Mechanistic modelling of drug target binding kinetics as determinant of the time course of drug action *in vivo*

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Chapter 1. Mechanistic models enable the rational use of *in vitro* drug-target binding kinetics for better drug effects in patients

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Abstract

Introduction: Drug-target binding kinetics are major determinants of the time course of drug action for several drugs, as clearly described for the irreversible binders omeprazole and aspirin. This supports the increasing interest to incorporate newly developed high-throughput assays for drug-target binding kinetics in drug discovery. A meaningful application of *in vitro* drug-target binding kinetics in drug discovery requires insight in the relation between *in vivo* drug effect and *in vitro* measured drug-target binding kinetics.

Areas covered: In this review, the authors discuss both the relation between *in vitro* and *in vivo* measured binding kinetics and the relation between *in vivo* binding kinetics, target occupancy and effect profiles.
We conclude that more scientific evidence is required for the rational selection and development of drug-candidates on basis of *in vitro* estimates of drug-target binding kinetics.

Expert opinion: To elucidate the value of *in vitro* binding kinetics measurements, it is necessary to obtain information on system-specific properties which influence the kinetics of target occupancy and drug effect. Mathematical integration of this information enables the identification of drug-specific properties which lead to optimal target occupancy and drug effect in patients.

Abbreviations: GPCR: G-Protein Coupled Receptor, HTRF: Homogeneous Time-Resolved Fluorescence, NA: Not Available, PET: Positron Emission Tomography, SAW: Surface Acoustic Wave, SPECT: Single Photon Emission Computed Tomography, SPR: Surface Plasmon Resonance, TO: target occupancy.