Introduction to Drug Discovery

Step-by-step from project initiation 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 the compound/biologic's 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

Course Summary (Slide 11)

1. The Drug Discovery Landscape: (Slides 12-31)

Typical Drug Discovery Considerations:

- **Essential elements.**
- **Drug Discovery strategies.**
- **Typical Milestones, decision points.**
- **Drug Discovery Pipeline.**
- **Patenting Drug Discoveries.**
- **Drug Discovery costs and drug revenues.**
- **Reducing attrition.**
- **Drug Discovery Nomenclature.**
- **Scientific skills base required (Medicinal Chemistry, Biology, ADMET/DMPK, Informatics/Artificial Intelligence).**
- **Informatics, Artificial Intelligence (AI).**
- **Major Drug Categories.**
- **Small Molecules v. Biologics as drugs.**

2. Project Initiation: (Slides 32-38)

Best Practice in Project Initiation:

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

Continued

Introduction to Drug Discovery

3. Target Protein Selection. (Slides 39 - 81)

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

- Target selection approaches.
- Target Validation/Hypothesis generation.
- Project Risks/Rewards.
- Genomics and Proteomics in Target selection.
- Cellular Location of Drug Target.
- Target tractability.
- Learning from the Past: Major classes of Target proteins for existing small molecule drugs: GPCR, Ion Channels, Nuclear Receptors, Kinases - why they are so frequent Drug Targets.

4. Lead / Lead Series Identification. (Slides 82 -166)

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.
- Target Protein production.
- Bioactivity assays / formats: Low / Medium / High throughput assays Bioactivity assays in cell culture.
- Potency measurement of compound /biologics.
- Mechanisms of Protein Target enzyme inhibition/activation and receptor antagonism/agonism.
- Kinase assay.
- Potency analysis - key constants and parameters: IC_{50} and K_i Inhibition kinetics.
- New Inhibition approaches: Targeted Protein Degradation (PROTAC: Protein Targeting Chimeras).
- Pitfalls in bioassays.
- Cell culture, Stem cells, Organoids in Drug Discovery.
- Selectivity Determination. Use of Target Engagement approach.
- Biostructural Analysis of Target Protein-Compound Complex (X-Ray, Cryo-electron Microscopy and Deepmind / AlphaFold).
- Virtual Compound -Target Protein Docking.
- High Throughput Screening (HTS).
- Real Compound library / virtual *in silico* compound library and its screening.

Continued

Introduction to Drug Discovery

Lead / Lead Series Identification (continued)

- ***in silico*** **compound library/ virtual screening of the virtual library.**

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

- **ADMET definitions**
- **Cellular permeability - adsorption of a compound in the gut.**
- **The blood-brain barrier.**
- **Drug Metabolism:**
  - **Cyp 450.**
  - **Glucuronidation.**
  - **P-glycoprotein.**
  - **Peptide metabolism.**
  - **Metabolic stability.**
  - **The Prodrug Strategy.**
  - **Compound-non-specific Protein binding.**

Medicinal Chemistry:

- **Drug Discovery Iterative cycle.**
- **Designing small molecule drugs.**
- **Multidimensional Optimisation (MDO) / Structure Activity Relationships (SAR).**
- **Drug-Protein Target non-covalent bonding chemistry.**
- **Key chemical groups involved in target binding.**
- **Drug design physical-chemical parameters: Lipinski/ Verber/ Schultz 'rules'.**
- **Compound synthesis.**
- **Solid Phase Compound Synthesis.**
- **Example of Medicinal Chemistry of a Human kinase W inhibitor.**

Continued

Introduction to Drug Discovery

Lead Identification (Continued):

Animal Disease Model Studies:
Efficacy in animal models of disease, examples:
Inflammation.
Cancer.
HIV-AIDS.

6. Clinical Candidate Identification. (Slides 167-189)

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

- **Typical activities.**
- **Formulation.**
- **Pharmacokinetics (PK) and Pharmacodynamics (PD).**
- **Toxicology Assay Methods.**
- ***In silico* toxicology, Toxico: genomics/-proteomics.**
- ***In vitro* toxicology assays:**
  - **Cell metabolic viability.**
  - **Genotoxicity: Ames / Micronucleus / Teratogenesis.**
- **hERG.**
- **Clinical Candidate Stage Interfacing With Development - ' Entry into Humans Enabling '.**

Course Summary (190).

Exercises: (Slides 193- 199)

(Mini - Exercises are held throughout the course).

Course Ends (200)

Appendix (201-203)