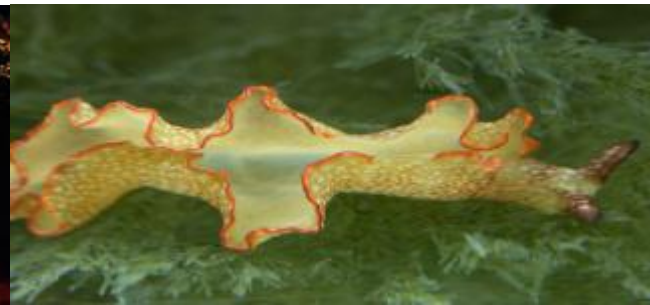




Marine Resources & Medicine

Yondelis[®] : A successful, high-value application of marine resources





1. PharmaMar

A Spanish biopharmaceutical company: leader in developing anticancer compounds of marine origin

2. Blue Biotechnology

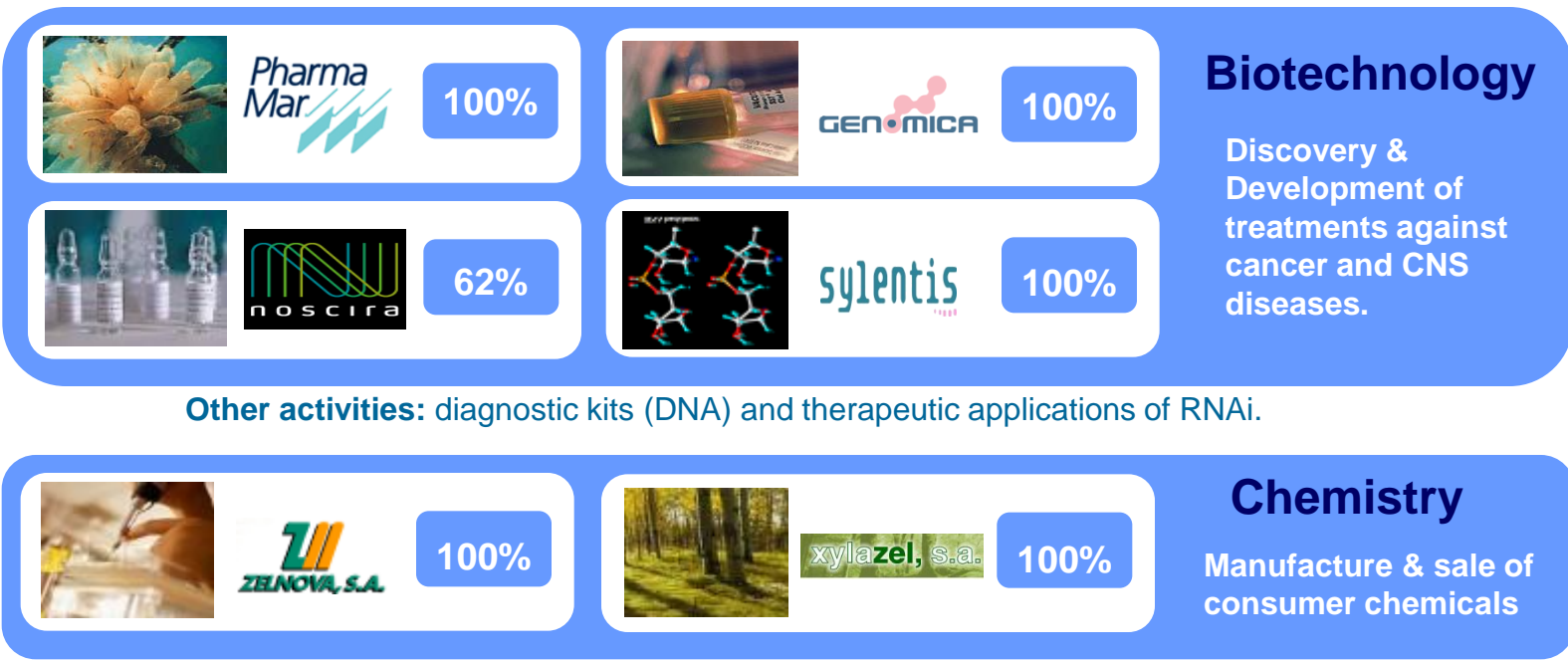
The potential of marine resources for fighting disease.

3. A success story: Yondelis

A successful, high-value application of marine resources



Zeltia



Founded: 1986
HQ: Madrid (Spain)



- ✓ **Unique bio-pharmaceutical company** (€450 M, 20 years).
- ✓ **Unique library** of marine organisms (> 120.000 samples).
- ✓ **PharmaMar: the first company in the world** to develop and market a drug of marine origin to fight cancer (Yondelis®).

