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Allosteric modulation and ligand binding kinetics at the Kv11.1 channel

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Stellingen

bij het proefschrift

Allosteric modulation and ligand binding kinetics at the K_v11.1 channel

1. Most drugs associated with (Torsade de Pointes) TdP in humans are also associated with the K_v11.1/hERG channel block at concentrations close to the free plasma concentrations found in clinical use.

Redfern, W., et al. Cardiovasc. Res. 2003, 58, 32-45.

2. Screening efforts to avoid drug blockage of the K_v11.1/hERG channel led to the recent discovery of novel compounds that, ironically, increase channel activity. Studies are needed to determine whether activators can safely counteract the consequences of a reduced hERG-channel current in LQTS.

Sanguinetti, M. C.; Tristani-Firouzi, M. Nature 2006, 440, 463-469

3. In addition to classic early studies on enzymes, there are now examples of small molecule allosteric modulators for all superfamilies of drug targets encoded by the genome, including ligand- and voltage-gated ion channels, G protein-coupled receptors, nuclear hormone receptors, and receptor tyrosine kinases.

Christopoulos, A., et al. Pharmacol. Rev. 2014, 66, 918-947

4. Drug binding to the K_v11.1/hERG channel is likely to be a highly dynamic process with multiple drug and channel conformations contributing to binding for any given drug. It is likely that the development of accurate computer models of drug binding kinetics combined with structural studies will be needed to fully understand and ultimately overcome this complex safety-pharmacology problem.

Vandenberg, J. I., et al. Physiol. Rev. 2012, 92, 1393-1478

5. An obvious strategy to reduce the proarrhythmic risk of drugs with unintended I_{Kr} blockade is by lowering their K_v11.1 affinity via chemical modifications. Alternatively, complementary drugs that lessen the proarrhythmic risk of inadvertent K_v11.1 blockers can be developed potentially allowing the (i) reintroduction of medicines

previously recalled from the market because of their $K_v11.1$ -related cardiotoxicity and (ii) admission of new drugs with fortuitous I_{Kr} -blocking effects.

This thesis, chapter 4

6. Negative allosteric modulators of the $K_v11.1$ channel could be beneficial in LQT syndromes induced by genetic loss-of-function or pharmacological inhibition of both $K_v11.1$ and $K_v7.1$ channels.

This thesis, chapter 5

7. Analyzing slow association and/or fast dissociation characteristics as a “novel marker” might be beneficial for profiling and reducing $K_v11.1$ cardiotoxicity of drug candidates.

This thesis, chapter 6

8. $K_v11.1$ blockers with similar potencies (IC_{50} values) but distinct binding kinetics can have markedly diverse proarrhythmic properties, suggesting the necessity to extend $K_v11.1$ inhibition assays with studies on investigating the dynamics of drug-channel interactions.

Di Veroli, G. Y., et al. J. Cardiovasc. Electrophysiol. 2014, 25, 197-207; this thesis, chapter 7

9. Natural abilities are like natural plants, which need pruning by study.

Francis Bacon

10. “Fail fast, fail cheap” is a good slogan for hERG-induced cardiotoxicity but a disaster for research.

11. Good scientists are always working at the edge of possibilities. The progress and outcome of their studies may often yield further technical and scientific problems rather than explicit and desirable answers.

12. Thinking is a compulsory course for every Ph.D candidate to become an expert.