New drugs from the ocean: Pharmamar (Madrid/Spain)

20,000 Leagues under the Sea

The Spanish company Pharmamar explores the depths of the oceans in search of marine products for the treatment of cancer. Their first success, a drug for the treatment of soft tissue sarcomas, has just got European-wide approval.

Like Captain Nemo, the mysterious character created by Jules Verne, Jose María Fernández Sousa-Faro decided to seek his fortune in the depths of the oceans. His reasons were not, however, as obscure as Nemo's. He had inherited the Zeltia Group from his father, a Spanish company that produced diverse goods, from protective products for wood, to pesticides and pharmaceuticals. It was 1986. Spain was joining the European Union and Fernández decided that his company would require some original and innovative projects to face this new and challenging scenario. He was a biochemist with some previous experience in biotechnology. This was the background that led him to create Pharmamar, a biotech company aimed at the discovery and development of novel marine-derived drugs for the treatment of cancer.

Nature's treasure chest

And why not? Traditional pharmacology was largely built on natural products obtained from plants and microorganisms of terrestrial origin. But this was just a matter of proximity. It was known, however, that marine environments comprised the larger part and the greatest biodiversity of the biosphere. It has been estimated that marine species comprise approximately a half of total biodiversity. Millions of years of evolution in the oceans have led to a wide diversity of life on our planet. In fact, the oceans hold 34 of the 36 phyla of life, some of them (i.e. Ctenophora, Echinodermata, Porifera, Phoronidea, Brachiopoda and Chaetognata) restricted to the oceans. In addition, due to the special ecological conditions they have to cope with, marine organisms display multiple exclusive physiological processes and a complete collection of biochemical novelties. Pharmacologically, the main problem was access to this promising biochemical arsenal. In 1986 Jose María Fernández thought that the available technology was already up to the task, and he decided to take on the challenge.

First in Spain ever

Last July, Pharmamar got its first important success. At last, its leading drug Yondelis got approval from the European Agency

Photos (5): Pharmamar

Just a small contingent of Pharmamar's staff, which is, with a total of 262 employees, one of the main biotechnological companies in Spain.

for the Evaluation of Medicinal Products (EMEA) for the treatment of soft tissue sarcomas. Yondelis is the first antitumor agent ever produced by a Spanish company. Its approval is a milestone in the history of this company and the first serious reward for 20 years of work, €400 million of investment and not a single euro of revenue yet. Hopefully, it also opens the gate to further future development.

Nowadays Pharmamar is one of the main biotechnological companies in Spain. It employs 176 graduates and about 40 postdocs, out of a total of 262 staff. With headquarters in Madrid (Spain) and Boston (USA), it boasts about 20,000 m^2 of facilities, half of which are dedicated to research and development. The pride of the company is a collection of more than 42,000 frozen samples of marine organisms assembled during surveys all around the globe. The collection, one of the largest in the world, is the base of Pharmamar's research. From its samples they have obtained about 7,000 new chemical entities, covering 30 new families of compounds. They have also developed about 110 inventions, and applied for 1,410 patents to protect them, half of which have already been granted. Finally, besides the recently authorized Yondelis, they have four more antitumor agents undergoing clinical trials.

42,000 frozen samples

It now looks that Pharmamar's gamble on the ocean depths was opportune. Today many other companies and research institutes around the world are exploring the pharmacological potential of the sea. Hundreds of new marine therapeutic entities are described every year and there are even some specialized journals periodically publishing findings in this field. However, in spite of these good signals, there is the general feeling that the blooming of marine pharmacology is taking longer than expected. A probable cause for this slow development is the lack of sufficient private investment. Most of the main pharmaceutical companies have considered this research difficult, laborious, expensive and risky.

Discovering underwater secrets. Marine environments comprise the larger part and the greatest biodiversity of our planet. Millions of years of evolution have led to a wide diversity – the oceans hold 34 of the 36 phyla of life.

