

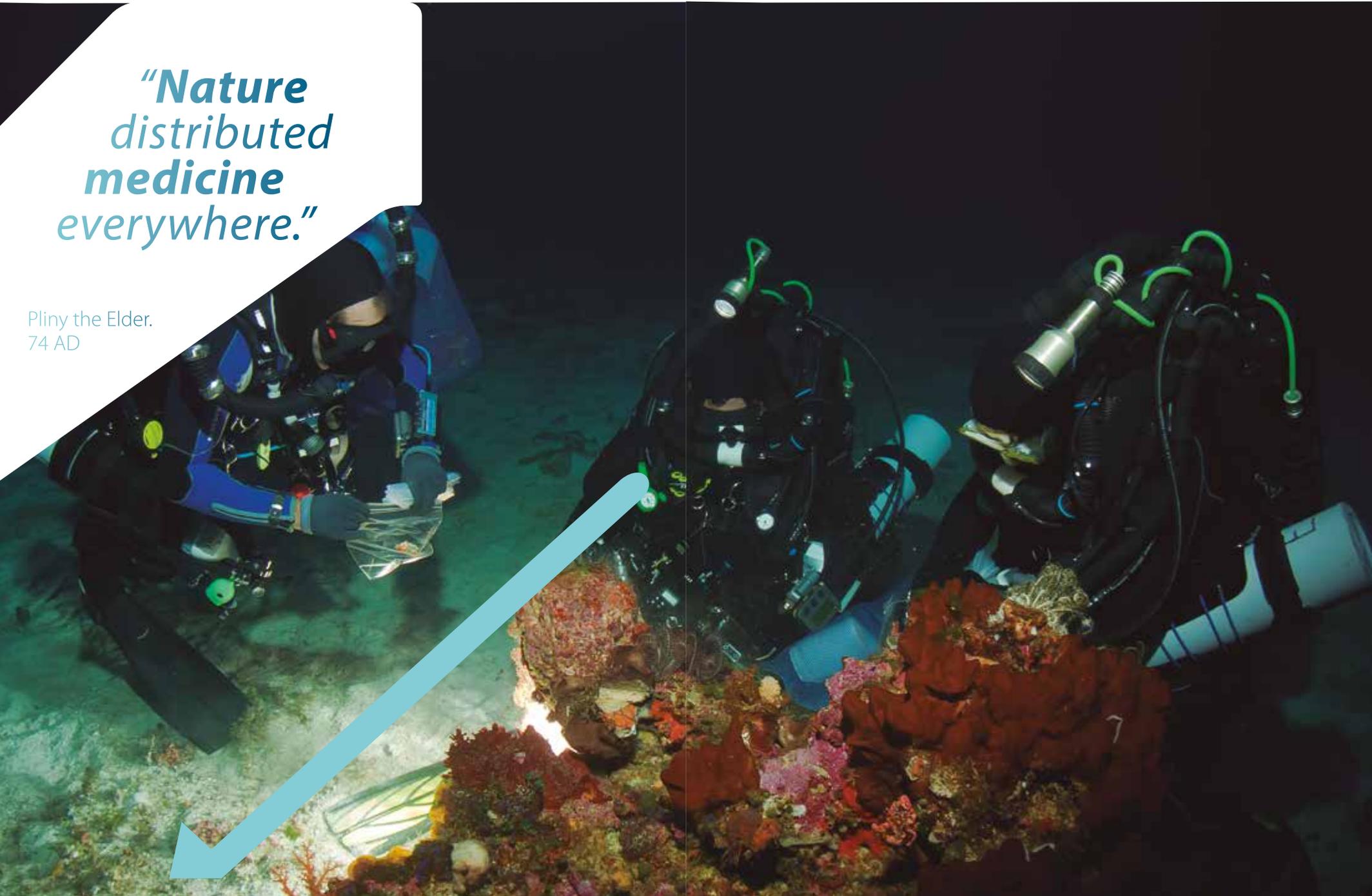


Marine- inspired **Oncology**



**“Nature
distributed
medicine
everywhere.”**

Pliny the Elder.
74 AD



Leaders in marine biotechnology



Group
structure

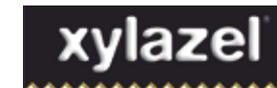


Oncology Company

Other business

Biopharmaceutical

Chemical



PharmaMar is a global biopharmaceutical company, focused on oncology and committed to research and development which takes inspiration from the sea to discover molecules with antitumor activity. It is an integrated company that seeks innovative products to provide healthcare professionals with new tools to treat cancer. Its commitment to patients and to research has made it a world leader in the discovery of antitumor drugs of marine origin.

