G-protein-coupled receptors show their potential

This year's Ariëns Award winner is Paul Insel. He was awarded for his work on G-protein-coupled receptors. 'There are around 120 'orphan' receptors that may represent untapped opportunities.'

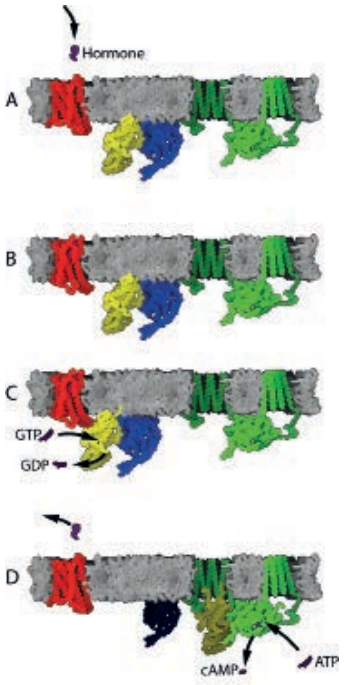
MARYSA VAN DEN BERG

Since 1985, the Dutch Society for Pharmacology (NVF) has been recognising the work of outstanding international pharmacologists with the annual Ariëns Award. It was named in honor of the Dutch professor Eef Ariëns, one of the founders of the field of pharmacology. This year's winner is Paul Insel, Vice-Chair and Distinguished Professor of Pharmacology and Distinguished Professor of Medicine at the University of California, San Diego. "Winning this award brings back good memories", says Insel. "Professor Ariëns and I corresponded in the 1980s. My recent work also matches nicely with some of his early ideas."

SCARRING

Insel primarily focuses on G-protein-coupled receptors (GPCRs), the largest family of signaling receptors in the human genome and that of almost all mammals. "GPCRs mediate vision, smell and taste", explains Insel, "but they are also crucial to how cells, organs, and tissues communicate with each other. These receptors bind and respond to a wide range of substances: photons, small chemical compounds, proteins, hormones, neurotransmitters and much more. Furthermore, GPCRs are the largest family of targets for currently approved therapeutic drugs."

Insel recently published on their expression in fibroblasts of the heart and its implications. With injury and inflammation, these fibroblasts are activated and produce connective tissue, which sometimes leads to scarring, or fibrosis. Until now there has been no effective treatment for this condition, says Insel. "We are working on the hypothesis that



'Winning this award brings back good memories'

stimulating or blocking certain GPCRs can block or even reverse fibrosis", he elaborates. "We found, for example, that the GPCR second messenger cyclic AMP [adenosine monophosphate, ed.] can reduce or even reverse the pro-fibrotic activity of fibroblasts. The GPCRs involved in this process are thus potential targets for novel drugs. We have started similar experiments in lung fibroblasts."

As of yet, no drugs have derived from Insel's research, but this should be a matter of time. Insel: "We found a GPCR involved in pulmonary arterial hypertension (PAH) that wasn't recognised before. We made a monoclonal antibody to this GPCR, which inhibits features of the pulmonary arterial smooth muscle cells from PAH patients. Thus, this GPCR and antibody have the potential for treatment of PAH."

ORPHANS

To explore this line further, Insel is currently looking for additional funding. Many questions remain. "For instance, there are about 120 GPCRs which are 'orphans', meaning we don't know how they are activated or what they do", says Insel. "My colleagues and I are studying several of those in order to learn about their expression, actions and regulation. We have discovered orphan GPCRs whose expression is low in healthy cells but quite high in cells that are diseased. So we think that these receptors may be intriguing drug targets, as well as regulators of cell function." Orphan GPCRs, as Insel emphasises, may thus represent untapped opportunities. "Especially since I was originally trained as a physician, it would be very pleasing to me to see that our work can one day lead to a drug that will help patients."