

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/62615> holds various files of this Leiden University dissertation.

Author: Xia, L.

Title: Corpora non agunt nisi fixata : ligand receptor binding kinetics in G protein-coupled receptors

Issue Date: 2018-05-30

Propositions

Corpora Non Agunt Nisi Fixata:

Ligand Receptor Binding Kinetics in G Protein-Coupled Receptors

1. Although the ligand-GPCR complex can be observed, the detailed molecular recognition or complex stability is unknown.

Chapter 1 of this thesis.

2. The concept and study of drug-target binding kinetics have emerged since the evolution of modern pharmacology.

Chapter 1 of this thesis.

3. Steady-state potency metrics (i.e. K_i and IC_{50}) are often used to characterize drugs targeting GPCR in a traditional early-phase drug discovery endeavor. However, there is mounting evidence to show that high affinity drug candidates cannot prevent high attrition rates in clinical trials.

Chapter 1 of this thesis.

4. The story of rimonabant might be tarnished by low public and regulatory acceptance for a drug designed to counteract the consequences of our abundant lifestyle. Focus should now return to motivating patients to control their caloric intake and increase physical activity. Although cumbersome, this approach is causal and safe. New strategies to more effectively achieve these lifestyle changes are needed.

S Matthijs Boekholdt, Ron J G Peters. Rimonabant: obituary for a wonder drug. The Lancet, vol 376, 2010, 489–490.

5. Our knowledge of the structure and function of A_3 AR has evolved dramatically in the last decade, but still this receptor, that we classically like to imagine similar to the double-personality of the character in the famous novel by Robert Louis Stevenson “The strange case of Dr. Jekyll and Mr. Hyde,” continues to be particularly enigmatic in its dichotomy between good and evil...Clearly, more comprehensive investigations are required to interpret these discrepant observations and to induce the A_3 AR to gradually reveal its secrets; in effect to discover where and/or when it behaves like Dr. Jekyll and where and/or when it becomes Mr. Hyde.

Stefania Gessi et al. The A_3 adenosine receptor: An enigmatic player in cell biology. Pharmacology & Therapeutics, Vol 117, 2008, 123-140.

6. The SPA technology not only improved the speed and throughput of the kinetic radioligand binding experiments, but also provided more, more precise and more accurate data.

Chapter 6 of this thesis.

7. There is no disputing the importance of statistical analysis in biological research, but too often it is considered only after an experiment is completed, when it may be too late.

Statistics for Biologists, nature.com

8. For an average scientist, perhaps 1% of experiments actually work. But for the superstar, it could be as high as 2%.

Robert J. Lefkowitz, A serendipitous scientist. Annual Review of Pharmacology and Toxicology, Vol 58, 2018, 17-32.

9. Science should not, and need not, be shackled by journal publication.

The shackles of scientific journals. The Economist, Mar 25th 2017.

10. The pharmaceutical industry has been, and will likely always be, the largest employer of medicinal chemists, and academic departments need to be more responsive to the needs of the discipline's largest employer if both communities are to thrive.

Michael F. Rafferty, No Denying It: Medicinal Chemistry Training Is in Big Trouble, Vol 59, 2016, 10859–10864.

11. I think I speak very poor English, but anyway I dare to say. This is very important. (我想我英语讲得不好, 但我敢于讲。这一点是非常重要的。)

The Speech in the Embassy of China in Washington, D.C., President Jiang Zemin. 1997.