Introduction to Drug Discovery

Step-by-step from project initiation and Target Selection through lead compound/biologic identification to selection of the candidate for clinical trials. Science-based, focussing on small molecule drugs with comparisons to biopharmaceuticals.

- ❑ **Selection of a target human protein whose modulation results in the desired therapeutic effect.**
- ❑ **Obtaining a compound/biologic capable of carrying this out *in vitro* and in animal disease models.**
- ❑ **Prediction of safety and efficacy in humans via *in vitro* and animal model studies.**
- ❑ **The Science Base and Process of Drug Discovery - essential Biology, Medicinal Chemistry, ADMET/DMPK and Informatics required for obtaining a clinical candidate – and their phased use.**

Schedule*

1. The Drug Discovery Landscape:

Typical Drug Discovery Considerations:

- ❑ **Essential elements.**
- ❑ **Typical Milestones, decision points and pipeline.**
- ❑ **Drug Discovery:**
  - **Strategies.**
  - **Pipeline.**
  - **Costs and Revenues.**
- ❑ **Reducing attrition.**
- ❑ **Drug Discovery Nomenclature.**
- ❑ **Scientific skills base required (Medicinal Chemistry, Biology, ADMET/DMPK, Informatics/Artificial Intelligence).**
- ❑ **Small Molecules *v.* Biologics as drugs.**

2. Project Initiation:

Best Practice in Project Initiation:

- ❑ **Project Origins.**
- ❑ **Generating a TPP (Target Product Profile).**
- ❑ **Selecting a viable Project.**

3. Target Protein Selection.

How to select the right protein drug target for the disease.

- ❑ **Target Validation/Hypothesis generation.**
- ❑ **Target selection approaches.**
- ❑ **Genomics and Proteomics in Target selection.**
- ❑ **Drug action at the cellular level.**
- ❑ **Target tractability.**
- ❑ **Major classes of Target proteins for existing small molecule drugs:**
  GPCR, Ion Channels, Nuclear Receptors, Kinases. Their structure and function.

4. Lead / Lead Series Identification.

The path to obtaining a lead or lead series with the quality attributes to become a Clinical Candidate.

Key *in vitro* Scientific Tools in Drug Discovery:

- ❑ **Key steps in Lead identification.**
- ❑ **Bioactivity assays of compounds, Low/Medium throughput screening, Pitfalls, Bioactivity assay formats, Stem cells, Organoids.**
- ❑ **Potency and Selectivity quantification - key constants and parameters.**
- ❑ **High Throughput Screening (HTS), Virtual compound e-pre-screening.**
- ❑ **Company compound library.**
- ❑ **Biostructural Analysis: X-Ray diffraction, Cryo-electron Microscopy and Deepmind.**

***In vitro* ADMET methodologies and their application:**

- ❑ **ADMET definitions.**
- ❑ **Cellular permeability - adsorption at the gut and blood brain barrier.**
- ❑ **Dug Metabolism: Cyp 450 / Glucuronidation / P-glycoprotein / Metabolic stability / Protein binding.**
- ❑ **The Prodrug Strategy.**

Medicinal Chemistry:

- ❑ **Multidimensional Optimisation (MDO)/ Structure Activity Relationships (SAR).**
- ❑ **Drug-Protein Target bonding chemistry.**
- ❑ **Key chemical groups involved in target binding.**
- ❑ **Drug design physical/chemical parameters. Lipinski/Schultz 'rules'.**

Animal Model Studies:

Efficacy in animal models of disease, examples:

- ❑ **Inflammation.**
- ❑ **Cancer.**
- ❑ **HIV-AIDS.**
- ❑ **Essential attributes of a Lead Compound.**
- ❑ **Phasing of Scientific activities in Lead Identification for small molecules.**

5. Clinical Candidate Identification.

Final 'polishing' of the lead with a view to its nomination as a Clinical Candidate.

- ❑ **Essential attributes of a clinical candidate.**
- ❑ **Manufacture. Formulation.**
- ❑ **Pharmacokinetics (PK) and Pharmacodynamics (PD).**
- ❑ **Toxicology and Toxicology Assays.**
- ❑ **hERG.**
- ❑ **Complete Data Package Analysis - Allometric Scaling.**
- ❑ **Clinical Candidate nomination.**
- ❑ **Entry into Human Enabling stage.**

Course Summary

Course Ends

*** Interactive Group Exercises are held throughout.**