110
Patent families

450
Million €
invested in
R&D

120.000
Marine
samples in the
collection

700
New chemical
entities
discovered

>70
Countries
where Yondelis
is sold

300
Employees

5
Compounds
in clinical
development

THERAPEUTIC AREA	INDICATION	CLINICAL DEVELOPMENT				
		PHASE I	PHASE II	PHASE III	REGULATORY	MARKET
ONCOLOGY						
Yondelis® <i>Trabectedin</i>	Soft Tissue Sarcoma(STS) – 2nd/3rd line					
	Relapsed Ovarian cancer (Yondelis+Doxil)- 2nd/3rd line					
	STS with Translocations – 1st line					
Aplidin® <i>Plitidepsin</i>	Multiple Myeloma					<i>Aplidium albicans</i>
	T-cell lymphoma - non cutaneous					
Zalypsis®	Multiple Myeloma					
	Ewing Sarcoma					
PM01183	Pancreatic cancer					
	Ovarian Cancer (Resistant)					
	Breast cancer					
	Leukemia					
	Combination Studies					
PM060184	Solid tumours					
						<i>Synthetic</i>

Life originated from the sea

34 of 37 phyla of life in sea
(compared to only 17 on land)

Macro-organisms
(invertebrates)



Micro-organisms
(bacteria)



Environmental DNA
(metagenomics)



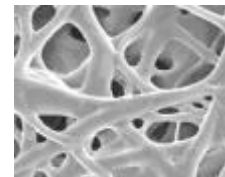
Sea has higher biodiversity than land

- ⇒ Higher chemical diversity
- ⇒ Many potential applications



Medicines &
Research Tools

Personal care
& Nutrition



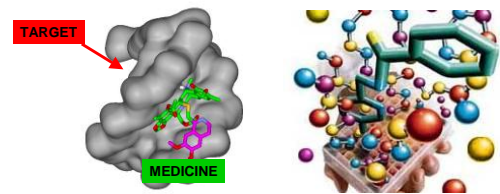
Biomaterials

“One of most exciting technology sectors”.

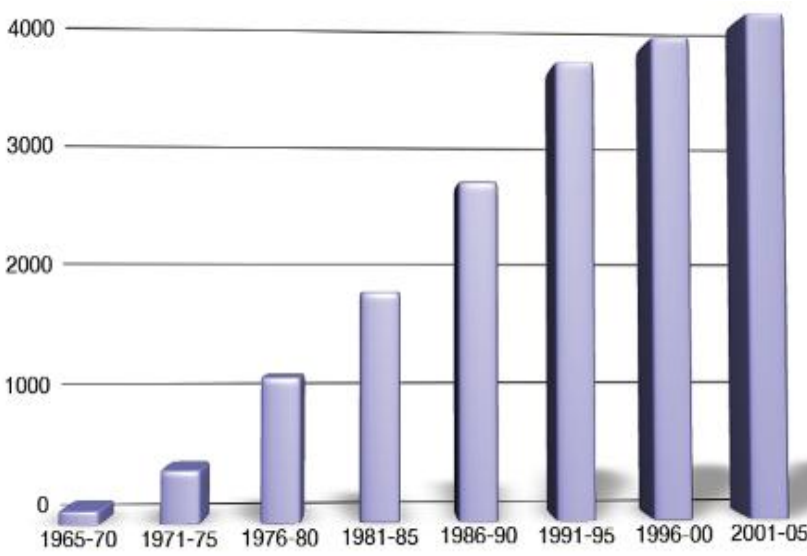
Blue Biotechnology = Marine and aquatic applications of biotechnology.



Nature:
> 50% of the 1355 new chemical entities that have reached the market over the last 30 years **have origins in nature.**



Number of marine natural products reported (last 40 years)

