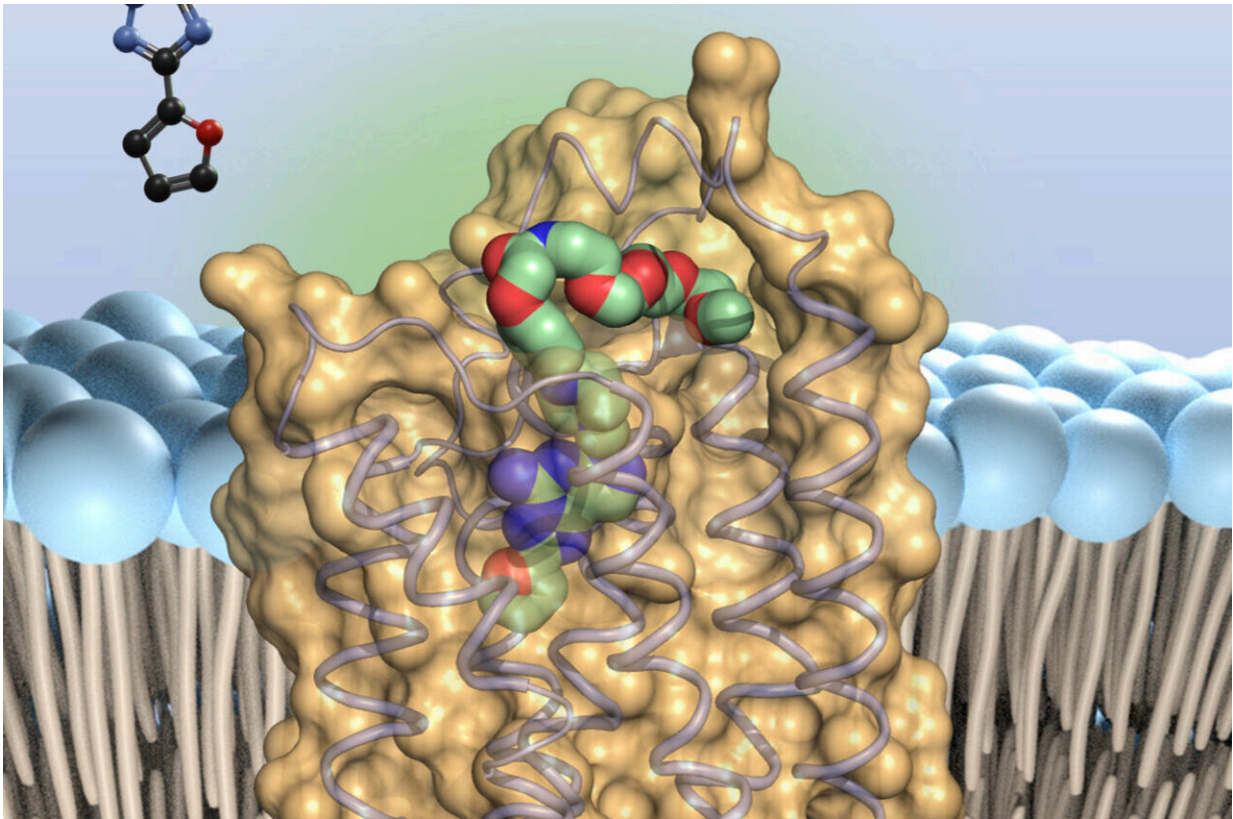


Study shows how bioactive substance inhibits important receptor

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The adenosine antagonist (colored) - binds to tiny antennae on the surface of the immune cells, the adenosine receptors of type 2A. This slows down the immune troops. Credit: University of Bonn

The A2A receptor regulates how vigorously the innate immune system attacks diseased cells. Researchers at the University of Bonn have now

been able to show for the first time how an important inhibitor binds to the receptor. In the future, the results will facilitate the targeted search for molecules that give the innate immune system more punch. These could for instance be used in the fight against cancer, but also against brain diseases such as Alzheimer's or Parkinson's disease. The final version of the study has been published in the journal *Angewandte Chemie International Edition*.

Anyone who enjoys reading thrillers knows: Before thieves break into a mansion, they like to toss a juicy chop over the fence, in which they have hidden a few sleeping pills. When the watchdogs get down to their second dinner, they succumb to deep slumber shortly thereafter. The jewels of the lady of the house change hands much more unperturbed after that.

Tumor cells often proceed in a very similar way: They cast out sleeping pills that paralyze the immune system. More specifically, they surround themselves with a cloud of adenosine, an important endogenous messenger. In this way, they disable the body's own "killer cells", which would otherwise cause the [cancer cells](#) to die.

This is because the adenosine molecules bind to tiny antennae on the surface of the immune cells, the A2A receptors (the abbreviation stands for "type 2A adenosine receptors"). This knocks out the defensive troops, so to speak. Researchers around the globe are therefore looking for molecules that can block the A2A receptor and prevent the paralyzing effect of adenosine.

Bombardment with X-rays

"Our study should make this search a lot easier," explains Prof. Dr. Christa Müller of the Pharmaceutical Institute of the University of Bonn. "We have added novel variants of a known inhibitor, a substance called

preladenant, to the A2A receptor. Then we created crystals from the receptor-inhibitor complexes—it's the first time in the world that this has been achieved with preladenant-like substances."

Crystallization made it possible to elucidate the structure of the complex. "To do this, we bombard the compound with X-rays," explains Tobias Claff, who performed the main part of the experiments. "The crystal diffracts the rays. The way it does this then allows us to deduce the spatial structure of the complex—right down to the arrangement of individual atoms and their interactions."

In this way, the researchers were able to show to which points of the A2A receptor preladenant binds. With this knowledge, it is now possible to specifically modify the inhibitor to give it better properties. In addition to having the strongest possible effect, drugs should for example not be broken down too quickly. They also need to be able to reach the place where they are supposed to do their work—in this case, the brain. "Our study will make it much easier to optimize the substance," Claff says with optimism.

A2A belongs to a group of receptors that regulate key functions in the body. They span the membrane of cells. The part of them that sits on the outside of the membrane serves as a sensor, receiving molecular signals like an antenna. When it does, it triggers specific reactions with its part that protrudes into the cell. This then activates certain genes, for example.

Dye bound to the inhibitory molecule

"These receptors are immensely important because of their central position," says Christa Müller, who is also a member of the Transdisciplinary Research Areas (TRA) "Building Blocks of Matter" and "Life and Health." "Many of them, however, are unfortunately

relatively unstable. This is unfavorable for X-ray structural analyses—crystallization takes days, sometimes even weeks." The researchers therefore specifically modified the A2A receptor at a single point, making it considerably more stable.

Additionally, they succeeded in attaching a dye to the preladenant with a kind of molecular string. "This allows us to control where in the tissue preladenant attaches to the A2A receptor," Müller says. At the same time, the length and flexibility of the nanostring ensures that the inhibitor is not obstructed from binding to the receptor.

Both advances could also serve as models for work with other receptors that belong to the same group. "The methods we have developed in Bonn in recent years will allow us to elucidate the structure of such and other cell membrane proteins in the future," the pharmacist is convinced. "There aren't many research facilities that can do this kind of structural analysis of extremely complex molecules."

More information: Tobias Claff et al, Single Stabilizing Point Mutation Enables High-Resolution Co-Crystal Structures of the Adenosine A 2A Receptor with Preladenant Conjugates, *Angewandte Chemie International Edition* (2022). [DOI: 10.1002/anie.202115545](https://doi.org/10.1002/anie.202115545)

Provided by University of Bonn

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