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### A novel methodology to assess the brain regional target site unbound drug concentration: Shortcut for assessment of spatial receptor occupancy in preclinical studies

#### Abstract

The Combinatory Mapping Approach (CMA), including a set of *in vitro* and *in vivo* methods was recently proposed by our group as a discovery/development tool to assess unbound drug neuropharmacokinetics (neuroPK) [1]. CMA allows evaluation of pharmacokinetics in the entire brain. The method has been further refined to measure local neuroPK properties of drugs, referred to as CMA-ROI (ROI stands for region of interest). The performance of CMA-ROI was tested on the set of well-studied antipsychotics. The approach was used to address the following questions: i) to what extent are antipsychotics transported across the blood-brain barrier in different brain regions, the blood-spinal cord barrier and the blood-CSF barrier; ii) how are antipsychotics subsequently distributed in the regions of the brain and in the spinal cord; iii) how much free drug is available to bind to the desired target(s). Spatial receptor occupancy was assessed and compared to the experimentally determined values. Generally, good agreement was established between predicted using CMA-ROI methodology and observed cortical 5-HT<sub>2A</sub> and striatal D<sub>2</sub> receptors occupancy of studied antipsychotics.

#### References

1. Loryan I, Sinha V, Mackie C, Van Peer A, Drinkenburg W, Vermeulen A, Morrison D, Monshouwer M, Heald D, Hammarlund-Udenaes M: **Mechanistic understanding of brain drug disposition to optimize the selection of potential neurotherapeutics in drug discovery.** *Pharmaceutical research* 2014, **31**:2203-2219.