

Major discovery on the mechanism of drug resistance in leukemia and other cancers

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A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

A mechanism that enables the development of resistance to Acute Myeloid Leukemia (AML) anticancer drugs, thereby leading to relapse, has been identified by Kathy Borden of the University of Montreal's Institute for Research in Immunology and Cancer (IRIC) and her collaborators. Kathy Borden is a Principal Investigator at IRIC and a

professor at the university's Department of Pathology and Cell Biology. The development of drug resistance is one of the main problems in clinical oncology and the cause of relapse in many patients.

The new discovery, recently published in the prestigious scientific journal *Nature*, constitutes a major breakthrough in the fight against AML, one of the deadliest forms of leukemia, because it immediately suggests strategies to overcome drug resistance. Furthermore, the type of drug resistance the team identified is likely implicated in other cancers and a successful new treatment regimen based on these findings could have broad applications in treating cancer.

Previous work by Professor Borden's team had indicated that the use of ribavirin, a compound that was originally developed as an [antiviral drug](#), could result in real benefits for certain cancer patients. With support from The Leukemia & Lymphoma Society of the USA, a first clinical trial using ribavirin to treat poor-prognosis AML patients was performed under the supervision of Dr. Sarit Assouline and Dr. Wilson Miller of the Segal Cancer Center at the Jewish General Hospital in Montréal.

"This first clinical study yielded extremely promising results in most patients, including remissions, with no significant treatment-related toxicity. However, as is often the case when using a single drug, all patients eventually relapsed," recall Drs. Assouline and Miller. The multi-center study also included patients from the Hôpital Maisonneuve-Rosemont (HMR) in Montreal and the McMaster University/Hamilton Health Sciences Center in Hamilton, Ontario.

In their recent article, the researchers describe why, in most of the patients, ribavirin as well as the standard chemotherapeutic drug cytarabine (Ara-C), eventually become ineffective at killing cancer cells. "By studying drug resistant cancer cells from AML patients and head and neck tumors, we found that a gene called "GLI1" is dramatically

overactive in these cells," explains Hiba Zahreddine, doctoral student in the laboratory of Kathy Borden and first author of the Nature article.

"With the help of our colleagues at Pharmascience Inc. we were then able to show that this results in a specific chemical change to the drugs, that prevents their toxicity toward the cancer cells," continues Professor Borden.

Fortunately, drugs that inhibit the activity of GLI1 are currently available and the scientists showed that these drugs could switch the [cancer cells](#) back into a ribavirin-sensitive state. It is hoped that when used in combination-therapy with ribavirin (or more standard chemotherapy), these drugs will prevent the development of [drug resistance](#) in patients. The team has now received approval from Health Canada to undertake a new clinical trial to test the novel drug combination in AML patients.

As part of its research partnership with Université de Montréal, Pharmascience Inc. will continue to manufacture and provide the ribavirin necessary for this clinical trial. "If this new approach is successful, it could have very broad applications since the mode of action of ribavirin suggests that it could be effective against up to 30% of all cancers including some types of breast, prostate, colon, stomach and head and neck cancers in addition to AML," explains Morris Goodman, co-founder and Chairman of the Board of Pharmascience Inc.

More information: Zaheddine HA, Culjkovic-Kraljacic B, Assouline S, Gendron P, Romeo AA, Morris SJ, Cormack G, Jaquith JB, Cerchietti L, Cocolakis E, Bergeron J, Leber B, Becker MW, Pei S, Jordan CT, Miller WH, Borden KLB. The sonic hedgehog factor Gli1 imparts drug resistance through inducible glucuronidation, *Nature*, 2014.

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