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PRESS RELEASE

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Gene responsible for relapses in young leukemia patients

ATF5 polymorphisms influence efficacy of E. coli asparaginase

MONTREAL, October 24, 2011 – One of the causes of resistance to cancer treatment in children is now beginning to be elucidated. Acute lymphoblastic leukemia patients with a particular form of the ATF5 gene are at higher risk of having a relapse when treated with *E. coli* asparaginase, a key chemotherapy drug for this type of leukemia. This is what a study by Dr. Maja Krajinovic published in the *Blood*, the journal of the American Society of Hematology, reveals. Dr. Krajinovic is an investigator at the Sainte-Justine University Hospital Research Center, which is affiliated with the University of Montreal.

Dr. Krajinovic's team focused on asparaginase, one of the drugs in a chemotherapy "cocktail" administered to young patients during the intensification phase of their treatment.

They observed that *E. coli* asparaginase therapy was associated with an increase in relapses when administered to patients who had particular polymorphism (special form) of the ATF5 gene. In fact, this gene regulates asparagine synthetase, an enzyme that produces asparagine, which in turn feeds cancer cells.

"In the presence of this polymorphism that, as we demonstrated, modifies the transcription rate of the ATF5 gene, it is possible that the medication, rather than preventing the proliferation of leukemia cells by reducing the rate of asparagine, does just the opposite by creating feedback that triggers cancer cells to produce asparagine themselves," explains Dr. Krajinovic.

The discovery of a form of gene associated with high rates of relapse during treatment with *E. coli* asparaginase opens the door to the possibility of selecting a type of pharmacological treatment based on a patient's genetic profile, an approach that reflects the shift toward personalized medicine. "If a DNA test detects the implicated polymorphisms in children, it will be possible to predict the risk of relapse or side effects," exclaimed Dr. Krajinovic. "The clinician can then propose an alternative treatment or adjust the dose accordingly."

Since the introduction of combination chemotherapy, the rate of pediatric survival without relapse has skyrocketed to about 80%. Yet some patients still resist treatment or present side effects. Pharmacogenetic research strategies involve studying the reaction to each drug used for combined chemotherapy based on various patient genetic profiles so as to design treatment plans that increase efficacy and reduce side effects in patients.

Dr. Krajinovic has published a number of similar studies that focus on antifolate, another drug used in combination regimens to treat acute lymphoblastic leukemia.

Study Details

The study, led by Dr. Maja Krajinovic, an investigator in the Viral and Immune Disorders and Cancers research axis at the Sainte-Justine University Hospital Research Center and the Departments of Pediatrics and Pharmacology at the University of Montreal, was published online on the October 4, 2011 in the scientific journal *Blood*. Dr. Daniel Sinnett, an investigator working in the same research axis, conducted with Dr. Krajinovic polymorphism-related functional assays. Dr. Sinnett is also an author of many studies on the genetic determinants of acute lymphoblastic leukemia, including a recent study on natural killer cells published in collaboration with Dr. Ali Ahmad as principal author. The study was published in the August 4, 2011, issue of *Blood* and was reviewed in an editorial that underscored the originality of the work.

The study was funded by the Canadian Institutes of Health Research (CIHR), the Leukemia and Lymphoma Society of Canada, the Charles Bruneau Foundation and the Fondation des Gouverneurs de l'espoir. Drs. Maja Krajinovic and Daniel Sinnett also held National researcher carer award from the Fonds de recherche en santé du Québec (FRSQ) in conjunction with this work. The functional studies were conducted in part within the context of one of the projects of Genome Quebec and Genome Canada.

Links:

- [Dr. Maja Krajinovic's profile at Sainte-Justine University Hospital Research Center](#)
- [Dr. Daniel Sinnett's profile at Sainte-Justine University Hospital Research Center](#)
- Abstract of the study "[ATF5 polymorphisms influence ATF function and response to treatment in children with childhood acute lymphoblastic leukemia](#)"

About the CHU Sainte-Justine Research Center

The CHU Sainte-Justine Research Center is a leading mother-child research institution affiliated with the Université de Montréal. It brings together more than 1200 people, including over 200 researchers and clinician-researchers and 450 graduate and post-graduate students who carry out fundamental, clinical, and evaluative research on mother and child health. Research work falls under six research axes, namely Health Outcomes; Brain Diseases; Musculoskeletal Diseases and Movement Sciences; Viral and Immune Disorders and Cancers; Fetomaternal and Neonatal Pathologies; and Metabolic Health. It is focused on finding innovative prevention means, faster and less invasive treatments, as well as personalized approaches to medicine. The Center is part

of the Sainte-Justine University Hospital Centre, which is the largest mother-child centre in Canada and one of the four most important pediatric centres in North America. For more information, please visit www.chu-sainte-justine.org/research/

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