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Researchers shed pharmacological light on formerly 'dark' cellular receptors

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Bryan Roth, MD, PhD

Our cells are constantly communicating, using neurotransmitters and hormones to signal to each other. Molecular receptors on each cell receive these chemical signals and allow cells to accomplish a task important for health. Astonishingly, for about half of these receptors, the chemical signals remain unknown. These "orphan receptors" are highly expressed in particular tissues but their functions remain a mystery. They are considered "dark" elements of the genome, and yet they hold great potential for drug development for a variety of diseases and conditions.

Now, scientists at the University of North Carolina School of Medicine (UNC) and University of California, San Francisco (UCSF) have created a general tool to probe the activity of these orphan receptors, illuminating their roles in behavior and making them accessible for drug discovery. The creation of the research tool - which involves computer modeling, yeast- and mammalian cell-based molecular screening techniques, and mouse models - was published today in the journal *Nature*.

This work will help researchers learn how orphan receptors interact with molecules inside the body or with drugs. Specifically, the UNC and UCSF scientists used their new tool to find a novel probe molecule that can modulate the orphan G protein-coupled receptor 68 (GPR68, also known as OGR1), an orphan receptor that is highly expressed in the brain.

"GPCRs are the single most important family of therapeutic drug targets," said Brian Shoichet, PhD, professor of pharmaceutical chemistry at UCSF. "About 27 percent of FDA-approved drugs act through GPCRs. They are considered to be among the most useful targets for discovering new medications."

The new probe molecule, dubbed "ogerin," turns on GPR68, activating its signaling role. To understand how this activation of GPR68 affects brain function, the investigators gave it to mice and put them through a battery of behavioral tests. Mice that had been given ogerin were much less likely to learn to fear a specific stimulus. This "fear-conditioning" is controlled by the hippocampus, where GPR68 is highly expressed. But ogerin had no effect on mice that lacked this receptor.

To demonstrate general research applicability, the UNC and UCSF researchers also used their technique to find molecules that can modulate GPR65, another orphan receptor.

"We provide an integrated approach that we believe can be applied to many other receptors," said Bryan L. Roth, MD, PhD, co-senior author of the *Nature* paper and the Michael Hooker Distinguished Professor of Protein Therapeutics and Translational Proteomics in the Department of Pharmacology at UNC. "The goal is to quickly find drug-like compounds for these receptors. This should facilitate discovery of novel and safer therapeutics for a host of diseases."

Xi-Ping Huang, PhD, co-first author and research assistant professor at UNC, said, "We used yeast-based screening techniques to find compounds that activate an orphan receptor. Then [co-first author] Joel Karpiak, a graduate student in Shoichet's lab at UCSF, created a computer model and searched libraries of millions of compounds to find out what kind of molecular structure ensures proper binding and interaction with a specific receptor. Then, back in the lab, we tested new molecules and found a novel ligand."

A ligand is a chemical that binds to a specific part of a protein, such as a receptor.

"The fact that GPR68 is highly expressed in several tissues, especially the brain, and that it is a member of the large GPCR family, suggests that this discovery can be further leveraged for drug discovery," Shoichet said.

Currently, few drug developers would seek drugs for a target with an unknown role in human biology. With new evidence of the role of GPR68 - and a molecule that can modulate that role - the door has been opened for further research studies, both basic and applied.

"The druggable genome is an iceberg that is mostly submerged," Shoichet said. "This paper illuminates a small piece of it, providing new reagents to modulate a previously dark, unreachable drug target. Just as

important, the strategy should be useful to many other dark targets in the genome."

Roth's lab is well known for developing technologies to probe biological function. His team developed DREADDS (Designer Receptors Exclusively Activated by Designer Drugs), for which he was given an NIH BRAIN Initiative grant. First results on work from that grant were reported earlier this year with the development of a second kind of DREADD.

For the *Nature* paper, Roth's lab teamed up with Shoichet lab, which developed the computational method to screen more than 3.1 million molecules for potential activity on GPR68. The goal was to predict those very few molecules that could modulate the receptor. This eventually led them to the molecule ogerin. The same approach also helped the team discover compounds that activated or modulated GPR65, suggesting that the approach could help scientists discover ligands for other understudied and orphan G protein-coupled receptors.

"Orphan receptors could be a great source of therapeutics," Huang said. "But it has been difficult to study them. The research community has needed an approach that works, and that's why we put so much effort into this."

More information: Allosteric ligands for the pharmacologically dark receptors GPR68 and GPR65, DOI: 10.1038/nature15699

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