Title: Drug target residence time: a misleading concept

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Drug target residence time: a misleading concept

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Highlights

- Examples in support of the residence time literature are incomplete and misleading
- There are no examples of residence time significantly outlasting pharmacokinetics
- The importance of the on-rate in target binding is often overlooked
- Singling out residence time is a sub-optimal way to drive a drug discovery program

Since the importance of drug target residence time was first highlighted more 10 years ago, slow binding kinetics has received much attention in the drug discovery literature, and indeed within pharmaceutical research. However, the residence concept as presented in most papers is supported by rather misleading simulations and arguments, and by examples where compounds are taken out of their pharmacokinetic context. Moreover, fast association is typically more desirable than slow, and advantages of long residence time, notably a potential disconnect between pharmacodynamics (PD) and pharmacokinetics (PK), would be partially or completely offset by slow on-rate. Therefore, plain potency is likely a better predictor of drug development success than is residence time.

Keywords: residence time; binding kinetics; off-rate; rebinding.
Teaser: The residence time concept as presented in recent literature is supported by rather misleading examples, simulations, and arguments. Plain potency is likely a better predictor of drug development success than residence time.

Introduction

Increasingly often, I come across long residence time being used to denote the mode of action of a certain inhibitor or lead compound, or the suggestion that optimizing residence time can be a valuable drug discovery strategy. By contrast, researchers rarely claim that high affinity would be a successful approach for their project, or that high potency will be the desired mode of action for their inhibitors. However, more often than not, potent compounds will have long residence times, and there is little difference between desiring long residence time and pursuing high affinity. It is apparent that the introduction of the residence time concept [1] has led many drug discovery scientists to believe that long residence time offers something extra that plain potent compounds do not.