
UNIVERSITY OF NOTTINGHAM

Studying how drugs bind to living cells

This year's Ariëns Award winner is Stephen Hill, for his work on fluorescent ligands and G-protein-coupled receptors. 'Our NanoBRET technology really opened up the field of ligand binding studies.'

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 Everhardus Jacobus Ariëns, one of the founders of the field of pharmacology.

Histamine receptor

This year's winner is Stephen Hill, professor of molecular pharmacology at the University of Nottingham and current president of the British Pharmacological Society. 'I know Professor Ariëns as one of the original molecular pharmacologists. It is an honor to continue in his footsteps.'
Hill's PhD research focused on the histamine H1-receptor. He was the first ever to perform a radioligand binding study. 'That always kept ticking along; I never could drop my interest in binding interactions of G-protein-coupled receptors, or GPCRs', says Hill. 'I only moved from regular radioligands to fluorescent ligands for my binding studies because of the exciting opportunity to use them with confocal microscopy to study ligand binding dynamics in single cells. I find it exciting to now be able to monitor the binding of drugs to living cells in real time.'

'I find it exciting to monitor this in real time'

Collaboration

Hill's lab has an international lead in developing new fluorescent probe techniques and applying them to single molecule-interaction studies. It all started with, again, the histamine H1-receptor. 'We spent a lot of time modifying the antagonist for this receptor so that a fluorescent label could be attached to it without the molecule becoming too big', says Hill. 'We managed to use a linker to keep the fluorescent molecule away from interfering with the pharmacological warhead of the receptor ligand.'
A few years ago USA-based company Promega showed interest in collaborating with Hill's team. 'This company had just developed NanoLuciferase and wanted to take in our fluorescent binding approach. Together we came up with NanoBRET: bioluminescence resonance energy transfer, whereby the NanoLuciferase on the N-terminus of the receptor is within 10 nanometres of the binding ligand.'

Revolution

NanoBRET revolutionises the binding studies of receptors. Hill and his collegues tested the technology in several GPCR-families: histamine receptors, beta-adrenoceptors, adenosine receptors and the P2Y2-purine receptors. 'It worked stunningly well in all those receptor families', he says. 'We almost had no nonspecific binding and we were able to analyse the binding of an amazingly broad range of concentrations of the fluorescent ligand. I believe our NanoBRET technology really opened up the field of ligand binding studies further.'
The next step for Hill and his research group is using the advantages in genetic engineering to tag and view endogenously expressed receptors. 'We want to use gene editing to put our probes onto receptors under their endogenous promotors to make sure we can track the activity of the receptor at a normal expression level. The NanoBRET technology gives us the sensitivity to do that.' ●