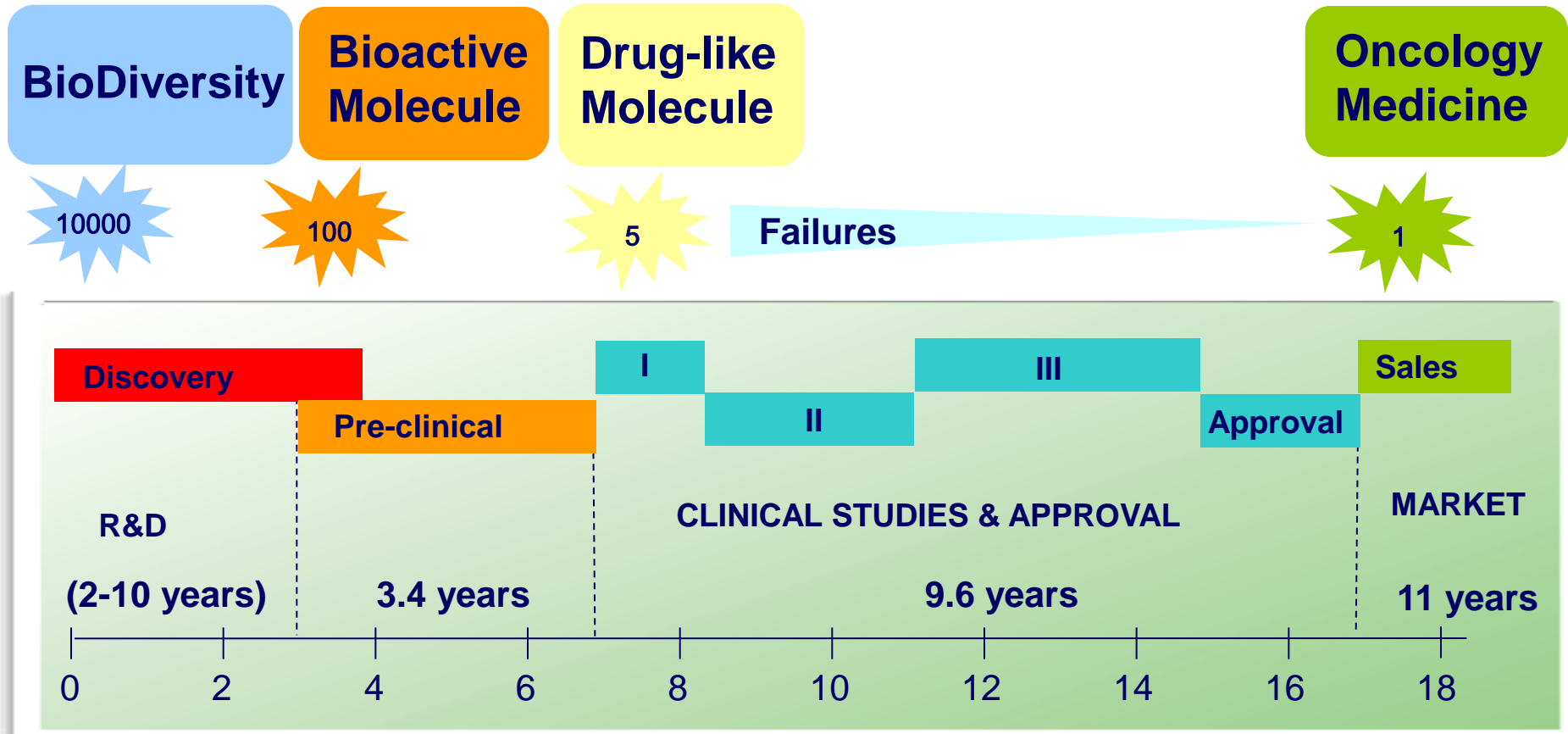


Marine Biodiversity:
 Increasing numbers of “**exciting leads**”.... but marine drug discovery remains largely an academic pursuit.

- ✓ **Structural Diversity**
- ✓ **Potency** (inherent activity)
- ✓ **Largely** unexplored
- ✓ **Evolution** against challenges
- x **Sourcing** (political hurdles)
- x **Legal uncertainty** (patents)
- x **Technological**
- x **Scientific** (isolation, synthesis)



The Drug Development Process



Paclitael (TAXOL) : > 20 years from Structural Determination (Bioactive molecule) to FDA approval

Cost ~ \$ 802 mill.* Only 2 in 5 Marketed Drugs recover costs

BioDiversity

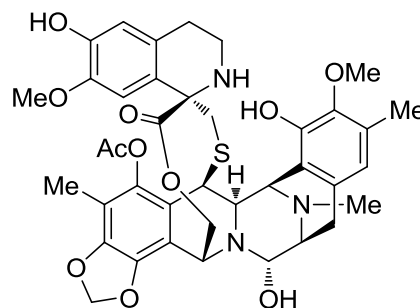
Ecteinascidia turbinata:
small soft bodied marine
animal (**sea squirt**).

Yondelis

Oncology
Medicine



Bioactive Molecule



Lives in shallow coastal waters (0-15m)
in the **Caribbean** & temperate regions of
the **Atlantic** & **Mediterranean**.

Approved for ST
Sarcoma (July 2007)
& platinum-sensitive
ovarian cancer
(September 2009).

