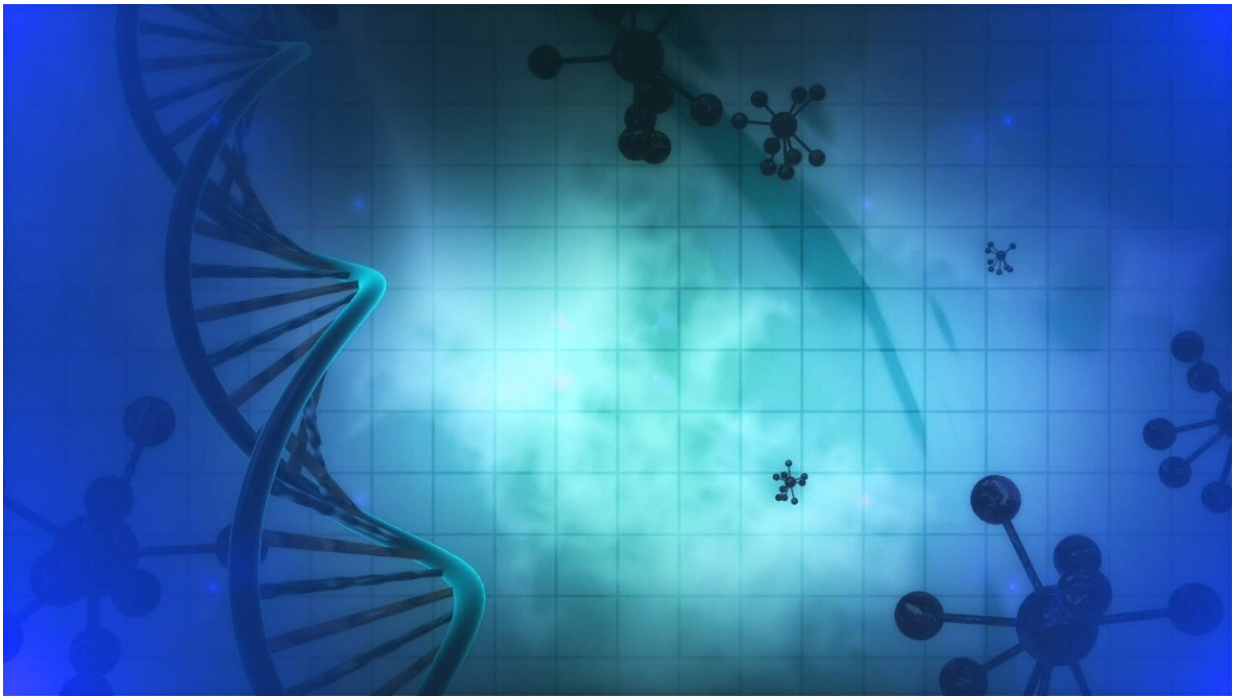
Molecular simulations show how drugs block key receptors

June 24 2020



Credit: CC0 Public Domain

Many pharmaceuticals work by targeting what are known as 'G-protein-coupled receptors.' In a new study, scientists from Uppsala University describe how they have been able to predict how special molecules that can be used in new immunotherapy against cancer bind to these receptors. The researchers' calculation methods, presented in the journal *Angewandte Chemie* are a vital contribution to future structure-based

drug design.

G-protein-coupled receptors (GPCRs) are among the protein target groups of the greatest importance for drug development. These receptors react to, for example, light, flavors, smells, adrenaline, histamine, dopamine and a long list of other molecules by transmitting further biochemical signals inside cells. The researchers who carried out the survey of GPCRs were rewarded with the Nobel Prize in Chemistry in 2012.

Today, roughly 30 percent of all drugs on the market have GPCRs as their target proteins. Some drug molecules, such as morphine, activate the receptors (agonists) while others, such as beta blockers, inactivate them (antagonists).

One important GPCR is the adenosine A2A receptor. Its antagonists can be used in new immunotherapy against cancer. Jointly with the biopharmaceutical company Sosei-Heptares, the researchers Willem Jespers, Johan Åqvist and Hugo Gutierrez-de-Terán of Uppsala University have succeeded in showing how a series of A2A antagonists bind to the receptor and inactivate it.

With molecular dynamic simulations and calculation of binding energies, it became possible to predict how molecules from the pharmaceutical company would bind to the receptors and how strongly they do so. Thereafter, new antagonists were designed, and synthesized by chemists from Santiago de Compostela University, Spain. Three-dimensional structures of the complexes that form between these molecules and the receptor were then determined experimentally with X-ray crystallography. Computer calculations proved capable of predicting both the structure and the binding strength in the complexes with high precision.

"This is a solid step forward, and we managed to predict with great precision how this family of molecules bind the A2A receptor. Our calculation methods are now having a major breakthrough in structure-based drug design," says Hugo Gutierrez-de-Terán, who headed the Uppsala group's project.

More information: Willem Jespers et al. X-Ray Crystallography and Free Energy Calculations Reveal the Binding Mechanism of A2A Adenosine Receptor Antagonists., *Angewandte Chemie International Edition* (2020). DOI: 10.1002/anie.202003788

Provided by Uppsala University