Complexity of In Vitro Assays

In vitro data analysis in whole cell systems is complex [1] and time consuming, yet accurate data analysis and informed data interpretation are crucial early in the drug development process, especially when In Vitro-In Vivo Extrapolation (IVIVE) approaches are being used. A number of software tools exist for the analysis of in vitro data. However, these tools were developed for broad application and do not:

• support analysis of more complex in vitro experimental systems.
• possess appropriate statistical rigour.
• allow automated IVIVE.

In Vitro Models (e.g. Transporters)

When using whole cell systems (Figure 1) there is a need to account for:

• Interplay between metabolic, passive diffusion and active transport processes
• Possible simultaneous time dependent inhibition and competitive inhibition
• Contribution of metabolites to enzyme inhibition
• Nonspecific binding
• Intracellular binding
• Intra & Inter-assay, between donor variability
• Potential outliers

SIVA-Toolkit - Key Elements

The SIVA-Toolkit is a user friendly tool for the analysis of complex in vitro experimental data. In vitro assays and associated models included in the SIVA-Toolkit are shown in Figure 2.

Importance of In Vitro Transporter Modelling

• Results from two studies [3,4], showing the impact of modelling on the evaluation of P-glycoprotein (P-gp) kinetics are summarised in Figure 3 and Table 1.
• The likelihood of correctly simulating drug-drug interactions due to P-gp interactions with this compound will be very different if the correct kinetic parameters are not used.

Advantages of SIVA-Toolkit

Specialized - Specifically designed for drug discovery and early drug development scientists.

Easy to use- Provides user-friendly graphical interfaces with pre-defined library models for currently available in vitro assays. Complex data analysis without the need to know a coding language.

Links to other platforms - Potential for linkage to other platforms (e.g. Phoenix)

Statistical rigour – Ready-made structural models are integrated in a user-friendly manner with powerful nonlinear fitting models in a statistical environment.

Ease of documentation- Provides formatted printable reports with a summary of input parameters, experimental details and results.

Automated IVIVE- Integration of in vitro metabolic clearance data with established IVIVE approaches and physiological scaling factors for extrapolation of hepatic clearance in multiple species (human, dog, rat, mouse).

References


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