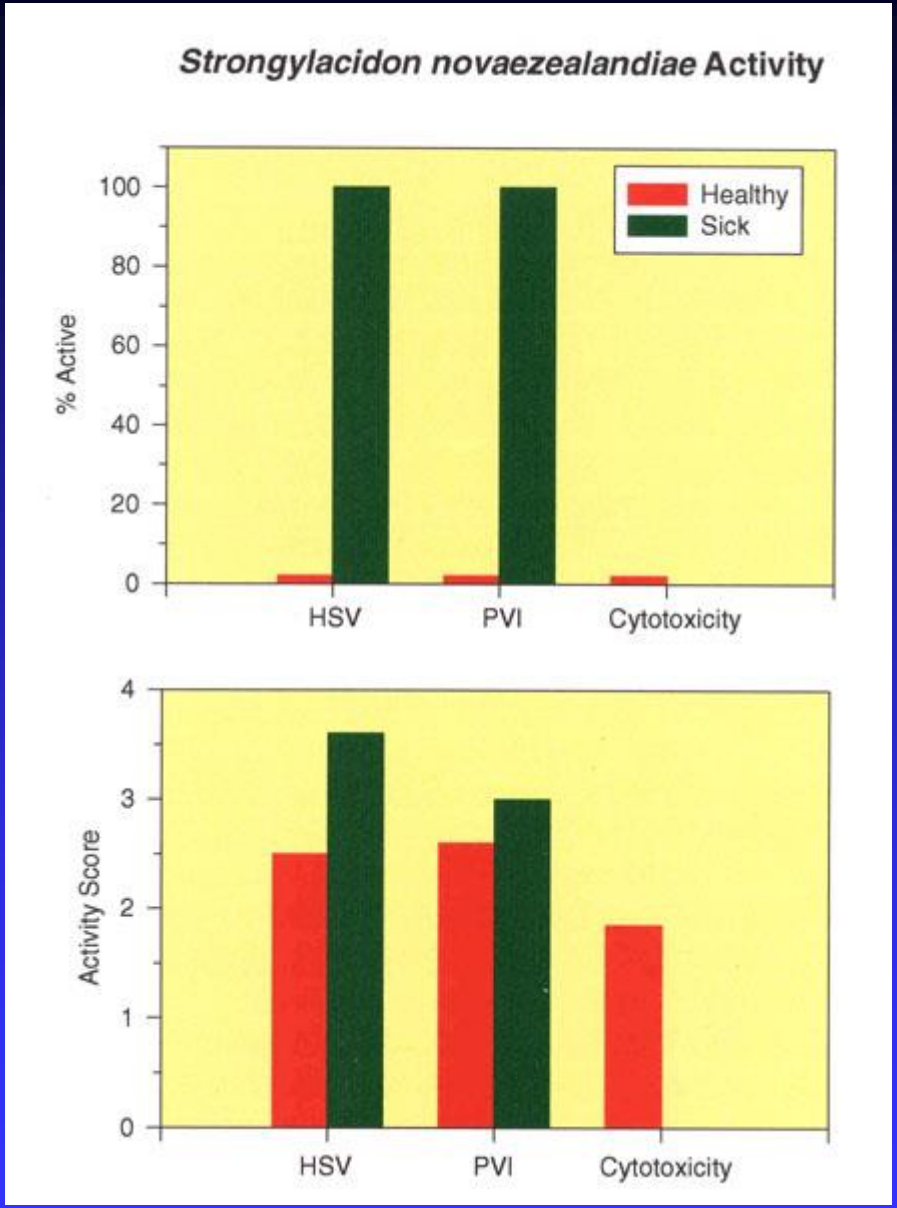


LEAD ID	MOA, ADME etc	3-7yrs
1 month-3yrs	3-5yrs	5>1
10,000 >10	10> 5	

Newman 2008


Inches
1
2
cm
1
2
3
4
5
6




Strongylacidon novaezealandiae Activity
% Active
100
80
60
40
20
0
Healthy
Sick
HSV
PVI
Cytotoxicity
Activity Score
4
3
2
1
0
HSV
PVI
Cytotoxicity