Researchers use whole living cells as 'templates' to seek for bioactive molecules

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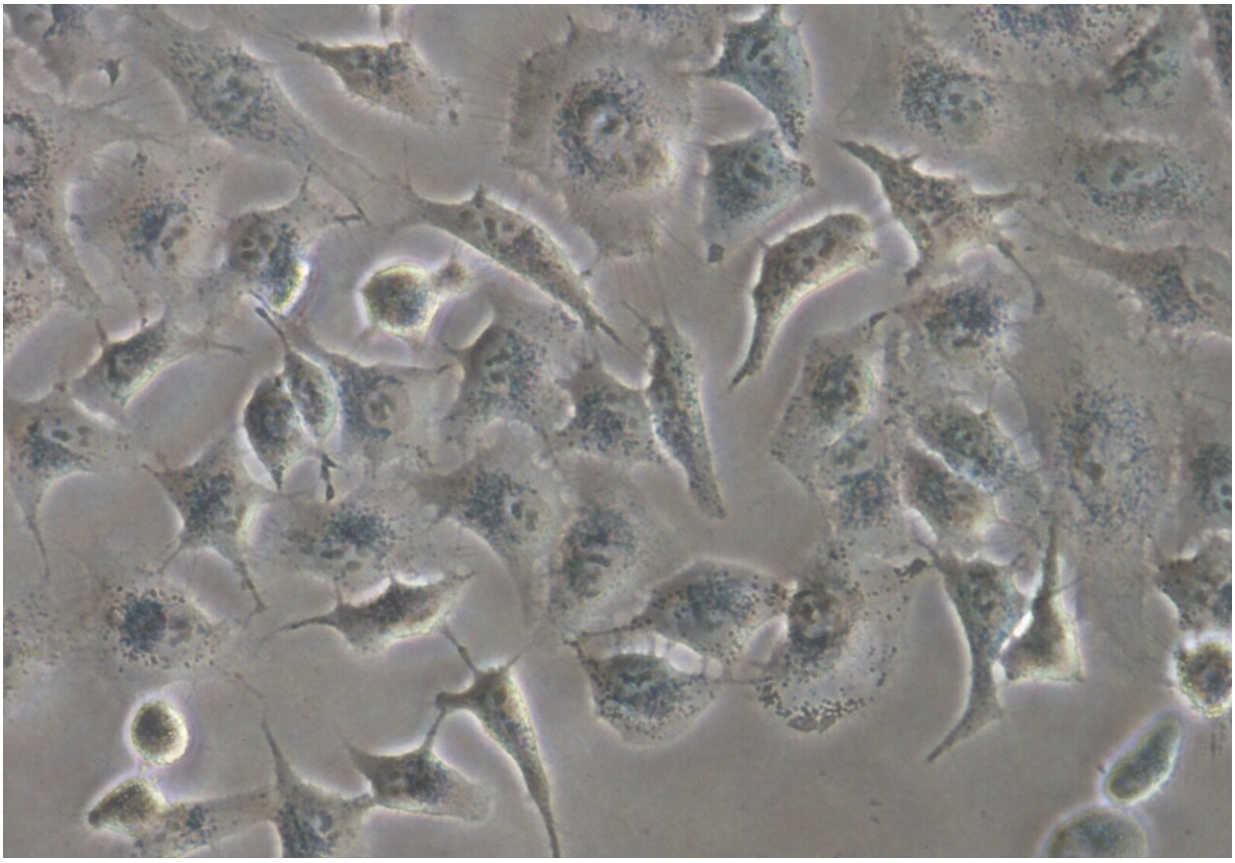

Human lung adeconarcinoma cell used in this research. Credit: Daniel Carbajo

A study performed by researchers at the Institute for Advanced Chemistry of Catalonia (IQAC) from the Spanish National Research Council (CSIC) pioneers the use of whole living cells (human lung

adenocarcinoma) in dynamic combinatorial chemistry systems. This research, published in the journal *Angewandte Chemie International Edition*, proposes a new methodology to discover new bioactive molecules in a realistic biological medium. This methodology could help in the future to develop methods to differentiate healthy versus cancer cells, or to protect the extracellular matrix against pathogens.

This new methodology is based on Dynamic Combinatorial Chemistry (DCC), which combines in a single process the selection, identification and preparation of molecules for a given application, accelerating the development of new functional compounds. Therefore, this methodology has a great potential in the rapid identification of new molecules with potential biological activity. In the present work, the group led by Ignacio Alfonso, from the Institute of Advanced Chemistry of Catalonia, pioneers the use of 'live templates' for the identification and optimization of new ligands (simple synthetic molecules) for biological targets.

"In our study we have worked with cancer cells used as a 'templates,' so the molecule able to interact with the outside of these cells (templates), will increase its concentration over the mixture of molecules that integrate the dynamic combinatorial library. The extracellular matrix is closely related to cellular communication and signaling, and it is essential in processes such as cancer metastasis or cellular infection by pathogens. Besides, it is the first barrier that a drug has to cross to enter our cells," explains the researcher. "Another hurdle is the difficulty to design molecules able to interact with the extracellular matrix due to its complex structure. But the results of our study allow us to identify and quantify the ligands for the extracellular matrix directly using living cells, which opens up multiple development possibilities in this field of research."

The next step was to synthesize the amplified molecule. Later, the

interaction between these molecules and the extracellular matrix of the living cells was confirmed by means of Nuclear Magnetic Resonance. Finally, after these studies with cells, assays between the identified molecules and chondroitin sulfate, the major component of the glycosaminoglycans in the extracellular matrix of this type of cells, were carried out. "We also used molecular dynamics simulations to understand the molecular recognition process that explains our results from a chemical point of view," explains Alfonso.

The methodology used in this study is an excellent research tool with potential applications in disease characterization and diagnosis. "It could lead to the faster discovery of bioactive molecules, since the selection is made in a medium that is more similar to the biological medium in which these biomolecules will act," concludes the researcher.

More information: Daniel Carbajo et al, Live-Cell-Templated Dynamic Combinatorial Chemistry, *Angewandte Chemie International Edition* (2020). DOI: 10.1002/anie.202004745

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