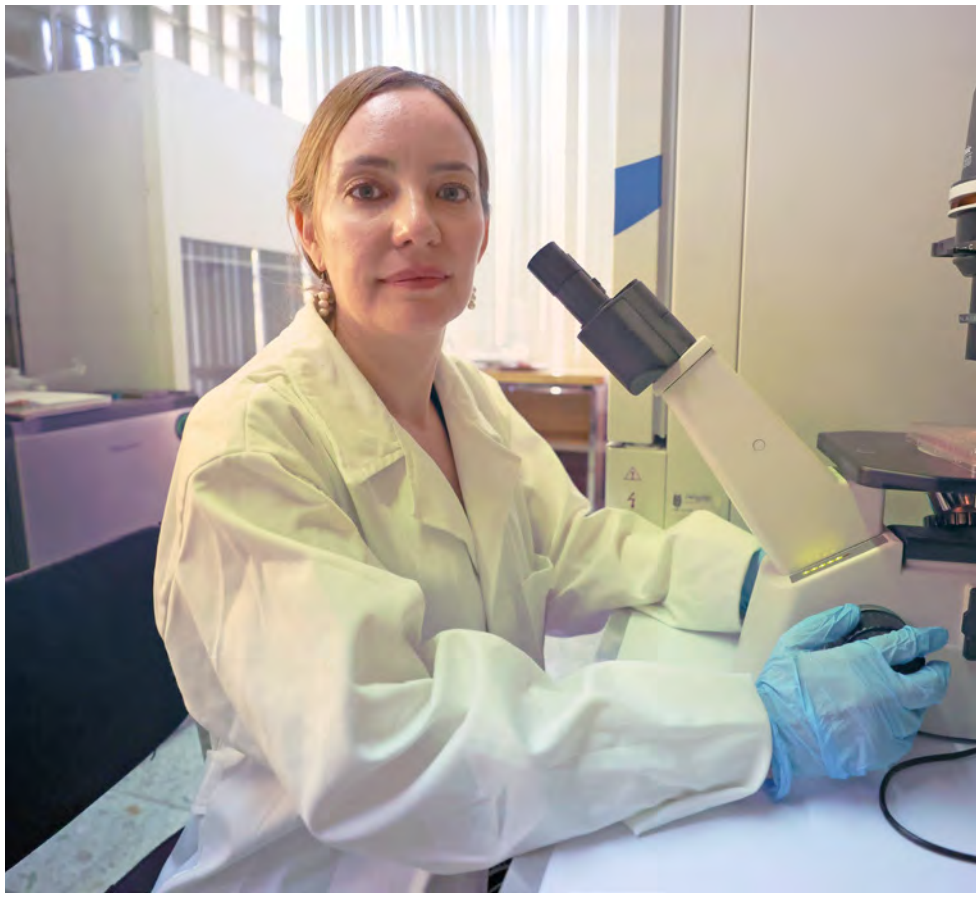
Existing DRUGS Evaluated to Inhibit Metastasis

Studies show that the compound loperamide was able to inhibit the biological response in 50% of the MDA-MB-231 breast cancer cell line



Marlet Themis Martínez Archundia, ESM scientist and postdoctoral in Bioinformatics at the Pasteur Institute in Paris, France.

Claudia Villalobos

While drug repositioning — finding new uses for already approved medications — is not a recent strategy, the rise of bioin-

has significantly increased interest in this approach. Through computational biology, researchers can more easily identify active substances previously authorized by institutions such as the U.S. Food and Drug Administration (FDA) as candidates for new treatments.

In this context, Dr. Marlet Themis Martínez Archundia, a researcher at the Escuela Superior de Medicina (ESM) of the Instituto Politécnico Nacional (IPN), is placing her hopes on this methodology. With support from the National Council of Humanities, Sciences, and Technologies (Conahcyt), she is conducting a frontier science project focused on identifying safe-use molecules that can inhibit metastasis, aiming to lay the groundwork for alternative treatments for cancer patients.

BREAST AND BRAIN CANCER

Dr. Martínez Archundia, a Level II member of the National System of Researchers (SNII), explained that her research focuses on breast cancer — a major public health issue in Mexico and across Latin America with high mortality rates — as well as glioblastoma, a type of brain cancer that, although less common, spreads malignant cells very rapidly to other areas of the body.

