UFRGS' Researchers Synthesize Fluorescent Anticancer Molecules

Compounds present good efficiency against breast and prostate cancer cells. One even shows low toxicity in healthy cells

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UFRGS' scientists of the Institute of Chemistry (IQ), in partnership with Unicamp (University of Campinas), managed to synthesize molecules that present good efficiency against breast and prostate cancer cells in lab tests. One of the substances also presents ten times less toxicity in healthy cells than cisplatin, a highly utilized chemotherapy medication. In August, the paper was featured on the front cover of the New Journal of Chemistry.

Fluorescent bioactive molecules in a solution under UV light – Photo by Divulgação

The research began with a partnership between the Organic Synthesis Research Laboratory, coordinated by Professor Dennis Russowsky, and the Applied Organic Photochemistry Rodembusch Research Group, coordinated by Professor Fabiano Rodembusch. The two research partners said they have been working together for five years and two years in this research. "I work with molecular hybridization, which involves combining two different substances to produce molecular hybrids. Once connected, these molecules can raise certain activities or express new ones," explained Russowsky. Rodembusch works with fluorescence, which is the emission of light by a substance that has been exposed to varied degrees of radiation. "Fluorescence is a powerful thing because it allows scientists to visualize, in the case of fluorescent probes, formerly unseen regions or phenomena," stated Rodembusch.

Part of the research group, PhD student Vanessa P. de Souza synthesizes molecules in the lab – Photo by Divulgação.

The researchers then united both their expertise: from Monastrol, a molecule with anticancer activity, they synthesized new hybrid compounds with fluorescent properties. Therefore, substances localization and activity inside cells can be visualized by scientists. "We can visualize the molecule's route inside the cell, in which organelle it is located, if it is attached to the cell wall or if it is inside the nucleus – in summary, we can visualize *in vivo* where exactly the molecule is operating," added Russowsky. The partnership with Unicamp comes in handy here: to see molecules activity inside the cell, we need confocal microscopy, technical expertise of Unicamp. Confocal microscopy allows researchers to stain organelles and other cell structures to observe where the molecule is operating. Researchers at Unicamp supplied us with cancer cell culture strains and performed tests on the molecules synthesized at UFRGS, preparing samples with varied concentrations of cancer cells and molecules. From these sample observations, they built graphs relating molecules activity curve and cell culture. For example: if researchers began testing 1000 cells and only 500 cells remained after a day of substance application, it would prove the chosen compound "killed" 500 cells in that period of time. "This is how parameters are defined – basically concentration, time, and the number of cells – to determine which substances are more potent against those cells," explained Russowsky.

Tests and results

Researchers synthesized six hybrid molecules, all derived from Monastrol, a synthetic substance known for its capacity to interrupt cell activity. "Sometimes a compound that can be very active against a cell line and slightly active against another, then we keep testing which type of fragment could be combined to improve its activity and compare its action in healthy cells," stated the researcher.

The synthesized compounds had their activity tested against three tumor cell lines: MCF-7 (breast cancer cells), Caco-2 (colon cancer cells), and PC3 (prostate cancer cells). The researchers discovered that three substances (named "8c", "8e", and "8f") produced good results against PC3 cell lines, similar to cisplatin results, a highly used medicine against cancer. Molecule 8c was nine times more efficient than Monastrol, the origin one, against prostate cancer cells. Molecules 8e and 8f also presented good results against breast cancer cells.

Besides activity, the toxicity parameter is also investigated to find out if substances are harmful or toxic to healthy cells. "If a highly toxic molecule to cancer cells is also toxic to the host, it is useless," Russowsky explained. In this hypothetic case, since cancer cells proliferate quicker, the compound would attack more cancer cells than healthy cells. However, the goal is to be toxic only to cancer cells. Using healthy prostate cell cultures, named PNT2, scientists observed that molecule 8c was also ten times less toxic than cisplatin, used as a guiding parameter for toxicity. Yet molecules 8e and 8f, which proved a good efficiency against breast cancer cells, were just as toxic as cisplatin.

The researchers stress that some properties might be lost when adding fluorescence to a molecule. However, the opposite happened to molecule 8c: "after being assembled to the originally bioactive compound, this fluorescent molecule not only illuminated the environment where it was but also raised nine times its toxicity against cancer cells," stated Russowsky. Rodembusch added: "The main result of our work is the creation of a compound that is both fluorescent and efficient against cancer cells. It is a privileged structure, both anticancer and fluorescent (visible to scientists)."

Research next steps and challenges

At this point, our readers must be wondering: "how are these results going to be used?" The researchers explain that, even though the results are promising, this is only the "first step of the staircase." Before any substance can be used effectively against cancer, there are many other steps to be followed.

The already performed study is called a preclinical *in vitro* trial (in cells). Russowsky explained the research's next step is a preclinic *in vivo* trial (in research animals) to investigate its safety in living beings. The After *in vivo* trial is followed by a four-stage clinical trial (in humans), which can take several years to be accomplished, each stage having to be validated by safety, efficiency, and risk/benefit tests.

Despite difficulties, Russowsky and Rodembusch aim to keep working on the subject. "The development of this research does not depend exclusively on a good project. We also need a workforce of students from doctorate's and master's programs and post-doctorates with us," stated Russowsky. The admission of new students varies a lot: "Sometimes we have four, five, six students entering [the research] in the same year; sometimes no one enters," he added. There are other factors involved, like the suspension of new scholarships and the distribution of existing ones: "We have almost 50 Professors in the Graduate Program in Chemistry but only 10 to 15 scholarships available in a year. The student is granted with the scholarship, not the Professor – being chosen by a student is a lottery-like process," explained Rodembusch. Other challenges are the need to partner with researchers from different areas, such as Health Sciences and Pharmacology, to perform clinical and *in vivo* trials and the need to be financed. A next step, however, is already being taken: patenting 8c molecule. The researchers are about to solicit the patent that must be soon sent to UFRGS' Secretariat for Technological Development (SEDETEC).

Translated into English by Marianna Gómez Strenge Tórgo, under the supervision and translation revision of Elizamari R. Becker (PhD) – IL/UFRGS