Conscience Shares Results of CACHE Challenge #5, Targeting MCHR1, a G-Protein Receptor Linked with Metabolic Disorders

Results show multiple routes to success against a high-value drug target, underscoring the value of methodological diversity

GPCRs are among the most important classes of drug targets

Toronto, ON, Canada, August 18, 2026 — Conscience, a Canadian non-profit dedicated to enabling drug discovery through open science and collaboration for the advancement of accessible treatments, is pleased to share the results and highlight the five top-performing teams for its fifth CACHE (Critical Assessment of Computational Hit-Finding Experiments) Challenge. CACHE Challenge #5 focused on MCHR1, a G-protein coupled receptor (GPCR) associated with metabolic disorders such as obesity and sleep regulation. GPCRs represent one of the most important classes of drug targets, making MCHR1 a scientifically and therapeutically relevant focus.

Designed to reflect the practical constraints that often shape real-world drug discovery efforts, Challenge #5 was presented with the absence of an experimentally determined protein structure. Participants were given large datasets of known molecules that bind to MCHR1 and asked to predict new, previously unexplored molecules capable of blocking its activity. All predicted compounds were independently tested by a world-leading laboratory on GPCR inhibition at the University of North Carolina, ensuring rigorous validation of the findings.

“CACHE #5 was our first challenge focused on a GPCR, a major therapeutic target class of hundreds of proteins. Most do not have experimentally solved 3D structures. We selected one of these proteins and asked CACHE participants to collectively identify the best computational methods to discover new drug-like ligands,” said Matthieu Schapira, CACHE’s Scientific Coordinator and Principal Investigator at the Structural Genomics Consortium and Professor at University of Toronto. “We expected to see ligand-based techniques, but in the end, most participants decided to build a 3D model of MCHR1 to guide their design.”

Participants in CACHE Challenge #5 primarily used two approaches. Most teams leveraged AI-predicted protein structures and structure-based design methods, while others relied on ligand-based approaches that used information from known binders to guide the design of new ones. Multiple teams identified active compounds with significant chemical novelty, but notably, the most potent hit came from a purely ligand-based technique that used a quantum chemical representation of molecules. The five top performing teams illustrate how these approaches were applied in practice. A team from Pharmacelera in Barcelona, led by Javier Vázquez, used a ligand-based approach, which involved decomposing molecules into fragments and recombining them in novel ways. Olexandr Isayev's team at Carnegie Mellon University used a receptor-based approach to refine the output of a ligand-based virtual screen. A team from Stanford University, led by Alex Powers, achieved positive results using a receptor-based generative model. Olga Tarkhanova of Chemspace LLC in Kyiv, Ukraine led a team that performed well by improving on an existing method using machine learning, combining top-predicted chemical fragments into a customized library for receptor-based virtual screening. Andrea Volkamer's team at Saarland University in Germany used an ensemble of diverse deep learning methods to select molecules and refine predictions.

"We congratulate the top-performing teams for their exceptional work and commitment to CACHE Challenge #5," added Schapira. "The results demonstrate the value of bringing together a range of perspectives and techniques, and I believe there are valuable lessons for the GPCR medicinal chemistry field."

The CACHE Challenges are governed by Conscience, in collaboration with representatives from leading companies involved in biopharmaceutical and life sciences research and development, and draw on small molecule design expertise from around the world. Since its inception, CACHE has worked to advance the field of computational hit finding through open, rigorous benchmarking. While no single breakthrough has yet emerged, recurring patterns across successful approaches are generating valuable insights and helping establish a stronger foundation for future advances in drug discovery.

Conscience has now announced the results of five CACHE Challenges, and there are currently three additional CACHE Challenges underway, with the ninth to be announced in late 2026.

Challenge #	Target	Launch Date	Status
CACHE #1	WDR domain of LRRK2, the most mutated protein in familial Parkinson's disease	01/12/2022	Complete; Identification of 7 promising molecules that show potential for new, more effective drugs for familial Parkinson's disease
CACHE #2	The conserved RNA binding site of SARS-CoV-2 NSP13, relevant for all coronaviruses	22/06/2022	Complete; Identification of 7 promising early-stage molecules that could lead to a new treatment against all coronaviruses
CACHE #3	Molecules to bind on a potential target to develop medicines against SARS-CoV-2	02/11/2022	Complete; Identification of 4 chemically novel molecules that show promise as starting points for drug development
CACHE #4	Novel molecules that bind to CBLB, a cancer immunotherapy target	09/03/2023	Complete; Identification of a chemically novel and bioactive molecule
CACHE #5	MCHR1, a G-protein coupled receptor (GPCR) implicated in metabolic disorders including obesity and sleep regulation	19/12/2023	Complete; Identification of potent candidate molecules, including compounds that demonstrated significant chemical novelty
CACHE #6	SETDB1, a multi domain protein involved in epigenetic mechanisms and an immuno-oncology target	08/05/2024	In Progress: R2 Experimental Testing
CACHE #7	Molecules that selectively inhibit PGK2, an enzyme essential for sperm motility and a promising target for non-hormonal contraception	12/08/2025	In Progress: R1 Predictions submitted 1500/2500 compounds in final preparation for shipment
CACHE #8	Ligands targeting GID4, a protein involved in cellular protein quality control. GID4 plays a role in the cell's protein disposal system	17/02/2026	In Progress: R1 Hit Identification predictions due September 1st, 2026.
CACHE #9	TBD	TBD	Expected late 2026

