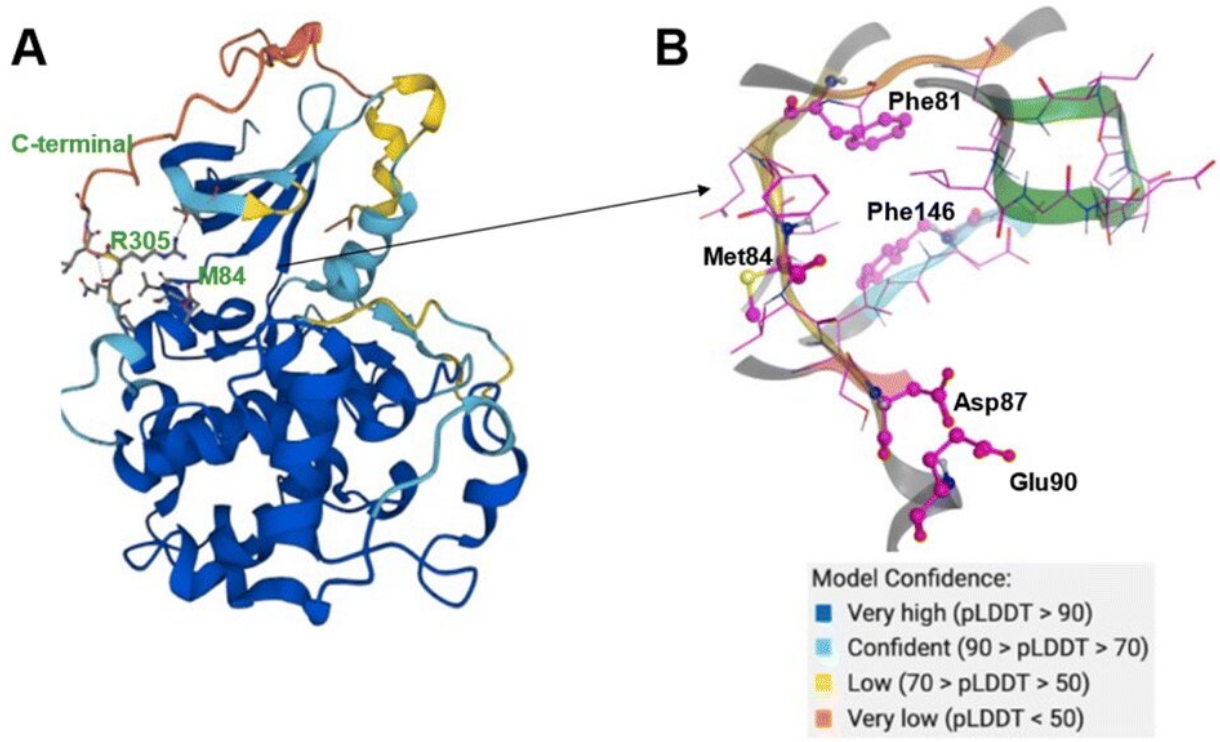
New study uses AlphaFold and AI to accelerate design of novel drug for liver cancer

January 19 2023



(A) The AlphaFold predicted structure of CDK20 (AF-Q8IZL9-F1-model_v1); (B) ATP pocket of CDK20 with a DFG-in (residue Phe146) conformation. Met84 is the hinge residue. P-loop is colored in green. Two acid centers Asp87 and Glu90 are located in the solvent-exposed region of the protein. Credit: *Chemical Science* (2023). DOI: 10.1039/D2SC05709C

New research uses AlphaFold, an artificial intelligence (AI)-powered protein structure database, to accelerate the design and synthesis of a drug to treat hepatocellular carcinoma (HCC), the most common type of primary liver cancer. It is the first successful application of AlphaFold to hit identification process in drug discovery.

This study by an international team of researchers, published last week in *Chemical Science*, is led by the University of Toronto's Acceleration Consortium director Alán Aspuru-Guzik, Chemistry Nobel laureate Michael Levitt, and Insilico Medicine founder and CEO Alex Zhavoronkov.

AI is revolutionizing drug discovery and development. In 2022, the AlphaFold computer program, developed by Alphabet's DeepMind, predicted protein structures for the whole human genome—a remarkable breakthrough in both AI applications and structural biology. This free AI-powered database is helping scientists predict the structure of millions of unknown proteins, which is key to accelerating the development of new medicines to treat disease and beyond.

In this new paper, AlphaFold was successfully applied to an end-to-end AI-powered drug discovery platform called Pharma.AI, including a biocomputational engine, PandaOmics, and a generative chemistry engine, Chemistry42.

Researchers discovered a novel target for HCC—a previously undiscovered treatment pathway—and developed a novel hit molecule—a molecule that could bind to that target—without the aid of an experimentally determined structure. This was accomplished in just 30 days from target selection and after only synthesizing 7 compounds. In a second round of AI-powered compound generation, researchers discovered a more potent hit molecule.

"While the world was fascinated with advances in generative AI in art and language, our generative AI algorithms managed to design potent inhibitors of a target with an AlphaFold-derived structure," said Alex Zhavoronkov, founder and CEO of Insilico Medicine.

"AlphaFold broke new scientific ground in predicting the structure of all proteins in the human body," said Feng Ren, co-author, Chief Scientific Officer and co-CEO of Insilico Medicine. "At Insilico Medicine, we saw that as an incredible opportunity to take these structures and apply them to our end-to-end AI platform in order to generate novel therapeutics to tackle diseases with high unmet need. This paper is an important first step in that direction."

Without AI, scientists must rely on conventional trial and error methods of chemistry that are slow, expensive and limit the scope of their exploration. As COVID-19 has demonstrated, the speedy development of new drugs or new formulations of existing ones is needed and increasingly expected by the public. AI has the potential to deliver this speed by transforming materials and molecular discovery, as it has done with just about every branch of science and engineering over the last decade.

"This paper is further evidence of the capacity for AI to transform the drug discovery process with enhanced speed, efficiency, and accuracy," said Michael Levitt, Nobel Prize winner in Chemistry, Robert W. and Vivian K. Cahill Professor of Cancer Research and Professor of Computer Science, Stanford University. "Bringing together the predictive power of AlphaFold and the target and drug design power of Insilico Medicine's Pharma.AI platform, it's possible to imagine that we're on the cusp of a new era of AI-powered drug discovery."

"What this paper demonstrates is that for healthcare, AI developments are more than the sum of their parts," said Alan Aspuru-Guzik, a

professor of chemistry and computer science at the University of Toronto and the Canada 150 Research Chair in Theoretical and Quantum Chemistry. "If one uses a generative model targeting an AI-derived protein, one can substantially expand the range of diseases that we can target. If one adds self-driving labs to the mix, we will be in uncharted territory. Stay tuned!"

Both Insilico Medicine and the Acceleration Consortium, a University of Toronto initiative that Aspuru-Guzik directs, are working actively to develop self-driving laboratories, an emerging technology that combines AI, automation and advanced computing to accelerate materials and molecular discovery. Accessible tools and data will help more scientists enter the field of AI for science, in turn helping to drive major progress in this area.

More information: Feng Ren et al, AlphaFold accelerates artificial intelligence powered drug discovery: efficient discovery of a novel CDK20 small molecule inhibitor, *Chemical Science* (2023). DOI: 10.1039/D2SC05709C

Provided by University of Toronto