New opportunity to treat drug-resistant leukemia discovered

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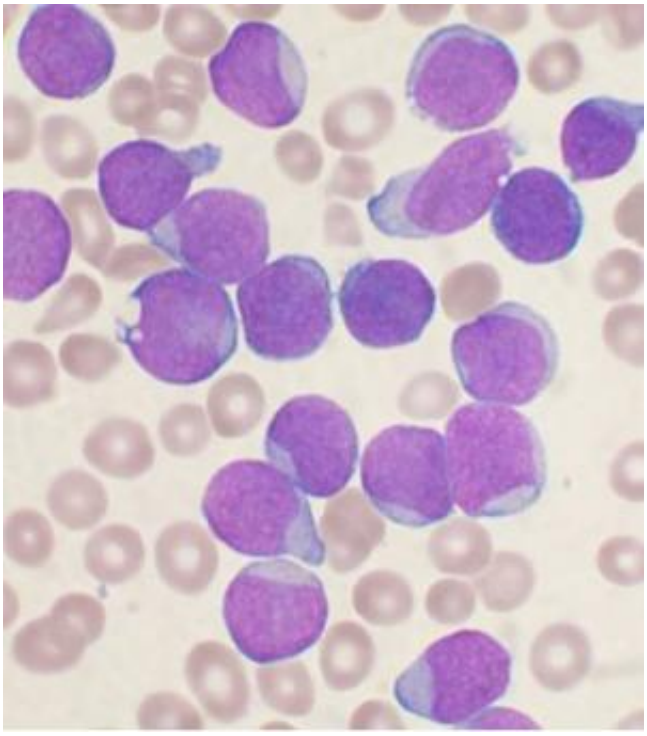

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

A study led by researchers at the Institute for Molecular Medicine Finland FIMM and Faculty of Medicine, University of Helsinki and the Helsinki University Central Hospital Comprehensive Cancer Center, in close collaboration with researchers at Pfizer, has identified a previously unrecognized action of Pfizer's axitinib as a potent inhibitor of the

dominant mutation that confers drug resistance to all well tolerated treatments in patients with certain types of leukemia. The findings of this international joint effort were published online today, 9 February, 2015, in the journal *Nature*.

The FIMM research team studied cancer cells from patients with chronic myelogenous and acute lymphoblastic leukemia (CML and ALL) that had developed resistance to currently available treatments. These cancers are driven by the BCR-ABL1 fusion protein, and resistance to treatment developed due to a new genetic mutation in the BCR-ABL1 fusion gene in the cancer cells.

There were two critical factors that were integral to the outcome of this study. First, the Drug Sensitivity and Resistance Testing (DSRT) method developed at FIMM made it possible to study the response of these cancer patients' leukemia cells to a large panel of drugs simultaneously, thus identifying axitinib as a promising drug candidate. Using this approach, the researchers found that axitinib, a tyrosine kinase inhibitor currently approved to treat certain patients with advanced renal cell carcinoma, effectively eliminated these patient-derived drug resistant leukemia cells.

"This screening method is a key component of FIMM's Individualized Systems Medicine strategy. The drug panel covers all approved and many emerging cancer therapeutics, and thus enables an individualized selection of potentially effective therapies for leukemia patients," explains Krister Wennerberg, FIMM-EMBL Group Leader and a corresponding study author.

Second, by coupling this screening method with Pfizer's deep oncology and structure-based drug discovery expertise, the researchers were also able to define the mechanism by which axitinib binds to the drug resistant version of the BCR-ABL1 protein, providing fundamental new

molecular insights into how cancer causing kinases can be blocked.

"If you think of the targeted protein as a lock into which the cancer drug fits in as a key, the resistant protein changes in such a way that we need a different key. In the case of axitinib, it acts as two distinct keys - one for renal cell carcinoma and one for leukemia" says Brion Murray, Pfizer Research Fellow and one of the lead authors of the study.

"Since axitinib is already used to treat cancer, its safety is known and a formal exploration of its clinical utility in drug resistant leukemia can now be done in a fast-track mode. Thus, the normally very long path from lab bench to bedside is now significantly shortened," says Kimmo Porkka, Head of Hematology at Helsinki University Central Hospital Comprehensive Cancer Center and one of the lead authors.

"Our findings highlight the power of drug repositioning, in other words, searching for novel uses for existing, emerging and abandoned drugs. This study shows what can be achieved when academic institutions and pharmaceutical companies team up to study effects of drugs using cells directly obtained from patients," says Olli Kallioniemi, the Director of FIMM.

"This high caliber publication is a great example of Pfizer's strong collaboration with academia to further advance research for patients with cancer," adds Murray. "Further research will determine whether these findings have the potential to significantly improve the standard of care for this select group of CML patients and patients with other related leukemias."

More information: Axitinib effectively inhibits BCR-ABL1(T315I) with a distinct binding conformation. Tea Pemovska, Eric Johnson, Mika Kontro, Gretchen A. Repasky, Jeffrey Chen, Peter Wells, Ciarán N. Cronin, Michele McTigue, Olli Kallioniemi, Kimmo Porkka, Brion

W. Murray & Krister Wennerberg. 2015. *Nature*:
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