Molecular biologists Robert Lefkowitz (left) and Brian Kobilka share this year's Nobel Prize in Chemistry.

NOBEL PRIZE

Nobel work boosts drug development

Chemistry prize honours studies of cell-receptor proteins.

BY RICHARD VAN NOORDEN

Robert Lefkowitz and Brian Kobilka both trained as medical doctors, but the allure of cell signalling drew them into basic research. And medicine has benefited handsomely: their research on proteins central to cell communication has aided the discovery of many pharmaceuticals and may open up ways to design more-selective drugs. Last week, it also earned the two researchers this year's Nobel Prize in Chemistry.

Lefkowitz, a garrulous, engaging New Yorker at Duke University Medical Center in Durham, North Carolina, and the notoriously reserved Kobilka of Stanford University School of Medicine in California have spent their careers studying G-protein-coupled receptors (GPCRs). These proteins loop across cell membranes, transferring external signals — such as spurts of hormones or bursts of neurotransmitters — into the cell, where they trigger cascades of biochemical activity.

At least 30% of all drugs target these membrane proteins, which form a family of around 800 closely related structures. One of the greatest medical inventions of the past century, the beta-blocker, calms the heart by attaching to GPCRs and blocking their reaction to the hormone adrenaline — although renowned British pharmacologist James Black did not know these details when he developed the first successful beta-blocker, propranolol, in 1964.

In the late 1960s, Lefkowitz began to tease

out the details of GPCRs, focusing on the β_2 adrenergic receptor (β_2 AR), a receptor for adrenaline. By the 1980s, his team — including Kobilka, who had joined the lab on a fellowship — had purified enough of the protein to clone and sequence it. The receptor's striking similarity to rhodopsin, a light receptor in the eye that had already been sequenced, was a “total shock”, says Lefkowitz, and hinted that such receptors might form a family.

As more of these proteins were identified, they were put to use in drug development, says Fiona Marshall, chief scientific officer of the GPCR-focused drug firm Heptares Therapeutics in Welwyn Garden City, UK. Rather than looking for a chemical's effects on animal tissue, chemists could screen thousands of compounds for their affinity for GPCRs in a test tube. Drugs discovered in this way include Pfizer's antiretroviral Maraviroc, which blocks HIV from binding to cells and was approved by

the US Food and Drug Administration in 2007.

After leaving Lefkowitz's group, Kobilka spent two decades trying to capture a crystal structure of a GPCR — a fiendishly difficult task thanks to their tendency to unravel when extracted from the cell membrane¹. In 2007, his team finally delivered the structure² of the β_2 AR, only the second GPCR structure imaged — rhodopsin, more robust than other GPCRs, was the first³, in 2000. Since then, researchers have worked out the structures of another 13 receptors. Last year, Kobilka's team revealed an even more impressive structure: the β_2 AR frozen in action, connected to an adrenaline-like compound at one end and the cell's internal G protein at the other⁴.

Knowing these structures could help drug researchers to design better-targeted compounds. Many drugs affect multiple closely related receptors: the schizophrenia drug olanzapine (Zyprexa), for example, hits as many as a dozen GPCRs. Only a few of these hits produce benefits, however — others are redundant, or involved in side effects such as weight gain. As more crystal structures become available to work with, drug companies may be able to design molecules that fit more snugly into selected GPCRs. Heptares, for example, has a drug candidate for treating Alzheimer's disease that affects a receptor for acetylcholine found in the brain, but avoids closely related receptors in the heart and the gut.

Lefkowitz, meanwhile, has shown that GPCRs don't always engage G proteins inside the cell, but can also attach to proteins known as β -arrestins⁵, an interaction that he thinks is responsible for some drug side effects. He and Kobilka are currently working on what will be their first co-authored paper in 25 years: a step along the way to a crystal structure of β -arrestin attached to a receptor. But there are never any guarantees of success when wrestling with these floppy, recalcitrant proteins. As Kobilka told a press conference last week, his perseverance is based on “irrational optimism: you just keep thinking that something's going to work”. ■

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