It's about time: novel drug discovery concepts for the molecular pharmacological characterization fo the cannabinoid CB2 receptor

Bouma, J.

Stellingen

Behorende bij het proefschrift

It's about time

Novel drug discovery concepts for the molecular pharmacological characterization of the cannabinoid CB_2 receptor

1. Now that it is possible to measure and follow real time GPCR signaling through multiple pathways, the next challenges are how to collect the relevant kinetic data over the correct time and space scales, and most importantly, how to extract meaning from these new, very rich data sets. (*Hoare, S.R.J., et al. Front. Cell. Neurosci.* 2022; 15, 814547)

2. While bias is detected easily, the synoptic nature of GPCR signaling makes translation of simple *in vitro* bias to complex *in vivo* systems problematic. (*Kenakin, T. Br. J. Pharmacol.* 2024; 16335)

3. The concept of kinetic context represents an important new consideration that should be routinely incorporated into contemporary chemical biology and drug discovery studies of GPCR bias and allostery. (*Lane, J.R., et al. Nat. Chem. Biol.* 2017; 13, 929-937)

4. Even if clinical success with selective CB_2R ligands is still elusive at the moment, recent progress in discovering a multitude of high-quality CB_2R ligands will enable a better understanding of CB_2R biology and the endocannabinoid system in general, thereby unlocking the receptor's full therapeutic potential. (*Brennecke, B., et al. Pharm. Pat. Anal.* 2021; 10 (3), 111-163)

5. To improve the preclinical to clinical translational perspective, it is important to continuously develop and adapt biologically, physiologically, and pharmacologically relevant *in vitro* assays that may provide novel insights beyond the initial application. (*this thesis, chapters 2, 3*)

6. In case of successful implementation, multiplex assays will contribute greatly to novel insights into agonist-induced GPCR pharmacology. (*this thesis, chapter 3)*

7. Studying point mutations, either disease-related, natural variants or topographically-inspired, offers opportunities for obtaining a fundamentally better understanding of receptor targeting and downstream signaling or their role in pathophysiology. (*this thesis, chapters 4, 6*)

8. Binding kinetic parameters may have an application beyond diffusion and efficacy, specifically shedding light on binding mechanisms. (*this thesis, chapters 3, 4, 5*)

9. Great things in science are never done by one person. They're done by a team of diverse and inspiring scientists. (adapted from *Steve Jobs*)

10. Like tea, knowledge often flows – but not always in a steady stream. Sometimes it pours, drips, or evaporates. Either way, one is usually thirsty for more. (adapted from *Anna Bruins*)

11. You can't use up creativity. The more you use, the more you have. (*Maya Angelou*)

12. A PhD is like the final set of your workout: there is too much weight, you're tired, but you keep on going.

Jara Bouma

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