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# *Drug Discovery*

*From Target to Clinic*

*A Medicinal Chemist's Perspective*

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# *The Process 1*

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- Overview
  - Drug Discovery metrics, time, money and go/no go.
  - Where are the critical decision points?
  - An early example of drug discovery

# *The Process 2*

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- Target Identification
  - Target families (Ion channels, GPCR, Enzymes)
  - Historical, siRNA, Mechanistic, Clinical
  - What sequencing the human genome did for us
  - Examples of target identification leading to clinical candidates
    - 3 Case Histories : CCR5 antagonists for HIV therapy

# *The Process 3*

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- Lead Identification
  - Primary and Secondary Assays
    - Radiolabel, Fluorescence, FLIPR, IMAP, IC<sub>50</sub> and K<sub>i</sub>,
    - Enzyme kinetics
    - Strategies for Enzyme Inhibition
    - Examples of inhibitors
    - 3 Case Histories : HIV Protease Inhibitors

# The Process 4

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- What makes a good lead?
- High-throughput Screening
  - Libraries and sample collections, physicochemical properties
    - Case History : Opiate receptor antagonist
  - Examples of HTS analysis
  - NMR based screening
    - Case History : Stromelysin Inhibitors
  - X-Ray based screening
    - Case History : Thrombin Inhibitors

# The Process 5

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- *In vitro* ADME/T, metabolism, CYP induction/inhibition
  - Metabolic routes and strategies to block metabolism
- Computational chemistry
  - Physicochemical Properties
  - HTS analysis, virtual screening, predictive models
  - Computational chemistry 101
    - Strength of interactions, Nature of interactions
    - Similarity searching
  - Empirical and mechanistic models to predict HERG Activity
  - ADME models
  - Structure-based design

# *The Process 6*

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- **Lead Optimisation**
  - In vivo models,
  - Off-target activity
  - Pharmacokinetics and Pharmacodynamics,
  - QSAR, computational chemistry, global versus local models
- **Case History : 5-HT<sub>2C</sub> Antagonists**
  - Plasma markers

# *The Process 7*

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- **Pre-clinical Evaluation**
  - Why do we do safety evaluation?
  - Safety and Toxicity
  - Formulation
  - Predicting clinical doses
- **Patents**
- **The Clinic**
  - Phase I, Phase II, Phase III
- **Case History:- Discovery of Gleevec**

# *The Process 8*

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- Case History:- Discovery of the NK<sub>1</sub> antagonist Emend™
  - From Target identification to clinic