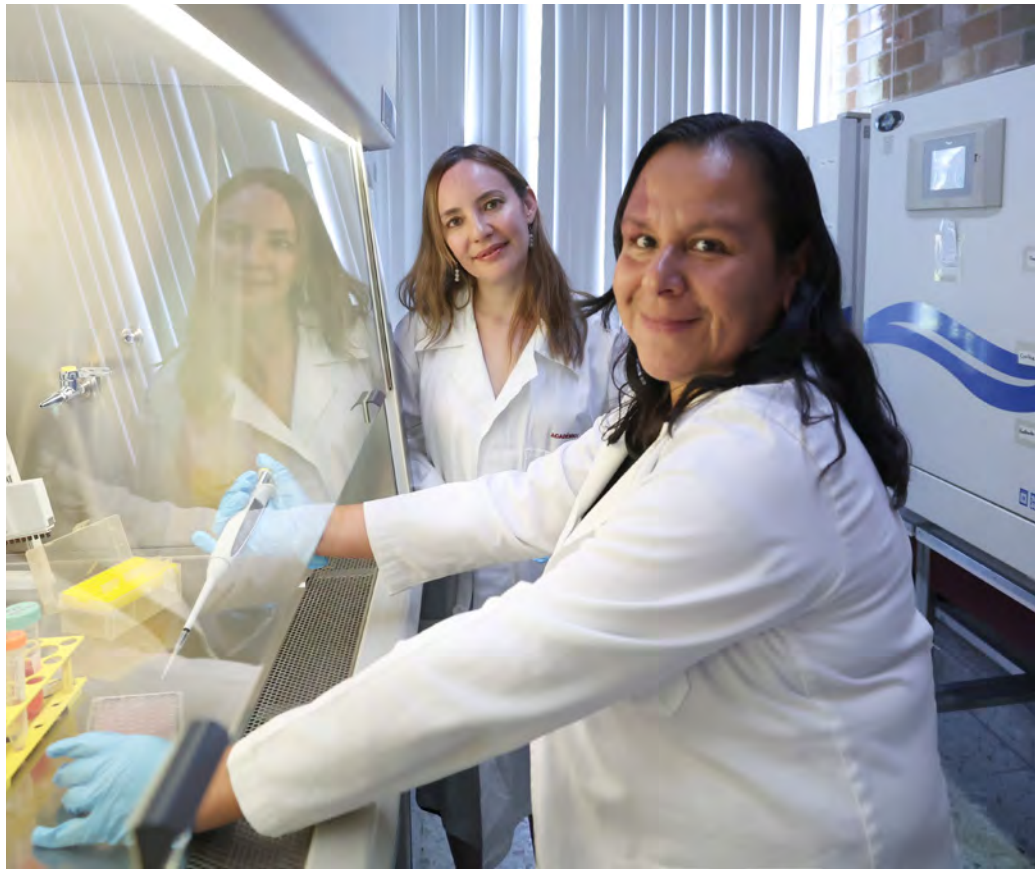
""Metastasis is a serious concern because a large percentage of cancer-related deaths worldwide are due to this process. When cancer cells divide and migrate to other organs, survival rates drop significantly. Our goal is to curb this dissemination through drug repositioning, so that first-line treatments such as chemotherapy or radiotherapy can be more effective," said the bioinformatics postdoctoral researcher from the Institut Pasteur in Paris, France.

As part of the first phase of the project, Dr. Martínez Archundia and her team used bioinformatics techniques to analyze approximately 1,600 compounds. They then carried out molecular docking studies to predict the affinity of these compounds with a membrane protein known to play a key role in metastasis: Tetraspanin CD-151.

Of the compounds analyzed, two were selected that, according to in silico studies, showed a higher likelihood of binding to Tetraspanin CD-151, potentially inhibiting metastasis. This process occurs when CD-151 interacts with another adhesion protein called Integrin alpha 3 beta 1, which triggers signaling cascades that result in uncontrolled cell division associated with metastasis.

INTERESTING FACT

It is estimated that in 2020, there were 20 million new cases of cancer in the world, so the different types of neoplasms are a public health concern in the world.



Martha Cecilia Rosales Hernández, ESM researcher, has extensive experience in medicinal chemistry.

Thus, the research aims to prevent the interaction between these two proteins to stop the spread of malignant cells throughout the body, said the scientist, who was recognized as a mentor in science by the British Council in 2022.

POTENTIAL DRUG

According to molecular docking and molecular dynamics simulations conducted in silico, the compounds with the greatest potential to inhibit the interaction involved in metastasis were loperamide and glipizide — the former used to treat diarrhea and the latter for type 2 diabetes.

Dr. Martínez Archundia reported that glipizide did not show favorable results in any breast cancer or glioblastoma cell lines. However, loperamide was tested on two breast cancer cell lines, MCF-7 and MDA-MB-231. While no response was observed in MCF-7 cells, a mechanism to inhibit migration was identified in the MDA-MB-231 line.

These studies were carried out in collaboration with Dr. Martha Cecilia Rosales Hernández, a researcher at ESM and Level III member of SNII, who has extensive experience in medicinal chemistry and conducted the biological evaluation of the compounds on the cell lines.

