Tranylcypromine antidepressant shows promise as cancer treatment

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A retinoid called all-trans retinoic acid (ATRA), which is a vitamin A-derivative, is already used successfully to treat a rare sub-type of acute myeloid leukemia (AML), however this drug has not been effective for the more common types of AMLs.

Team leader Arthur Zelent, Ph.D., and colleagues at the ICR have been working to unlock the potential of retinoids to treat other patients with AML. In a paper published in Nature Medicine today, they show that the key could be an antidepressant called tranylcypromine (TCP).

"Retinoids have already transformed one rare type of fatal leukemia into a curable disease. We've now found a way to harness these powerful drugs to treat far more common types of leukemia," senior author Dr. Zelent, from the ICR, said. "Until now, it's been a mystery why the other forms of AML don't respond to this drug. Our study revealed that there was a molecular block that could be reversed with a second drug that is already commonly used as an antidepressant. We think this is a very promising strategy, and if these findings can be replicated in patients the potential benefits are enormous."

ATRA works by encouraging the leukemia cells to mature and die naturally. The team thinks the failure of AML to respond to this drug may be due to genes that ATRA normally targets becoming switched off. In their search for a drug that could be used to reboot the activity of ATRA, the team looked to an emerging area of research called epigenetics. Epigenetic drugs do not target genes directly but instead

target whether genes are switched on or off. They discovered that inhibiting an enzyme called LSD1, using TCP, could switch these genes on again and make the cancer cells susceptible to ATRA.

Along with collaborators at the University of Münster in Germany, the team have already started a Phase II clinical trial of the drug combination in acute myeloid leukemia patients.

Co-author Kevin Petrie, Ph.D., from the ICR says, "Both the retinoid ATRA and the antidepressant TCP are already available in the UK and off-patent, so these drugs should not be expensive for the health service. AML remains very difficult to treat and sadly is often fatal, with rates of the disease projected to increase significantly as the population ages, so it is particularly pleasing to have identified this new treatment approach. Importantly, we believe these drugs are targeting only the cancer cells and leaving normal healthy cells largely untouched, so we are hopeful that they would have fewer side-effects for patients than standard drugs. We look forward to seeing the results of the clinical trials."

Samuel Waxman, M.D., the Founder and the Scientific Director of the Samuel Waxman Cancer Research Foundation added, "The Samuel Waxman Cancer Research Foundation has supported the work of Arthur Zelent for more than a decade. This major finding is the direct result of years of collaborative research to better understand the mechanism of action using a combination therapy of drugs that are already available on the market today, which may lead to faster cures for patients."

More information: * Retinoids are already licensed to treat a type of AML called acute promyelocytic leukemia (APL).

Inhibition of the LSD1 (KDM1A) demethylase reactivates the all-trans-retinoic acid differentiation pathway in acute myeloid leukemia with first author Tino Schenk from the ICR publishes in *Nature Medicine* on

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