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Editorial

Close relationships between *in vitro* ADMET and DMPK research in pre-clinical drug discovery

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I have recently been invited to become an editor of a new open-access journal, ADMET & DMPK. I am honored to take up this exciting and challenging position. At first glance, the journal name is just a combination of two acronyms/disciplines in the pharmaceutical industry: ADMET (absorption, distribution, metabolism, excretion and toxicology) and DMPK (drug metabolism and pharmacokinetics), which sounds odd. Practically speaking, ADMET refers to a suite of *in vitro* assays that address various aspects of the pharmacokinetic performance of a drug, while DMPK more often refers to a drug's *in vivo* pharmacokinetic performance. On thinking about it in more depth, it makes perfect sense to consider these two disciplines together, as a good DMPK profile of a drug candidate would be difficult to achieve without optimal ADMET properties, and both play an indispensable role in pre-clinical drug discovery. Here, I will share my views on the synergistic roles of these two disciplines, and how our new journal might help to foster the development of ADMET and DMPK.

The discovery and development of a new candidate drug is a resource intensive and challenging process in the pharmaceutical industry. It involves evaluating the parameters affecting the likely success of a drug candidate in the preclinical, clinical and commercial phases of drug development. To maximize the chance of success in the clinic, it is crucial to generate and optimize quality lead compounds in the discovery phase. Ideally, the discovery project should include: (1) a sound clinical hypothesis, (2) the right drug target and (3) the right chemical agents/series, with demonstrated exposure through the preferred route of administration in a pre-clinical species. To effectively guide drug discovery efforts during lead optimization, it is essential to develop a pharmacodynamic model, which provides a means with which to evaluate whether the exposure level of the tested compound is sufficient to elicit a desirable pharmacological response. Clearly, pharmacokinetic studies provide a measure of the exposure level of the tested compound, which directly addresses item (3).

The prevalence of high throughput and combinational methods in drug discovery has led to an increase in the number of new chemical entities to be evaluated in the early discovery phase. Standard pharmacokinetic studies are no longer able to cope with the number of tests required. To mitigate the risk of failure due to poor pharmacokinetics, the pharmaceutical industry has developed medium/high throughput *in vitro* ADMET studies to evaluate potential lead compounds before carrying out

pharmacokinetic studies in pre-clinical species. Table 1 lists representative examples of some *in vitro* ADMET assays.

Table 1. Some common in vitro ADMET assays

Assay	**Issue(s) to be addressed**
Caco-2 permeability	Oral absorption
Transporter study	Oral absorption, drug–drug interactions
Protein/serum binding	Distribution
Hepatocyte stability	Metabolism
Gut stability	Metabolism
CYP450 inhibition	Drug–drug interactions
Metabolite identification	Metabolic mechanism
hERG /cardiac ion channels	QT liability, cardiotoxicity

Physicochemical properties such as aqueous solubility, dissolution, lipophilicity and chemical stability are often regarded as the key parameters governing the ADMET properties. For instance, a poorly soluble research compound may suffer from incomplete oral absorption, which could lead to low systematic exposure, and highly lipophilic compounds are likely to show high metabolic clearance. With the advance in numerical/statistical techniques, it is now possible to use the knowledge base from existing research compounds/drugs to build predictive models for *in silico* assessment of ADMET and physicochemical properties. The *in silico* approach is very useful in the drug design process and for prioritizing the synthetic and/or testing resources for those compounds that are most likely to show good pharmacokinetic profiles.

It is not uncommon to encounter situations in which the potential lead compound shows good physiochemical properties and reasonable ADMET properties, but exhibits poor systematic exposure in a pharmacokinetic study. Bespoke ADMET studies could then be used as problem solving tools to identify such issues. Typical examples could be the differentiation between gut and hepatic metabolism, and the effects of uptake transporters and/or efflux transporters in absorption or clearance. In such cases, ADMET and DMPK studies should be conducted together as necessary with the aim of identifying the root cause and guiding the design of new compounds/approaches to address the problem. As the chemical series progresses, all available data from pharmacokinetic studies and *in vitro* ADMET studies could be used for scaling purpose. Generally, a simple allometric approach may be used to extrapolate the animal data to human data and thus predict pharmacokinetic parameters and, together with pharmacokinetic/pharmacodynamic data, the therapeutic dose levels in humans.

I hope this journal will provide a platform for all scientists working in ADMET and DMPK areas to publish their results/research findings in a timely manner. The journal welcomes original scientific contributions from all areas of absorption, distribution, metabolism, excretion, toxicology and pharmacokinetics of drugs. I firmly believe in the importance of exchange of knowledge and shared learning, which will help drug discovery scientists to come up with better quality lead compounds, and hopefully to minimize costly clinical failures.