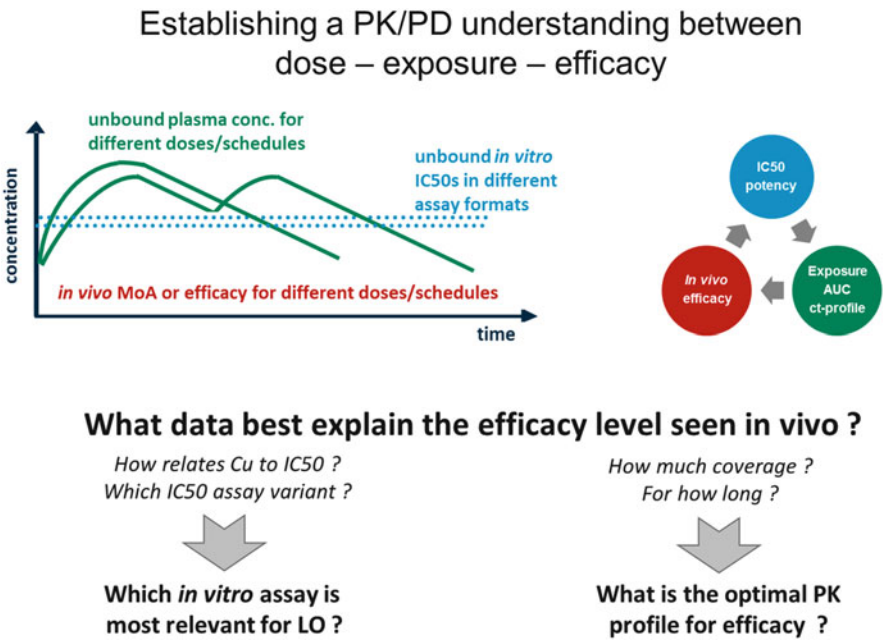


**Fig. 5** Illustration of the iterative approach of applying different doses/schedules of a compound to explore the pharmacological activity in vivo based on defined MoA or efficacy readouts in relation to the coverage of the potency (e.g. unbound in vitro IC50) by the corresponding unbound plasma concentration–time profile. This information triggers a learning cycle to establish (1) what type of in vitro potency assay is most relevant for the in vivo activity and (2) what shape a concentration–time profile should have to enable the desired level of target engagement

properties of the lead compound(s) need(s) to be optimised in order to get there (Fig. 5).

## 2.3 Lead Optimisation

The decision to start the optimisation of a lead structure class endorses a significant investment into a project assigning the allocation of large amounts of resources in medicinal chemistry, pharmacology, drug metabolism and pharmacokinetics and many other disciplines to embark on a multidimensional optimisation of the chemical starting matter to improve the liabilities of the lead structure. The ultimate goal of the optimisation is to generate a drug candidate molecule which carries substantial evidence not only to be efficacious in a well-defined indication and patient population but also to be able to be administered safely and conveniently to humans.

DMPK efforts during the LO phase concentrate on those aspects which are critical (1) to change the PK profile of the compounds such as to enable efficacy, (2) to avoid/reduce the potential of the compounds to elicit safety risks and