Tortoise or hare? **Using Binding Kinetics to pick prime drugs.**

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Selectivity of kinase inhibitors is one of the main challenges faced by researchers, often making it difficult to balance potency and pharmacokinetics while avoiding severe toxicity. It is now understood that drug safety in the human body is difficult to achieve by solely taking into account affinity. Indeed, there is growing evidence for the physiological relevance of the interplay between binding kinetics and pharmacokinetic parameters.

By using only the affinity constant, researchers not only miss the opportunity to modulate target selectivity but also perturb the duration of action and tune the therapeutic index through modification of binding kinetics.

Which drug crosses the line first, the fast-acting hare or the slow-moving tortoise? With this question in mind, we decided to study if the early evaluation of binding kinetics is a powerful tool to improve decision-making. We have found that compounds with identical affinity towards multiple kinases can exhibit dramatically different kinetics such that the on and off-rates of the drug-target complexes differ by orders of magnitude. This means that kinetic selectivity can still exist even in the absence of binding selectivity. The implicit relationship between selectivity and therapeutic index makes this fact extremely useful and demands that kinetic selectivity also be taken into account.