With subsidiaries in Europe and the United States, PharmaMar has an important pipeline of drug candi-

dates and a robust R&D oncology program. It develops and commercializes Yondelis® in Europe and has other clinical-stage programs under development for several types of solid and hematological cancers, lurbinectedin (PM1183), plitidepsin, and PM184.

PharmaMar fully owns other companies: GENOMICA, Spain's leading molecular diagnostics company; Sylentis, dedicated to researching therapeutic applications of gene silencing (RNAi); and two other chemical enterprises, Zelnova Zeltia and Xylazel.

PharmaMar
is the **first company** in
the world to research, develop
and market a **marine-based**
drug to fight cancer



The sea as a source of inspiration



The sea covers 70% of the planet and holds 80% of all life. Down through the millennia, marine organisms have evolved a range of substances with biological activity that they use for survival, defense, attack and communication. These substan-

ces hold great promise for the development of new drugs.

PharmaMar is conducting a multi-phase research program to discover and develop new antitumor compounds of marine origin.

✓ In a **first phase,**

the samples of marine organisms are gathered (mostly invertebrates), studying later their taxonomy and beginning to assess their biological activity in tumor cells. Nowadays, the company has the world's largest collection of marine organisms: nearly 200,000 samples of macro- and micro-organisms.

✓ In a **second phase,**

the substance responsible for the activity is isolated and its chemical structure is established. A chemical synthesis process for its industrialization is designed. Then, the pharmaceutical formula of the new compound is defined. "In vivo" models are designed to test the efficacy in a range of different tumors. If the results are positive, research begins with cancer patients.

As a result of this research process, the company has a portfolio of products that are at various stages of clinical development.





From **Spain** to the rest of the **world**

PharmaMar was the first company in the world to develop a marine-based cancer drug from discovery through to commercialization. PharmaMar's Yondelis® (trabectedin) was the first antitumor drug of marine origin to be approved for commercialization, specifically to treat soft tissue sarcoma. PharmaMar has also obtained approval for Yondelis® in treating ovarian cancer in the European Union. It is available in close to 80 countries and in

the main oncology markets: the US, Europe and Japan.

Under a licensing agreement with PharmaMar, Janssen Products, L.P. has the rights to develop and sell Yondelis® globally except in Europe, where PharmaMar holds the rights, and in Japan, where PharmaMar has granted a license to Taiho Pharmaceuticals.



From its facilities in Madrid, PharmaMar produces for the rest of the world, synthesizing the active molecules for drug manufacturing, and undertaking secondary conditioning to meet the commercial demand and forecasted needs for clinical trials and compassionate use programs. All the process is done with the agility and rigor required to guarantee industrial scale manufacture and supply of its products, always in strict compliance with Good Manufacturing Practices (GMP), regulatory requirements and the regulations on protecting our workers and the environment.

“In the relatively near future, the marine environment in all of its manifestations will be producing leads to novel treatments against cancer and other diseases”.

Chabner, Bruce: “Marine anticancer compounds in the era of targeted therapies”. Publicaciones Permanyer. Colección: International Oncology Updates, 2009. 168p.



GENOMICA S.A.U.

A leader company in **molecular diagnostics**

GENOMICA was born in 1990 and it was the first private company in giving support in molecular diagnostics.

It focuses its activities in the field of genetic analysis, and it is also

a pioneer in technology transfer. Its objective is to improve current methods for molecular diagnostics and DNA profiling with reliable, automated tools that conform to the highest quality standards.

R&D is a priority.
GENOMICA reinvests a significant percentage of their profits to develop new techniques and products.



The company has the following **lines of business:**

1. Design, development and sale of in vitro diagnostic kits based on low-density **microarrays**, which can then be automatically read and interpreted with SAICLART® software.

This reliable, robust platform, called **CLART®**, permits the **detection of multiple targets in a single run**, allowing for quick and effective clinical decision-making.
2. Genetic identification and filiation, an area in which the company is a **leader**.

GENOMICA was the first Spanish company to obtain **accreditation by ENAC** (Spain's National Accreditation Agency).
3. NGS (Next Generation Sequencing Service): **services and sequencing led** by tailored panels (R&D).

GENOMICA is firmly **committed to internationalization**. It currently operates in **more than 40 countries worldwide** and continues to **expand actively**.

