7th New Perspectives in DMPK Meeting

The physicochemical properties that drive optimal oral small molecule drug disposition were discovered many years ago. When physicochemistry for pharmacological potency overlaps with ADME physicochemistry, strategies for delivery of clinical candidates with the best balance of oral delivery and potency have been long established.

However, it has also been recognised that a significant number of high disease relevant pharmacological targets require physicochemistry that is not optimal for small molecule oral drug delivery.

Such small molecule 'intractable' targets include:

1) Peptidic GPCRs where a small molecule is required to prevent the binding of endogenous peptide ligands.
2) Protein/protein interactions where the small molecule is required to disrupt the association of 2 large proteins.
3) Kinases requiring high selectivity for binding over close family members
4) Protein degraders (PROTACs) which link a binder to a protein of interest to an E3 ligase

The physicochemical properties required to potently modulate such targets often require significant size/MW, lipophilicity and hydrogen bonding capacity that puts small molecules at odds with the requirements for extensive oral delivery. In these circumstances, compromises or risks have to be taken relative to desirable clinical PK and ADME properties. As compounds become larger and more lipophilic, they tend to drive to failures in high throughput in vitro systems (hepatic clearance, passive permeability, protein binding DDI etc) that were designed for the optimisation of more 'Rule of 5' compounds.

Despite these difficulties, a significant number of compounds against these more difficult to small molecule drug types are progressing and showing benefit in clinical studies.

This meeting should bring together medicinal chemists and DMPK colleagues to discuss the prosecution of small molecule drug discovery projects against these 'intractable' targets. It aims to review both successful and unsuccessful strategies that have been employed. With a view to arriving at best practices that will enable more successful outcomes in the area. What are the properties that mean such molecules can be orally absorbed?

As such it should appeal to DMPK and medicinal chemistry colleagues who are charged with prosecuting projects against targets that require non-Rule of 5 physicochemistry.

If you have an example of both unsuccessful and successful approaches in this area, please consider submitting an abstract for poster or presentation.