The road to Insurmountability: Novel avenues to better target CC Chemokine Receptors

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PROPOSITIONS

The road to Insurmountability

Novel avenues to better target CC chemokine receptors

1. Crystal structures provide answers to key questions related to the design and development of small-molecule modulators of chemokine receptors.
   This thesis, Kufareva I. et al., Curr Opin Pharmacol 2016, 30, 27-37

2. The discovery of intracellular binding sites among chemokine receptors, and GPCRs in general, combined with the array of strategies for targeting such sites, opens up new approaches to better study and target these receptors.
   This thesis

3. The intracellular binding site opens the door for the design of both selective and multi-target insurmountable antagonists.
   This thesis

4. *In vitro* characterization of binding affinity and binding kinetic parameters of drug candidates in all relevant species for pre-clinical studies is necessary to improve the preclinical and clinical translation of drug efficacy.
   This thesis, Chapter 7

5. When targeting chemokine receptors, prolonged high receptor occupancy is key to achieve *in vivo* efficacy in inflammatory and immune diseases.
   This thesis, Schall T. J. and Proudfoot A. E. I., Nat Rev Immunol, 2011, 5, 355-363

6. The recent clinical failures in several chemokine receptor antagonist programs could in part be attributed to trying to target complex diseases with an antagonist for a single receptor.
   Horuk R, Nat Rev Drug Discov. 2009, 8, 1, 23-33

7. The rational design of multi-target compounds is far from being an easy task, dealing with the crucial issues of selecting the right target combination, achieving a balanced activity towards them, and excluding activity at the undesired target(s), while at the same time retaining drug-like properties.
   Ramsay R. et al., Clin Trans Med 2018, 7:3

8. Ligands, synthetic or natural, are the single most powerful tool for elucidating GPCR mechanisms and physiology—data that will not only help to better understand the largest class of membrane proteins, but likely also translate into better therapies.
   Wacker, D., et al. Cell 2017, 170, 414-427

9. Pharmacology has always been a multidisciplinary science and it has been the biochemists, chemists, pharmacists, physiologists and clinicians coming from other disciplines who have made it what it is today… Pharmacology is a way of thinking and designing experiments.
   Stephen Hill, Br J Pharmacol, 2006, 147, 27-37

10. Enthusiasm combined with critical thought—what else do we need in science!
    Adapted from a quote by Rosa Luxemburg

11. One should approach science as an impressionist painting: you can focus on the brushstrokes, on the texture, or the colors, but you need to take some distance in order to appreciate the beauty in the big picture.

12. He who gets close to a good tree, is protected by a good shade (*El que a buen árbol se arrima, buena sombra le cobija*).