Drug discovery is essentially a design process and, in common with most design disciplines, requires simultaneous optimisation of multiple parameters, including potency, chemical tractability and ADME (Absorption, Distribution, Metabolism and Excretion) properties, to be efficient and successful. Recent developments in Medicinal Chemistry and Biology have markedly increased the rate at which new molecules can be synthesised and screened for potency against a drug target. This throughput has far outstripped the rate at which data can be generated experimentally on the ADME properties of compounds, resulting in the perception that ADME optimisation represents a bottleneck in the discovery process. One solution to this situation is to harness the wealth of data residing in the chemical diversity produced in current discovery libraries, by screening diverse sets of compounds in mechanistic ADME in *vitro* screens and building predictive computational models with the output. This is the basis of the predictive ADME approach which has been adopted successfully by ArQule and other Companies.

The availability of a suite of predictive *in silico* ADME models allows multiple properties to be determined and considered throughout the drug discovery process, from library design to candidate selection. Experimental data is not required as input to the models, consequently ADME properties can be predicted using virtual structures prior to compound synthesis.

This approach gives great flexibility in application of the models. Some examples include:

- **Design of libraries for screening.** Models with sufficiently high throughput can be used to pre-screen large virtual libraries for suitable ADME properties prior to synthesis and screening for potency. In combination with models for potency, focussed libraries can be designed with an appropriate balance of properties from the outset.
- **Lead optimisation.** The effects of structural modifications to a lead compound on it’s overall ADME properties can be assessed *in silico*, allowing a prioritisation of the most promising to be selected for synthesis and testing.
- **Interpretation of *in vivo* results.** *In silico* models of individual ADME mechanisms can be used to identify the cause of poor *in vivo* properties. For example, an observation of poor bioavailability could be associated with poor intestinal absorption, active efflux by transporters or a metabolic instability. Models of these processes can aid in identifying the cause, and thus direct efforts to overcome the problem.

Central to these applications is the ability to optimise multiple molecular properties simultaneously; essentially building profiles of individual molecules. This enables, for example, the ability to re-compute the overall ADME effects of any synthetic ideas addressing a specific metabolic or absorption problem. The very high throughput of *in silico* models is sufficient to remove any “bottleneck in optimisation” and permits
ADME properties to be considered in parallel with potency, chemical tractability and diversity at each stage of drug discovery.

We have built models of the main systems that control the systemic availability and distribution of drugs (figure 1).

Fig 1. The main ADME processes affecting an orally administered compound. Models currently available at ArQule are shown in dark purple, those currently under development are in light purple. Models in yellow are not available.

Our approach to model building extends from typical QSAR methods, which are often based on molecular descriptors, through semi-empirical calculations, to first principle quantum chemical calculations. Each of these approaches is characterised by a speed of computational throughput and their use is dictated by numbers of compounds to be examined. Thus descriptors based models can be used in virtual library design, involving millions of structures per day, whereas the quantum approaches can only be used on relatively small numbers (1000s). Modelling strategies can be used which filter first using the high throughput models, then place selected molecules through the low throughput/high resolution models.

It is increasingly important to integrate these in silico predictions of multiple ADME properties, along with assessments of compound potency, chemical tractability and toxicity, into an overall assessment of the suitability of a molecule as a potential drug. This enables projects to make choices about which chemical ideas to emphasise, and where problems are likely to arise with ADME properties. One approach we have developed for this has been to assign a numerical ‘score’ for each property based on the predicted value, and then to combine these into an overall consensus score for the molecule. This allows collections of compounds to be compared and ranked for ADME properties on the basis of a single number. These scores can be established as a profile for a suitable candidate from the start of a Project. Libraries and molecules can then be effectively filtered against that profile and scored automatically, enabling the Project to make choices of particular chemotypes, or to identify specific problems within a chemical series and attempt in silico optimisation away from it.

Reference: