IRB and PharmaMar invent a method to reproduce marine substances of pharmacological interest

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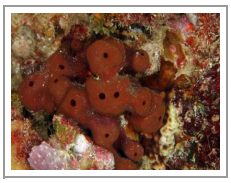
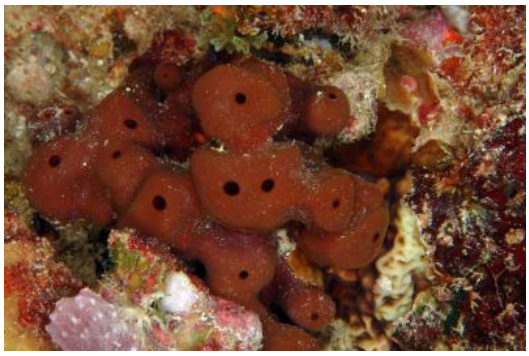


In 2008 the Spanish company PharmaMar, dedicated to developing marine-derived drugs against cancer, isolated a promising substance called pipecolidepsin A from the sponge *Homophymia lamellosa* collected off the coast of Madagascar. The Combinatorial Chemistry group at the IRB, led by Fernando Albericio, has been working alongside this company for twenty years. As part of a collaboration agreement, they worked together to reproduce pipecolidepsin A in the laboratory and have been successful in this endeavour.

The journal *Nature Communications* now reveals the procedure after the company obtained the patent, in which the researchers at IRB and PharmaMar appear as inventors. The two groups of scientists continue their lines of research and have launched an analogue programme to simplify the synthesis, reduce the time and cost of production and achieve a greater amount of material with which to start pre-clinical testing.

"Only 1 out of 10,000 promising molecules gets to become a drug. We have very much hope that pipecolidepsin A is one of these," says Fernando Albericio from the IRB, senior researcher of the study and professor at the University of Barcelona. Marta Pelay, first author of the article, has been able to produce four milligrams of this compound in the laboratory, but 100 are needed for extensive biological assays.



The marine sponge Homophymia lamellosa is the natural source of pipecolidepsin A.

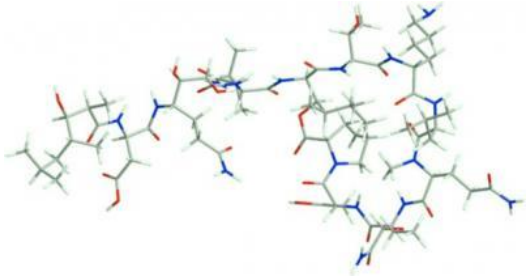
(Photo Credit: (PharmaMar))

The amount in-hand is now enough to test whether the activity of the synthetic molecule is comparable to that of the natural one, which kills tumour cells in eleven types of tissue: lung, prostate, colon, pancreas, ovary, sarcoma, leukaemia, liver, kidney, stomach and breast. "The analogue programme will enable us to perform more accurate biological studies to determine the most appropriate cancer to target," says Judit Tulla, chemist research associate in Albericio's lab and Pelay's mentor.

From a promising molecule to 37 more candidates

"Pipecolidepsin A is tricky, especially its centre, the heart of the molecule," explains Marta Pelay, who obtained her doctoral degree in February with a thesis related to this project. This molecule belongs to the family of "head-to-side chain" cyclodepsipeptides. It is a peptide, a small protein comprising 11 amino acids and one acid, arranged in the shape of a six with a central core containing a series of highly sensitive boundaries and including seven unnatural amino acids.

"Every day we have more complex molecules," explains Pelay, "but the effort has been compensated by a patent and the possibility, via the new synthesis method, to reproduce several interesting molecules that share similar structures. It is an uncharted field of research."



Structure of Pipecolidepsin A, which shows activity against eleven types of cancer.

(Photo Credit: (Author: Marta Pelay))

The "head-to-side chain" cyclodepsipeptides form a total of 38 known molecules. The advantage of these

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molecules, all of which are isolated from marine sponges, is that many show activity against, besides cancer cells, the HIV virus, resistant bacteria, and fungi of various types. Until now the pitfall was the synthetic reproduction.

"We have opened a whole new field of synthesis of molecules with therapeutic potential, none of which are on the market yet. We will have to wait until later this year to see if our endeavours lead to the development of a therapeutic molecule with the potential to become a commercial drug," concludes Tulla. In any case, and if all goes well, it will take a multi-million euro investment and at least 15 years for pipecolidepsin A to reach the market.

This is researcher Marta Pelay working at the IRB laboratories.

(Photo Credit: (J. Lanuza. IRB Barcelona))

Source: **Institute for Research in Biomedicine (IRB Barcelona)**

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