SYLENTIS S.A.U. Understanding RNA interference

SYLENTIS, founded in 2006, seeks innovative therapeutic agents based on RNA interference, a technology whose discoverers were awarded the Nobel Prize for Medicine in 2006. Sylentis focuses primarily on treatments for ophthalmology.

The company has two compounds in clinical trials for treating eye disorders along with other molecules undergoing preclinical development for the treatment of eye allergies and diseases of the retina.

RNA interference (RNAi) has revolutionized biology by making it possible to design and develop drugs from a totally new perspective. It can be used to selectively silence genes through post-transcriptional degradation of the messenger RNA that would lead to the corresponding protein or enzyme. Accordingly, the technique acts on specific enzymes involved in pathologies and enables them to be regulated through the rational design of drugs that can silence the expression of the gene that codes for the enzyme or protein.



1. Some diseases, such as glaucoma, appear when a specific protein is altered or produced in excess.



2. **DNA.**
The information required to produce each protein is stored in the DNA molecule, in the cell nucleus. The DNA, however, is such a large molecule that it cannot leave the nucleus with all the information that it contains.

3. **DNA RNAm.**
The DNA information is transferred to smaller molecules, known as the messenger RNA (RNAm), which contain the information required to generate the protein.

4. **RNAm Protein.**
The mRNA leaves the nucleus and is used as the template to produce the proteins. But, sometimes, altered proteins or high concentration can cause a disease.

Gene expression process



Drugs based on RNA interference (RNA) **block expression at this point reducing and regulating protein levels** (Gene Silencing Process).

These RNAi products are designed with computer tools using information from DNA databases and synthesized by chemical processes

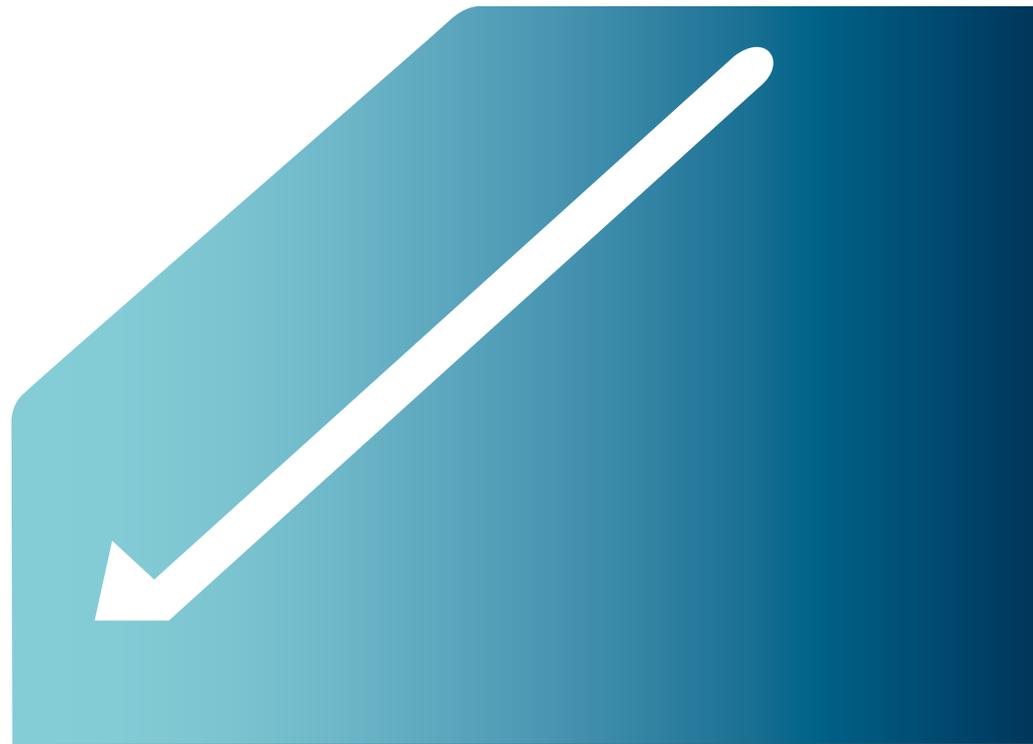


“Overall, it is estimated that between 0.4% to 1.8% of natural extracts

(from terrestrial plants to marine animals respectively)

of natural materia may contain anti-cancer principles.”

Ethnobotany and drug discovery:
the experience of the US National Cancer
Institute. Cragg GM, Boyd MR, Cardellina
JH, Newman DJ, Snader KM,
McCloud TG. Ciba Found Symp.
1994; 185:178-90





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