New opportunity for cancer drug development

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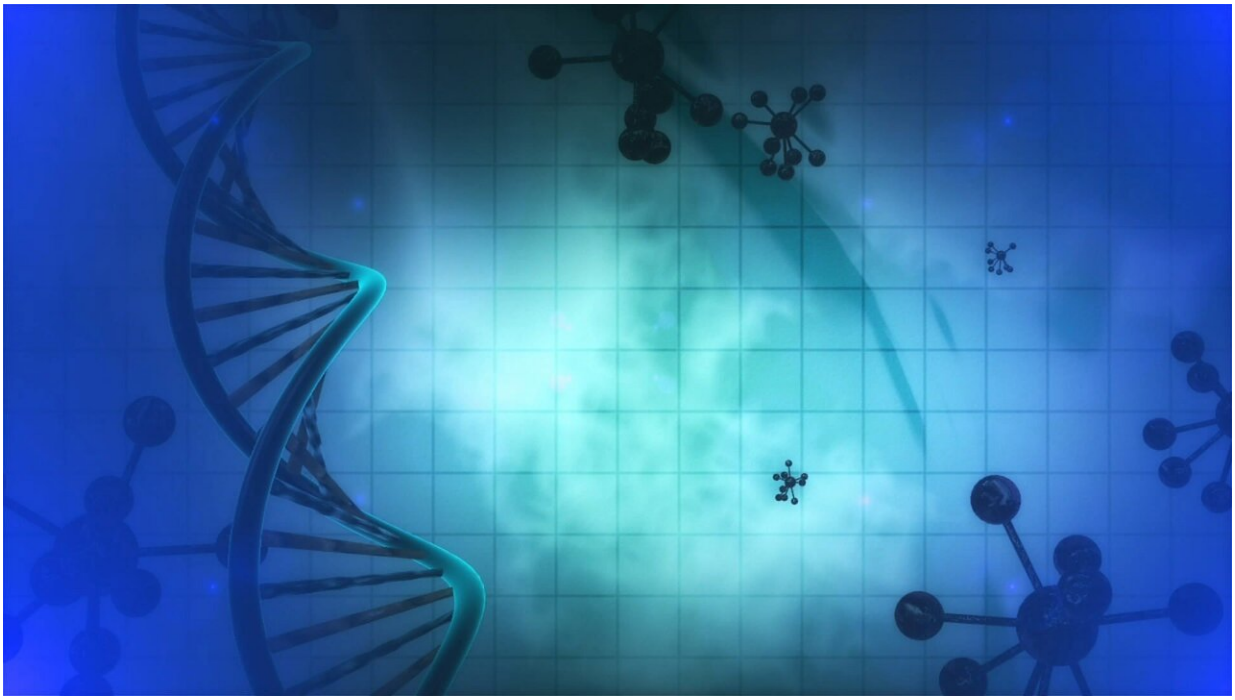

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After years of research on cell surface receptors called Frizzleds, researchers at Karolinska Institutet in Sweden provide the proof-of-principle that these receptors are druggable by small molecules. The results, which are published in the scientific journal *Nature Communications*, open the way for new strategies to treat different types of cancer.

For more than 20 years Frizzleds (FZDs) have been proposed as suitable therapeutic targets for the treatment of diverse forms of cancer and several other disorders, such as fibrosis and cardiovascular disorders. They belong to the family of G protein-coupled receptors, which are involved in the progress of many diseases and are very common targets for drugs.

Great efforts have been undertaken to attack FZDs using therapeutic antibodies and other biopharmaceuticals. It has not previously been possible to design small molecules that would target FZDs pharmacologically. The Schulte laboratory at the Department of Physiology and Pharmacology, Karolinska Institutet, has now repurposed an existing small-molecule drug targeting a related receptor and shown that it can bind to and activate FZDs.

"Our study provides proof-of-principle that it is possible to target FZDs with small molecules," says Professor Gunnar Schulte, who led the study. "This is a breakthrough laying the basis for development of novel and improved compounds that target FZDs for the treatment of different types of cancer."

Key to the discovery was on the one hand a basic understanding of FZDs as pharmacological receptors and on the other hand a technical advance in drug screening.

"However, the most important driving force was a clever, translational idea by postdoctoral fellow Pawel Kozielewicz in my lab, who identified the first small molecule that activates a Frizzled receptor," says Gunnar Schulte. "Furthermore, computer simulations performed by postdoctoral fellow Ainoleena Turku allowed validation of laboratory experiments presenting deep structural insight into receptor-drug interactions."

More information: Paweł Kozielewicz et al, Structural insight into

small molecule action on Frizzleds, *Nature Communications* (2020). DOI: 10.1038/s41467-019-14149-3

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