'Corrective genes' closer thanks to enzyme modification

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Scientists from the Université de Montréal and McGill University have re-engineered a human enzyme, a protein that accelerates chemical reactions within the human body, to become highly resistant to harmful agents such as chemotherapy, according to a new study published in The *Journal of Biological Chemistry*.

"Our team modified and decoded an enzyme structure," says Joelle Pelletier, a professor at the Université de Montréal's Department of Chemistry. "We discovered, to our surprise, that our intervention allowed the heart of the enzyme to increase its mobility. This unusual mobility caused the enzyme to resist the chemotherapy agent methotrexate - a result we never predicted and one that offers promise."

The research team made its discovery as it sought ways to help correct genetic diseases. "Our goal is to improve the injection of corrective genes in people suffering from genetic diseases," say Pelletier who is also co-director of PROTEO, a Quebec-based research group on the function, structure and engineering of proteins. "This discovery will lead to promising new avenues."

"We were intrigued to find the enzyme's internal flexibility was impacted by our modifications and that this fact played such a crucial role for resistance," says Albert Berghuis, a professor at the McGill University Department of Biochemistry and Canada Research Chair in Structural Biology. "We can now harness this insight to further advance therapies for genetic diseases such as leukemia."

More information: The paper, "Multiple Conformers in Active Site of Human Dihydrofolate Reductase F31R/Q35E Double Mutant Suggest Structural Basis for Methotrexate Resistance," published in *The Journal of Biological Chemistry*, was authored by Jordan P. Volpato, Elena Fossati Jonathan Blanchet, Lucie Poulin, Vanessa Guerrero and Joelle N. Pelletier of the Université de Montréal; Brahm J. Yachnin and Albert M. Berghuis of McGill University. www.jbc.org

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