Authorized in **73**
countries, 39 outside
the European
Economic Area.



2001: Co-development Agreement **CENTOCOR**
ORTHO BIOTECH (J&J) outside Europe.

2009: Licence **TAIHO PHARMACEUTICAL** Japan.

Advantages: Only method at start of development !!

1 Tonne = 1g ET-743
Low yielding !!

Sea farms

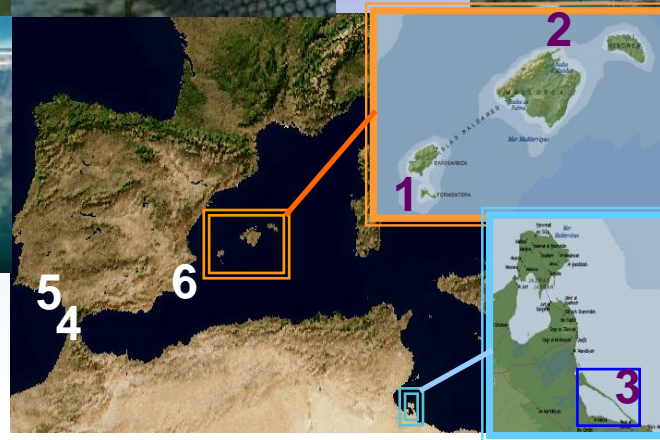


Artificial facilities (tanks containing sea-water)



Production Areas:
included the
Atlantic coast:

- Cadiz (4)
- Huelva (5)



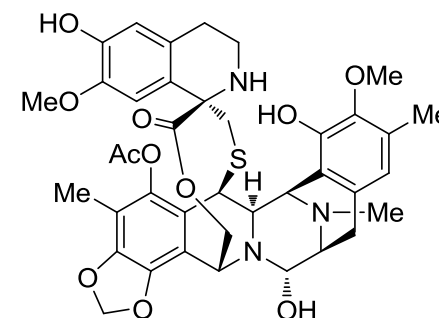
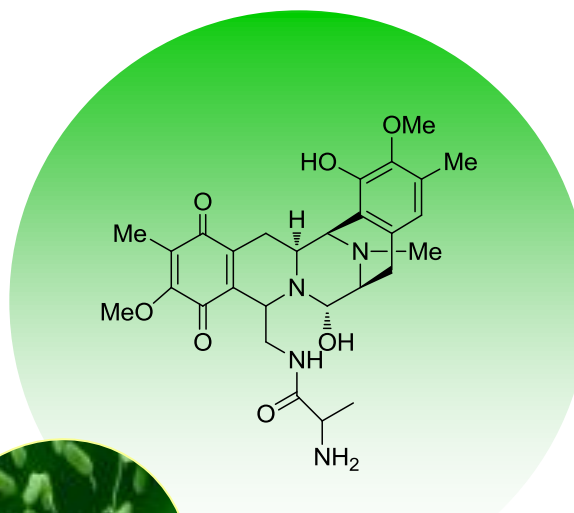
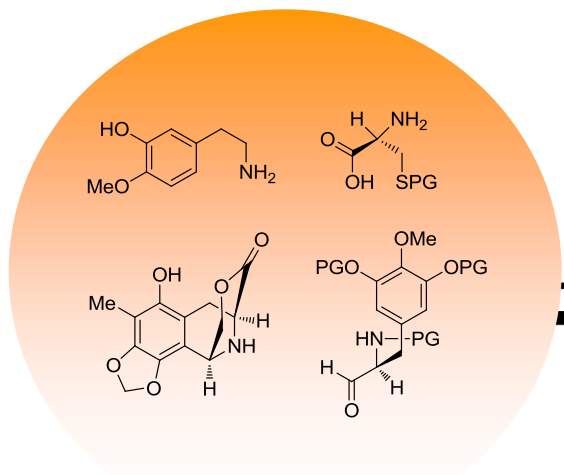
Limitations

- Seasonal (May – Oct)
- Cost & security of supply
- Low yield & variable quality
- Complex extraction & purification
- Logistics (transport of frozen organism)

Total Synthesis (1996), > 50 steps



0.1-1g



Pseudomonas fluorescens



Hemi-synthesis



> 100g

Current Industrial
Process for GMP Yondelis®
manufacture *

- 2000 - First large-scale fermentation
- 2001 - Commercial route defined (laboratory scale)
- 2002 - First synthetic batch [2003 – end of *mariculture*]
- 2005 - Synthetic material used for first time in clinical study

