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Stellingen
bij het proefschrift

Drug-target residence time
A case for the adenosine $A_1$ and $A_{2A}$ receptors

1. The importance of kinetics in drug-target interactions, and particularly the residence time of a drug at its target, is increasingly recognized to play a pivotal role in determining both the efficacy and toxicity of a drug. 

   *Zhang, R. and Monsma, F. Curr Opin Drug Discov Devel, 2009, 12:488-496*

2. The *in vivo* duration of drug action not only depends on macroscopic pharmacokinetic properties like plasma half-life and the time needed to equilibrate between the plasma and the effect compartments, but is also influenced by long-lasting target binding and rebinding. 


3. Manipulating physicochemical properties such as lipophilicity or molecular weight can lead to tuned drug-target residence times. However, these ‘intuitive’, ‘one size-fits-all’ approaches are very likely too simple and may increase the concern of binding to collateral targets, thereby resulting in unwanted side effects. 

   *This thesis, Chapter 2*

4. During the binding and unbinding process tremendous hydration and dehydration of both the ligand and the receptor is involved, which appears to be a critical process of great generality for a ligand’s association to and egress from its receptor. 


5. A strategy is warranted that comprises both a structure-kinetics relationship study (SKR) and a classical structure-affinity relationship study (SAR). This may offer added value to the traditional metrics of affinity-based drug evaluation. 

   *This thesis, Chapter 2 and Chapter 4*

6. Kinetic models incorporating the mean lifetime of specific complexes will be required to fully explain the nature of agonist efficacy. 

   *Sykes DA et al. Mol Pharmacol, 2009, 76:543-551; this thesis, Chapter 5*
7. The strength of mathematical simulations is not restricted to validating experimental data. It also facilitates our understanding of complicated ligand-receptor interactions especially for those experimental observations otherwise difficult to interpret. 
_This thesis, Chapter 6 and Chapter 7_

8. The value of binding kinetics to drug discovery will be increased through an improved ability to identify optimal kinetic mechanisms and define kinetic structure activity relationships. 

9. “Unknown unknowns; known unknowns; unknown knowns; known knowns” pretty much sketches the four statuses of a PhD student.

10. Punctuality is a good virtue—particularly for one who studies binding kinetics.

11. Proper chemistry and decent cooking are alike. The only difference is that when it starts to smell, the former works, while the latter does not.

12. “…Just play. Have fun. Enjoy the game.”
_Michael Jordan_