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Current Challenges Towards Assessing CNS Penetration in Man

The discovery and development of new medicines to treat diseases of the CNS is one of the most challenging undertakings of today's pharmaceutical industry, with the rate of attrition being higher than in any other therapeutic area. This high risk of failure for new CNS drugs is linked to the extraordinary complexity of the anatomy and physiology of the human brain and its pathologies. Furthermore, the vasculature of the brain serves as a formidable obstacle for the exchange of many blood-borne solutes as well as drugs between blood and brain, known as the so-called blood-brain barrier (BBB).

Currently, CNS penetrability of new compounds is addressed from early on in the drug discovery process with a sequential use of tools of increasing complexity which range from *in silico* predictions, to *in vitro* models and *in vivo* animal studies. While the repertory of methods is rapidly expanding, our understanding of CNS penetration in conjunction CNS disposition remains insufficient, making it difficult to make sound decisions based on the presently available battery of assays. One very promising way out of this problem is to focus activities on a more stringent hypothesis-driven lead optimisation, away from a merely technology-driven screening paradigm. The rational use of mechanistic studies will allow to understand and subsequently to predict the behaviour of compounds in the body and the brain. By application of classical and modern PK modeling and simulation tools it will be possible to integrate data from different *in vitro* and *in vivo* studies, thereby generating a working understanding of the pharmacokinetics and pharmacodynamics of potential drug candidates in the CNS. Such an understanding will also be paramount to define PK parameters which are favourable for the desired indication, to guide the preclinical development of the compound (e.g. dose selection, tox testing) and ultimately to increase the chances for a successful phase II study in human (i.e. efficacy, therapeutic window).

The growing emphasis on translational medicine to bridge the gap between CNS research and drug development and the concerted application of new technologies, in particular brain imaging, may not only accelerate the discovery and improve the success rate of new CNS drugs, but may also give a fresh boost to the motivation for CNS drug development.