* Cuevas & Francesch. *Nat. Prod. Rep.* 2009

Yondelis® Development Timeline

1



Marine Organism

E. Turbinata

2



Bioactive Molecule

ET-743

3



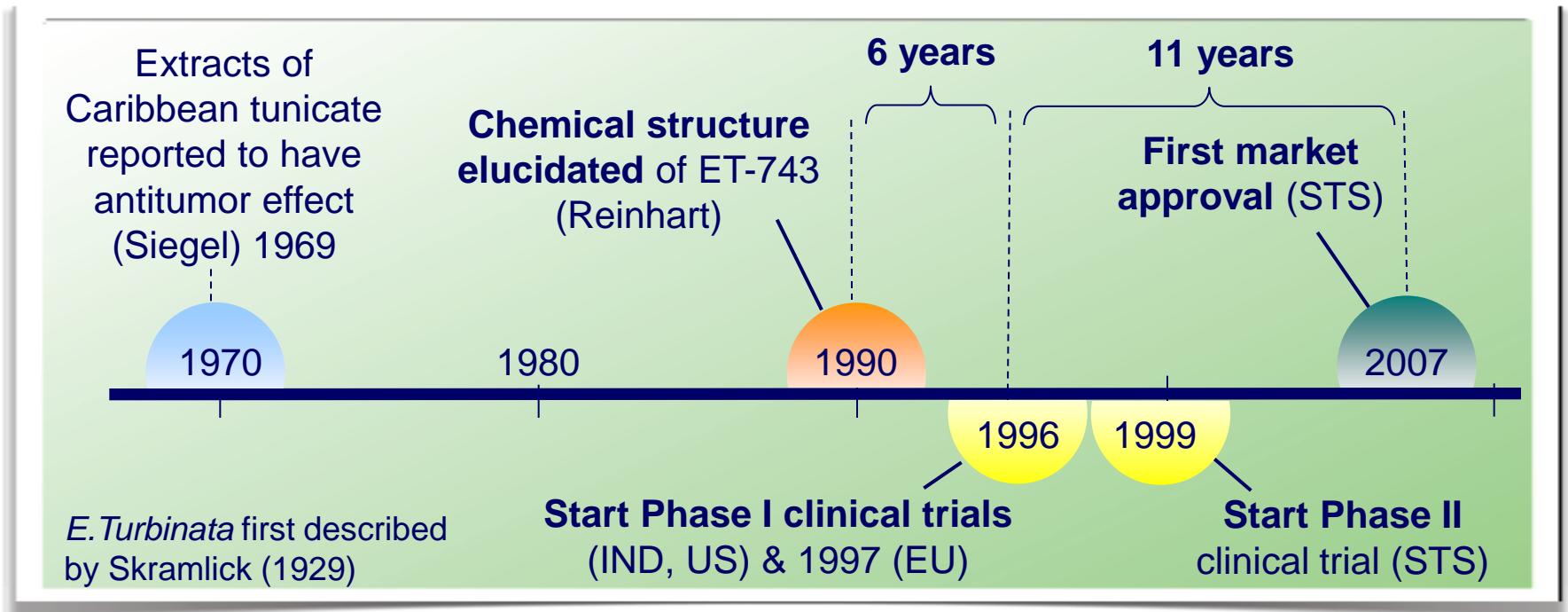
Drug

Yondelis®

4



Market



2005 - Synthetic material used for first time in clinical study.

- ❑ **Source:** access to marine samples & freedom to conduct Marine Research
 - Legal Certainty: CBD/UNCLOS and IP protection
- ❑ **Screening:** technical problems, “isolate & then test” or “test & then isolate”
- ❑ **Science:** knowledge generation requires excellent science (& scientists !)
- ❑ **The Supply Problem:** Key limitation, new technologies required
 - Recollection
 - Aquaculture (viable for food products - in its infancy for high value products)
 - Culture/fermentation of marine organisms
 - Chemical synthesis/semi-synthesis
- ❑ **Academia- Industry partnerships:** (currently largely academic)
- ❑ **Multidisciplinary research centres** for Marine Drug Discovery
- ❑ **Ecology:** to understand the natural function of marine metabolites
- ❑ **Awareness & Visibility**

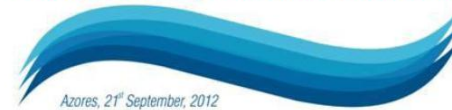
Marine Biodiversity has enormous potential !!

CBD = Convention on Biological Diversity (in force, December 1993)
UNCLOS = United Nations Convention on the Law of the Sea (in force, Nov 1994)



ATLANTIC FORUM

Coastal and Deep Sea Natural Resources



Marine Resources & Medicine



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