Speeding up the drug discovery process to help patients

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An international research team has developed a new strategy that can predict the potential clinical implications of new therapeutic compounds based on simple cellular responses. This discovery was partly led by scientists affiliated with Université de Montréal (UdeM), and represents a major step forward in developing more effective drugs with fewer side

effects, much faster than before. The researchers conducted their work at Centre de Recherche de l'Hôpital Ste-Justine and published their findings in the prestigious journal *Nature Communications*.

Developing new drugs is a long, complex and costly process. It starts with identifying the molecule or "ligand" (such as a drug, hormone or neurotransmitter) that can activate or block the target or "receptor" involved in a disease. Compound identification and validation is one of the most important steps in ensuring that a new drug provides an effective clinical response with the fewest possible side effects.

"Most new drugs tested on human subjects fail in clinical trials because the therapeutic response is insufficient. Developing a strategy that infers potential clinical responses early in the drug discovery process would significantly improve drug candidate selection," said Besma Benredjem, the study's co-lead author and a doctoral student in pharmacology at UdeM.

Finding the needle in a haystack

"Our main goal was finding a way to categorize a large number of drug candidates based on similarities in their effectiveness in triggering a multiplicity of cellular responses that help identify the therapeutic action of new compounds," said Professor Graciela Piñeyro, co-senior author of the study and a researcher at CHU Sainte-Justine. To accomplish this, she worked with Dr. Olivier Lichtarge of Baylor College of Medicine, who uses advanced bioinformatic analysis to compare and group ligands according to fairly comprehensive signalling profiles.

Drugs produce desired or undesired clinical actions by changing basic signals within cells. By grouping drugs with known clinical actions and new ligands, we can infer the clinical actions of new compounds by comparing the similarities and differences in their signals with known

drugs to promote desired clinical responses and avoid side effects.

This method of analysis was developed by using opioid analgesics as prototypes. This made it possible for the team to associate simple cellular signals produced by opioids such as oxycodone, morphine and fentanyl with the frequency with which respiratory depression and other undesirable side effects of these drugs were reported to the Food and Drug Administration's pharmacovigilance program. At the height of the opioid epidemic, when the risk of death by respiratory depression is at its highest, the team believes this new analytical strategy could lead to the development of safer opioids.

"Thanks to our findings, we can now classify a large number of compounds while taking a multitude of cellular signals into account. The wealth of comparisons this provides increases this classification's predictive value for clinical responses," said Professor Michel Bouvier, the study's co-senior author and a principal investigator of molecular pharmacology and Chief Executive Officer of UdeM's Institute for Research in Immunology and Cancer. "We think we can help patients by speeding up the drug discovery process so clinical trials can start earlier."

"Our next goal is to use a similar approach to test cannabis products that may produce harmful neuropsychiatric actions among young people, and identify which cannabis extracts are most effective at treating chronic pain," added Besma Benredjem.

More information: Besma Benredjem et al. Exploring use of unsupervised clustering to associate signaling profiles of GPCR ligands to clinical response, *Nature Communications* (2019). DOI: 10.1038/s41467-019-11875-6