Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol15Issue1abst014.pdf

Patterns in PK - Exploring and Navigating in PK-Space

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Introduction The aims were to explore and define underlying determinants for major pharmacokinetics (PK) of the pool of marketed drugs in humans, and to navigate and explore systematic patterns in the PK-space.

Method Major PK-data of marketed drugs with a molecular weight between ~100 and ~1100 were collected, or predicted using our proprietary *in-silico* system. Based on the collected data we applied principal components analysis to explore and define major underlying determinants for PK in humans.

Results The analysis resulted in a model with 2 significant factors, explaining as much as 81 % of the total variance of the PK-space. The *in-silico*-based predictions of PK-space positioning demonstrated good accuracy, with a median error of 0.5 unit along the axes (components 1 and 2 stretch over 8 and 6 units, respectively). Interesting and useful patterns emerged – different regions of the created PK-space are associated with different characteristics. For example, regions with compounds with major drug-drug-interactions (transport and/or metabolism) and food interactions, significant renal and/or biliary excretion and QT-prolongation risk emerged. Distinct and overlapping regions for BCS-classes and a zone with extended-release potential demonstrate the potential for biopharmaceutical assessments and predictions. Interestingly, compounds released on the market since 2012 are placed in a relatively narrow, central region with many typical properties and challenges. The PK-space also highlights regions out of reach, or with challenges, for *in-vitro* prediction methods.

Conclusions We succeeded in developing a valid PK-space covering the selected marketed drugs with MW between ~100 and ~1100. With the use of this new system the PK and associated risks and opportunities can be predicted with good accuracy from chemical structure only. We propose that the system can be very useful for optimization of lead compounds and drug development programs, for front-loading of decisions and for positioning and profiling *vs* competitor drugs.