New breakthrough in the molecular characterization of acute myeloid leukemia

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The multidisciplinary team comprising the Leucégène research group, a major project headed by Dr. Guy Sauvageau of the Institute for Research in Immunology and Cancer (IRIC) at the Université de Montréal and Dr. Josée Hébert of Maisonneuve-Rosemont Hospital (MRH), has just published a series of important observations on the

genetic and molecular characteristics of two leukemia subtypes in the prestigious journal *Nature Genetics*. The results of the study also suggest the possibility of a new combinatorial therapeutic approach for certain leukemias. The goal of the Leucégène project is to develop new tools for a more detailed classification of patients suffering from acute myeloid leukemia (AML) with a view to improving outcomes and more effectively guiding the choice of available treatment options. AML is a highly aggressive blood cancer that kills close to 1,000 people a year in Canada. Because this is a very complex cancer, current prognostic tests are imprecise in assessing risks and treatment choices in most patients.

The Leucégène team used next-generation DNA sequencing technologies to characterize genetic anomalies in over 400 AML samples from the Quebec Leukemia Cell Bank (QLCB). High-output screening approaches developed at IRIC were also used to study leukemia cell response to a number of chemical compounds acting on the cell signaling pathways often deregulated in these cancers. "This analysis represents an important effort at integrating IRIC's expertise in cell biology, genomics, bioinformatics and medicinal chemistry, and demonstrates how genetic and chemical approaches can reveal complementary information," points out Dr. Vincent-Philippe Lavallée, postdoctoral fellow in the laboratory of Dr. Sauvageau and lead author of the article.

The study in question concentrated on two AML subtypes involving rearrangements of mixed lineage leukemia (MLL) and allowed for identification of a gene expression profile common to the two groups and including new markers specific to these types of leukemia. The LOC100289656 gene, among others, seems to have a diagnostic value since it led to the discovery of MLL rearrangements never seen before in patients who had not been originally recognized as belonging to this group. The data obtained also confirmed the presence of mutations in a number of genes already associated with AML, including those of the Ras signaling pathway, and identified for the first time recurrent

mutations in the SPI1 gene. Finally, the chemical target demonstrated that MLL leukemia of the first group characterized by the presence of Ras mutations seems to have a heightened sensitivity to two types of molecule inhibitors, suggesting that a novel therapeutic approach combining these two types of drug could prove to be effective in certain patients. In the longer term, this sort of integrative approach should make possible a detailed analysis of other types of leukemia, as well as of solid tumors.

This study constitutes convincing validation of the chemogenomic approach developed by IRIC researchers and their colleagues. "A large-scale multifaceted project like this," explain Drs. Sauvageau and Hébert, "the results of which will have a real impact on patient health, was made possible thanks to the resolute commitment of Genome Canada, Génome Québec and AmorChem to supporting personalized medicine approaches. We also have to call attention to the dedication of our multidisciplinary team of researchers and physicians at IRIC and at MRH."

More information: "The transcriptomic landscape and directed chemical interrogation of MLL-rearranged acute myeloid leukemias." *Nature Genetics* (2015) DOI: 10.1038/ng.3371

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