Additional Quotes

“The Government of Canada congratulates the teams participating in CACHE Challenge #5 for their outstanding contributions to open and collaborative drug discovery. This initiative reflects Canada’s commitment to advancing research that addresses urgent health challenges, supporting innovative science, and promoting partnerships across borders. By fostering rigorous, accessible, and transparent research, the Government is helping accelerate the discovery of new treatments that have the potential to improve lives in Canada and around the world.”
— The Honourable Mélanie Joly, Minister of Industry and Minister responsible for Canada Economic Development for Quebec Regions

“Participating in the CACHE Challenge on MCHR1 was an excellent opportunity for us at Pharmacelera to evaluate our tools within a state-of-the-art framework. As a computational scientist, it is particularly rewarding to see how 3D QM-based descriptors can provide a distinctive approach to addressing novelty in molecular similarity searches, helping to overcome some of the traditional barriers to the discovery of novel bioactive molecules. Initiatives such as the CACHE Challenges help overcome limitations of current virtual screening benchmarks by offering a more realistic and challenging evaluation framework based on real drug discovery challenges. Continued efforts in this direction will help expand the boundaries of drug discovery and unlock new opportunities in pharmaceutical research.”
— Javier Vasquez, Senior Research Scientist at Pharmacelera S.L.

”The CACHE competition has been a valuable opportunity for our team to apply emerging computational methods to challenging problems in drug discovery. By enabling rigorous, systematic comparisons across diverse approaches, CACHE provides an important benchmark for the drug discovery community and helps cut through the noise in a rapidly evolving field. It has been especially rewarding to learn from the breadth of creative strategies being developed across the community.”
— Alex Powers, CTO of Flex Therapeutics

”Predicting novel antagonists for a GPCR with no experimental structure is one of the harder problems in structure-based drug discovery. Our Discovery Services team tackled it by combining physics-based virtual screening across ultra-large chemical spaces with active learning, using a synthon-based algorithm. This integrated strategy placed us among the highest-ranked scores in CACHE Challenge #5. We are proud of this result, and of what open community benchmarks like CACHE make possible: honest,

rigorous evaluation that drives the field forward."
— Olga Tarkhanova, PhD, CEO of Chemspace

"CACHE Challenge #5 was a great opportunity to combine deep learning with established CADD methods such as docking and MM/GBSA to tackle a challenging GPCR target without an experimental structure. It also enabled a highly rewarding collaboration between groups from Saarland University, DFKI, and HIPS on campus, and provided valuable experimental feedback for our computational predictions. Open, independently validated benchmarking initiatives like CACHE are essential for advancing the field, allowing us to prospectively evaluate and compare methods; and to learn from the wider community's results, not just our own."
— Andrea Volkamer, Professor at Saarland University

About Conscience

Conscience is a non-profit focused on enabling drug discovery and development in areas where open sharing and collaboration are key to advancement towards accessible treatments. It does so by encouraging and funding the open sharing of knowledge and tools, the use and improvement of artificial intelligence, and the development of policies that break down barriers of traditional drug development. Powered by a network that includes academics, industry, technologists, policy experts, and public support, Conscience seeks to drive innovation by turning drug discovery and development into a team sport. Its open science model brings unique value in areas where market solutions are limited, offering alternatives to traditional intellectual property models to make new accessible medicines so no one is left behind. Through key initiatives, such as its DMOS (Developing Medicines through Open Science) program and CACHE (Critical Assessment of Computation Hit-finding Experiments) Challenges, Conscience is accelerating the path to treatments for those who need them most. For more information, visit conscience.ca.

About the CACHE Challenges

The CACHE (Critical Assessment of Computation Hit-finding Experiments) Challenges offer an open competition platform to help accelerate one of the early stages of drug discovery. Researchers from academia, industry, and nonprofits are invited to deploy their best computational methods to predict small molecules that will bind to a predefined target linked to a specific disease, a critical step in the drug discovery pipeline known as hit-finding. Their predictions are evaluated and benchmarked in a state-of-the-art laboratory, by our partners at the Structural Genomics Consortium

(SGC). All the benchmarked results are shared openly and publicly with the world, and all chemical structures are made available without patent to all. Visit conscience.ca/cache-challenge/.

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