Nobel pioneers unlocked the cell door

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For most of the 20th century, scientists were puzzled by how cells in our body are able to sense and react to external conditions.

How, for example, do cardiac cells know how to raise the heart rate when we are startled?

Over decades, a concept evolved that cell surfaces are dotted with tiny proteins called receptors. These respond to body chemicals, smell molecules and light, essentially giving instructions to the cells on what to do.

But it was work in the 1980s, which on Wednesday earned the Nobel Chemistry Prize for Americans Robert Lefkowitz and Brian Kobilka, that gave flesh to this theory and transformed it into a platform for drug research.

G-protein-coupled receptors (GPCRs) are known to influence everything from sight, smell and taste to blood pressure, pain tolerance and metabolism.

They tell the inside of cells about conditions on the outside of their protective plasma membranes, to which the cells can form a response—communicating with each other and with the surrounding environment.

Up to half the drugs that exist today aim at these tiny protein receptors, as they play a major role in influencing conditions ranging from allergies

to depression and Parkinson's disease.

They are targeted by everything from anti-histamines to ulcer drugs to beta blockers that relieve hypertension, angina and coronary disease.

"G-protein coupled receptors have for a long time been the holy grail of membrane protein research," Mark Sansom, a professor of molecular biophysics at the University of Oxford, told Britain's Science Media Centre.

"They are fundamental to regulation of many physiological processes, from the nervous system to taste and smell. They are also a major class of drug target and are incredibly important to the pharmaceutical industry."

GPCRs today are a big family—so far, about 1,000 members have been found—as well as big business.

But when Lefkowitz began his research back in 1968, cell receptors were still a nebulous concept for which there was no practical evidence.

By attaching an iodine isotope to various hormones and mapping the radiation, he was able to find a receptor for adrenalin, called the beta-adrenergic receptor.

The next big step was in the 1980s, when Lefkowitz was joined by a post-doctoral fellow, Brian Kobilka.

Lefkowitz threw down a gauntlet. He asked him to isolate the gene that codes for the beta-adrenergic receptor—a task equivalent in those days to finding a needle in a DNA haystack.

Kobilka tenaciously took up the challenge and succeeded. When the pair

analysed the gene, they discovered that the receptor was similar to one in the eye that captures light.

In other words, there was a whole clan of receptors that looked alike and functioned in the same way, even when the stimulus (in this case, light or hormones) was different.

"It was a real eureka moment," Lefkowitz told Nature journal last year. "We realised, oh my god, they're all going to look like this. It's a whole family!"

Kobilka went on to further achievements in determining how GPCRs work.

Using X-ray crystallography, in which a beam of X-rays is used to derive a three-dimensional image of a protein, in 2011 he captured an image of the beta-adrenergic receptor at the precise moment when it is activated by a hormone and sends a signal into the cell.

"This image is a molecular masterpiece—the result of decades of research," the Nobel committee said on Wednesday.

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