New chemical modification of a natural compound for cancer treatment

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Gonçalo Bernardes, Principal Investigator at iMM and co-leader of the study. Credit: Gonçalo Ribeiro, iMM

Natural compounds often have promising therapeutic potential but using them to treat diseases is hampered due to toxicity or non-desirable effects. Now, a new study led by Gonçalo Bernardes, group leader at the Instituto de Medicina Molecular João Lobo Antunes (iMM; Portugal) and Professor at the University of Cambridge (Cambridge, U.K.), and

Gonzalo Jiménez-Osés, group leader at the Center for Cooperative Research in Biosciences (Derio, Spain), and published today in the scientific journal *Nature Chemistry* reports the development of new chemistry on natural compounds derived from Brazilian lapacho tree bark to obtain a therapeutic agent that could be an efficient treatment for acute myeloid leukemia.

Acute myeloid leukemia, the most common form of acute leukemia in adults, is an aggressive cancer that arises from an abnormal increase in the number of a type of immature blood cells, called myeloid cells. The survival rate of patients is only around 20% after 5-years, and there is a high occurrence of disease relapse.

"It's important to find new therapeutic strategies for acute myeloid leukemia. There are a lot of natural compounds with medicinal value that can't be used as therapies at the moment due to toxicity and negative effects in healthy cells. In our work, which was done in collaboration with Gonzalo Jiménez-Osés, we used these natural compounds and modified them in a way that controls their negative effects and allows us to take advantage of their therapeutic value," explains Gonçalo Bernardes, group leader at iMM and co-leader of the study.

In 2018, this team used machine learning to identify the targeting site of a compound from the lapacho tree bark that belongs to the family of ortho-quinones, called β-lapachone. These compounds are known for their potential to control the abnormal increase in the number of cells that characterizes cancer, and are good candidates for the treatment of leukemia.

"The compound that we explored in this study, called β-lapachone, is a promising drug to treat leukemia, but its reactive properties could have undesirable effects. In this work, we combined two strategies to minimize the negative effects of the compound. On one side, we added a

chemical group to this compound that protects from its reactive properties. It acts like a mask that covers the toxicity of the drug. This mask is released in a more acidic environment, that corresponds to the interior of cells. This leads to our second strategy. We attached the modified compound to a protein, an antibody, that delivers it directly to the interior of cancer cells," adds Gonçalo Bernardes.

"Cancer cells have certain markers that tell them apart from healthy cells. In acute myeloid leukemia we know that one of these specific markers, called CD33, is present in the cancer cells. We attached our natural product to an antibody that binds specifically to this CD33. This allows the drug to go through the body without damaging any healthy cells and when the antibody encounters the cancer cell, it binds to the CD33 marker and delivers the drug. At this moment it will turn into its active and toxic form, killing the cancer cell," clarifies Ana Guerreiro, co-second author of the study.

Besides the therapeutic interest of this approach for the treatment of acute myeloid leukemia, the chemistry that was developed in this study can be used for other valuable natural compounds, enabling the use of compounds with therapeutic potential that were previously inappropriate for medicinal use.

More information: Gonzalo Jiménez-Osés, Controlled masking and targeted release of redox-cycling ortho-quinones via a C–C bond-cleaving 1,6-elimination, *Nature Chemistry* (2022). DOI: 10.1038/s41557-022-00964-7.
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