National press release **05/05/2025**

Under embargo until 07 May 2025, 17h00 Paris time

A new class of molecules against cancer cells refractory to standard treatments

- Cancer cells with high metastatic potential are responsible for 70% of deaths by cancer, with standard-of-care treatments not eliminating them effectively.
- Molecules that can degrade their membranes and kill them have just been developed.
- Clinical trials are needed to confirm their effectiveness.

A new class of molecules capable of killing the cancer cells that are refractory to standard treatments and responsible for recurrence has just been developed by scientists at Institut Curie, the CNRS, and Inserm. This crucial advance in the fight against metastatic cancer is based on identifying the cellular site for ferroptosis initiation, a natural process, catalysed by iron, that sparks the oxidative degradation of cell membranes. These promising preclinical results will be published in the journal *Nature* on 7 May 2025.

Current anticancer treatments essentially target the primary tumour cells that proliferate quickly, but do not effectively eliminate specific cancer cells able to adapt to existing treatments and which exhibit high metastatic potential[1]. Yet metastases are responsible for 70% of cancer deaths.

A French research team from Institut Curie, the CNRS and Inserm has just developed a new class of small molecules that bring about the destruction of cell membranes, and hence triggers cell death. Led by scientists at the Laboratory of Biomedicine (Institut Curie/CNRS/Inserm)[2], this study is based on the remarkable properties of what are known as drug-tolerant persister cancer cells, with high metastatic potential. The latter express a large quantity of the protein CD44 at their surface, allowing them to internalise more iron, making them more aggressive and able to adapt to standard treatments. These cells are consequently more sensitive to ferroptosis, a cell death process catalysed by iron, which causes oxidation and the degradation of membrane lipids.

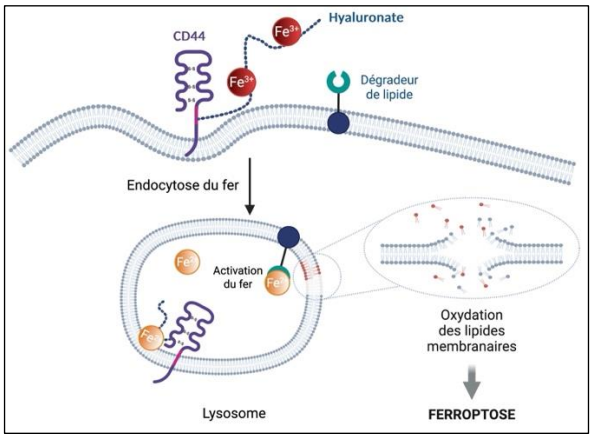
Thanks to innovative chemistry developed by the team led by Raphaël Rodriguez, researchers showed that the cell death initiated by iron in lysosomes[3] can alter the structure of intracellular membrane compartments. In the lysosomal compartment, iron can react with hydrogen peroxide, generating oxygen-centred radicals, highly-reactive chemical entities that damage cell membranes. This reaction then propagates in the cell forming lipid peroxides in the membranes of other cellular organelles, ultimately causing cell death. Ferroptosis thus results from the cell's failure to repair the membrane damage.

Using these initial discoveries, the scientists successfully conceived and synthesised a new class of small molecules that can activate ferroptosis: phospholipid degraders. The molecules possess one fragment that allows them to target the cell membrane (plasma membrane)—and to then accumulate in lysosomes via endocytosis—as well as another part that binds to and increases the reactivity of iron, which is abundant in this compartment of pro-metastatic cancer cells, thereby triggering ferroptosis. The molecule fentomycin (Fento-1) was designed to be fluorescent, allowing scientists to visualise it in the cell using high-resolution microscopy, as well as to confirm its localisation in lysosomes.

After the administration of Fento-1, the researchers observed a significant reduction in tumor growth in pre-clinical models for metastatic breast cancer, in addition to a pronounced cytotoxic effect on biopsies of pancreatic cancer and sarcoma patients, thereby confirming the treatment's effectiveness at the pre-clinical level[4] for these cancers, for which the effectiveness of standard chemotherapy is limited.

Clinical tests are needed to show that this ability to induce ferroptosis could serve as a therapeutic avenue that complements current chemotherapy in the fight against cancer, especially by targeting cancer cells that are pro-metastatic and refractory to standard treatments.

This research notably received support from the Ligue contre le cancer (3 Equipe Labellisées), the Horizon 2020 Research and Innovation Programme of the European Union (ERC), the Fondation pour la recherche médicale, the Fondation Charles Defforey–Institut de France, the Klaus Grohe Foundation, l'Institut national du cancer, the Ile-de-France Region, the ANR, the Fondation Bettencourt Schueller, the CNRS, Institut Curie, and Inserm.



Ferroptosis diagram. Iron is internalized in the cell via the protein CD44 present on its surface, allowing it to acquire metastatic properties and tolerance to standard treatments through epigenetic reprogramming, which plays a key role in cell adaptation. The activation of lysosomal iron by a phospholipid degrader causes the oxidation and rupture of cell membranes, leading to cell death.

Notes :

1 – Tumour cells that detach from their site of origin and migrate toward other parts of the body, forming new tumours known as metastases. This ability to spread is a characteristic of advanced cancers.

2 – This research primarily involved scientists from the Laboratory of Biomedicine (Institut Curie/CNRS/Inserm/PSL Research University), the Cancer Research Center of Marseille (Aix-Marseille Université/CNRS/Inserm/Institut Paoli Calmette), the APHP (Hôpital Paul-Brousse), the Institute of Molecular

Chemistry and Materials of Orsay (CNRS/Université Paris-Saclay), Harvard T.H. Chan School of Public Health, Helmholtz Zentrum München, Julius-Maximilians-Universität Würzburg,, Columbia University and the University of Ottawa.

3 - Lysosomes are the organelles responsible for the degradation of cell debris, biological macromolecules, foreign particles (bacteria, viruses, and parasites), and damaged intracellular organelles.

4 – Pre-clinical tests on animals showed a significant decrease in tumour volume after the lymphatic injection of Fento-1, with tolerance to treatment.

Bibliography :

Activation of lysosomal iron triggers ferroptosis in cancer

DOI : https://doi.org/10.1038/s41586-025-08974-4

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