And so, during recent years, the search for new therapeutic entities has largely relied upon either other natural sources or combinatorial chemistry and high-throughput screening (HTS) based on robotics and automatic processes.

The search for new drugs into the depths of the sea is indeed a difficult task. Instead of robots, Pharmamar requires experts in marine biology to plan and organize the sampling expeditions, and an international network of collaborators to access the seas around the world. It requires also ships, boats and even submersibles, and divers with experience in marine zoology and taxonomy. Collected samples are sent to Madrid for their classification and analysis.

Life underwater holds lots of bizarre surprises. Some of them could be perfectly suited for the development of drugs, hopes Pharmamar.

Underwater search with ships, boats and submersibles

At the lab, cancer biologists screen the extracts of the samples on specially developed biological model systems. Extracts showing interesting anti-tumour properties are then fractionated to purify the active compounds and elucidate their chemical structure. Then it's the turn of the biochemists. But promising compounds require more and more tests and analyses, for which the original sample soon becomes insufficient. Then it is necessary to get back to the sea for more samples of the same species. And this is not always so easy. The species under scrutiny may be difficult to find or scarce. Sometimes finding this extra supply becomes one of the most intricate parts of the process. The main goal at this point is to achieve the chemical synthesis of the

compound and get rid of the natural supply as soon as possible. But when synthesis is hindered, a detailed study of the biology of the species may become necessary, to pinpoint its distribution, the environments and areas it inhabits, and even its biological requirements to attempt its aquaculture.

Once they are purified, characterized and produced in sufficient amounts, marine leads undergo the same general development procedures as drug leads of any other origin. If possible, a whole set of chemical derivatives of the purified compound are synthesized and tested in search of improved pharmacological properties. Finally, preclinical and clinical tests have to be performed to verify that the toxicity and therapeutic efficiency of the lead fulfils the regulatory requirements of drug licensing authorities.

A tunicate-derived cancer drug

Yondelis (generic name: trabectedin) the Pharmamar drug that has just received the EMEA approval for the treatment of soft tissue sarcomas, is an isoquinolone alkaloid originally isolated from the Caribbean colonial tunicate *Ecteinascidia turbinata*. Its cytotoxic effects seem to result from the selective alkylation in GC-reach regions of the minor groove of DNA, that inhibits activated but not constitutive transcription. Yondelis is also currently undergoing clinical trials for the treatment of ovarian, breast, prostate and paediatric sarcomas. This remedy has been developed by Pharmamar in partnership with the Johnson & Johnson Pharmaceutical Research & Development (J&JPRD). J&JPRD will undertake the marketing of Yondelis in the USA, once approval is granted there.

The current Chairman of the Board, José María Fernández-Sousa, is a Full University Professor in Biochemistry at Madrid and Santiago de Compostela. He founded Pharmamar in 1986.

Other Pharmamar compounds already undergoing clinical trials for the treatment of solid tumors are Aplidin, a cyclic peptide originally isolated from the tunicate *Aplidium albicans*; Kahalalide F a cyclic peptide isolated from the Hawaiian sea slug *Elysia rufescens* and its algal diet *Bryopsis sp.*; and the derivatives of marine compounds Zalypsis and PM02734.

New focus on neurodrugs

But, of course, marine compounds may have therapeutic uses other than the treatment of cancer. And so, by the year 2000, to further exploit the therapeutic possibilities of Pharmamar's collection of marine compounds Jose María Fernández and the Zeltia Group had created Neuropharma. The aim of this new pharmaceutical company is the research and development of drugs for the treatment and prevention of diseases of the nervous system, especially Alzheimer's. Although also resorting to chemical design, Neuropharma counts on exclusive rights to use Pharmamar's library of marine organisms. And they are already claiming promising results.

Rafael Florés

Sweet ocean fruit. Do these flimsy creatures contain unknown pharmaceutical properties or raw materials for the next wonder drug?