"These findings motivate us to continue our investigations. We aim to apply loperamide at different concentrations to determine whether metastasis reduction can be further enha- - nced," said Dr. Martínez Archundia, a member of the IPN Health Network and the Mexico-France MUFraMex Network.

BINDING SITE

With around 35 scientific articles published in international journals, the researcher explained that, to strengthen the project, they also studied the precise binding site where Tetraspanin CD-151 and Integrin alpha 3 beta 1 interact. This segment, known as the QRD motif, is located in the second extracellular loop of the protein at the cellular level.

By identifying this specific site, we aim to ensure that the pharmacological target prevents the signaling cascade responsible for metastasis, and to understand its structural behavior through molecular dynamics simulations," she noted.

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Cell line cultivation

According to the IPN scientist, simulations are a highly useful computational method, allowing researchers to study structural evolution. "It's like having a movie of our protein in a physiological system that includes water and ions — a sort of microscope showing how the protein behaves," she explained.

Dr. Martínez Archundia emphasized that, although the current results are promising and loperamide has already passed all toxicological and safety tests (hence its FDA approval), this does not mean that it is yet authorized for use in breast cancer patients. However, the publication of these findings in scientific journals could lay the foundation for future authorization and clinical trials.

Developing new cancer treatments is challenging, as each cell line operates through different mechanisms. A drug's success in one type of cell does not guarantee its effectiveness in others. This is evident with loperamide, which was only effective in one of the two breast cancer cell lines tested.

Regarding triple-negative breast cancer — characterized by the absence of estrogen, progesterone, and HER2 receptors — Dr. Martínez Archundia pointed out that this subtype is particularly difficult to treat, as malignant cells are highly sensitive and resistant to chemotherapy. "In such cases, drug repositioning is unlikely to succeed," she noted.

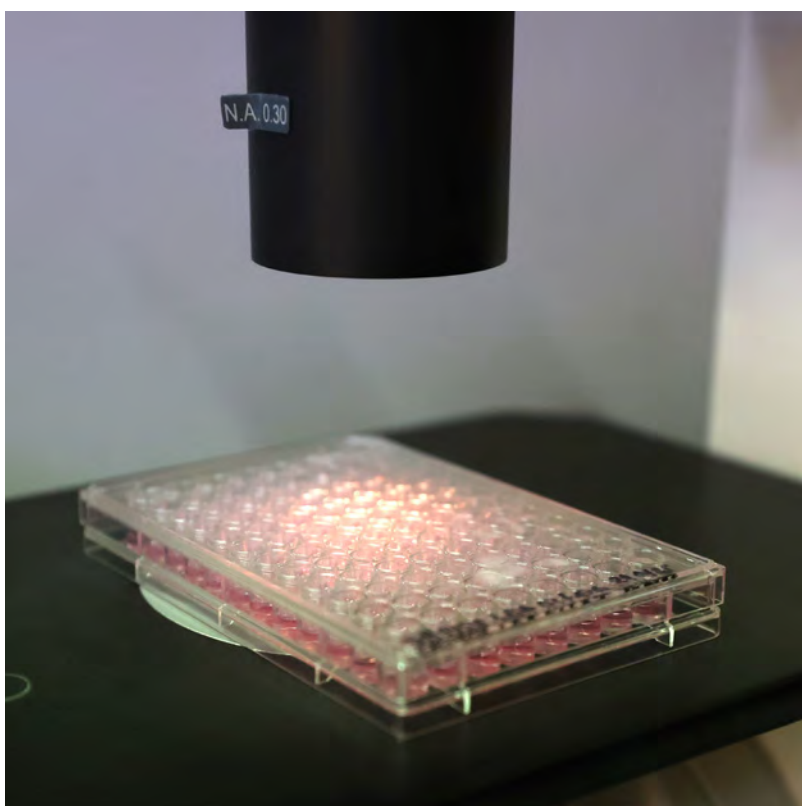
As for glioblastoma, the team will continue testing loperamide at various concentrations. Some other compounds that scored well in in silico evaluations may also hold promise for inhibiting metastasis.

THIRD PHASE

In addition to preparing a scientific article reporting the biological evaluation results, the research team will soon begin testing the compounds on fish and microalgae to determine their long-term toxicity in effluents. This phase will involve Dr. Miriam Azucena Hernández Zamora, a researcher at the Escuela Nacional de Ciencias Biológicas (ENCB).

"This aspect of the study is essential. If these drugs prove to be potential treatments against metastasis, it will be critical to include environmental considerations and ensure proper treatment of pharmaceutical waste," she stressed.

Dr. Martínez Archundia concluded by highlighting the importance of conducting frontier science projects like this one from an interdisciplinary and even transdisciplinary approach. "Each phase of the research requires different areas of expertise, and when combined, they significantly boost progress."



Biological evaluation of compounds of interest