Drug Discovery

Introduction to Drug Discovery

- **Drug discovery** is the process of finding and improving a substance that can produce a useful therapeutic effect.
    - It begins with a medical problem and ends, at the discovery stage, with a candidate suitable for further development.
- A hit shows activity in an initial test, a lead has evidence supporting further chemical improvement, and a candidate meets a wider set of requirements for development.
- Discovery therefore connects a biological hypothesis with chemical structures and experimental evidence rather than ending when one compound binds strongly.

The Main Questions in Drug Discovery

1. Biological Question

- Identify the biological process that contributes to disease and assess whether changing it could benefit the patient.
- A target may be an enzyme, receptor, channel, transporter, nucleic acid or another relevant biological component.

2. Chemical Question

- Assess whether a molecule can interact with the target in the required way and with sufficient selectivity.
- The molecule must have a workable balance of potency, solubility, stability and other properties.

3. Translational Question

- Determine whether an effective concentration can reach the intended site with an acceptable overall effect.
    - Activity in a purified-protein assay does not by itself establish activity in cells, animals or patients.

Hit, Lead and Candidate

- A **hit** is an initial compound with confirmed activity in a relevant test.
- A **lead** is a promising series with sufficient evidence and chemical scope for improvement.
- A **development candidate** is selected after a broader package of potency, selectivity, exposure, safety and manufacturing evidence has been assessed.
- A **lead series** contains related compounds built around a common chemical framework, so changing one structural feature at a time can reveal which features are important for activity.

First Hope

Copyright by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

The Role of Medicinal Chemistry

- Medicinal chemists change molecular structure and study how those changes affect biological activity and drug-like properties.
    - Each round of design, synthesis and testing should answer a specific question about the relationship between structure and function.
- **Structure–activity relationship (SAR)** describes how a structural change alters biological activity.
- The same change must also be checked for effects on absorption, distribution, metabolism and excretion (**ADME**), because good target binding alone does not ensure useful exposure.

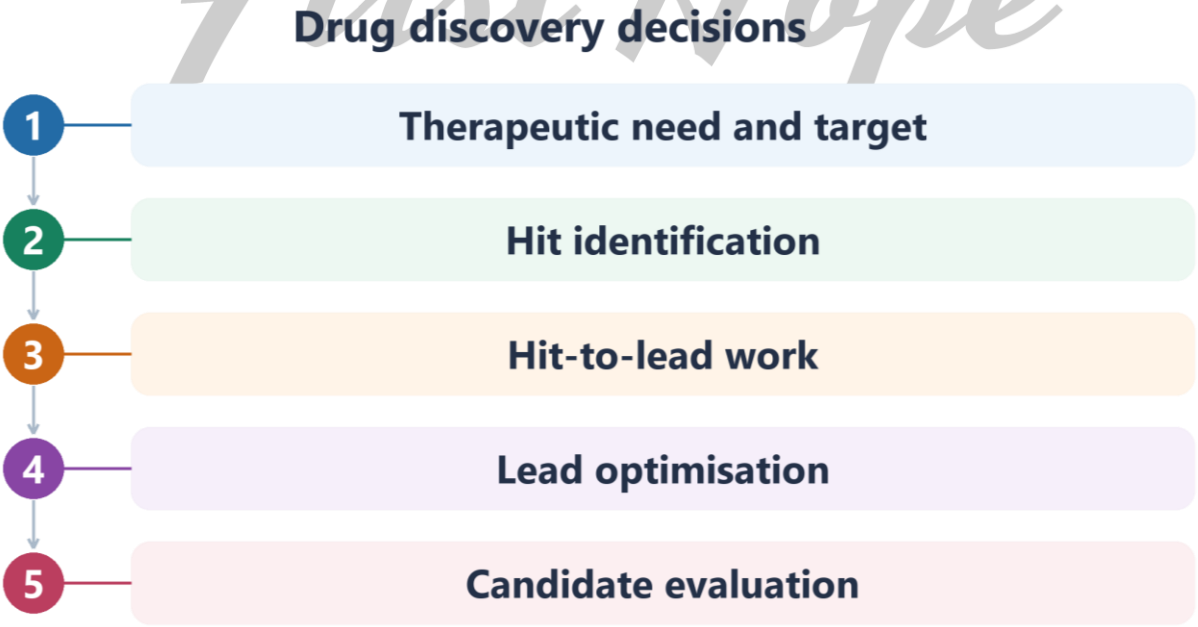
Stages of Drug Discovery

- Drug discovery and development proceed through linked stages, with feedback when a compound fails to meet a requirement.

From a Medical Need to a Development Candidate

- The sequence below is a decision framework: each stage provides evidence for continuing, modifying or stopping a chemical series.
- **For example,** poor exposure discovered during lead optimisation may require new analogues even when the original compound binds strongly.

First Hope



1. Define the Therapeutic Need

- Identify the disease, the intended patient population and the limitations of current treatment.
    - Specify the desired benefit and a realistic route of administration in an initial target product profile.

Copyright by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

2. Identify and Validate a Biological Target

- Select a biological component that is connected to the disease process.
    - Test whether changing its activity produces the intended biological effect rather than merely correlating with the disease.

3. Develop Suitable Assays

- An **assay** is a test that converts biological activity into a measurable result, such as a change in enzyme activity or a receptor-mediated signal.
- An assay must measure the relevant activity consistently and distinguish true effects from interference.
    - Positive controls, negative controls and repeat measurements establish whether a result can be trusted.

4. Identify Hits

- Screen compound libraries, examine natural products, use known ligands or apply structure- and fragment-based approaches.
    - Repeat the initial activity measurement and confirm the identity and purity of promising compounds.

5. Convert Hits into Leads

- Prepare related compounds to establish structure–activity relationships.
    - Improve activity while checking selectivity, solubility, permeability and chemical stability.

6. Optimise the Lead

- Balance target potency with exposure, metabolic stability and safety-related properties.
    - A very potent compound may still fail if it is insoluble, rapidly cleared or active at an undesirable target.

7. Select a Development Candidate

- Choose a compound with a convincing overall profile and a feasible preparation and formulation strategy.
    - Selection uses several properties together rather than the lowest assay concentration alone.
- The candidate should satisfy the intended product profile as a whole, including the intended route, useful duration of exposure and a practical path to manufacture.

Development Beyond Discovery

1. Preclinical Development

- Nonclinical studies assess pharmacology, exposure and safety, while manufacturing and formulation work provide suitable material.

Copyright by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

2. Clinical Development

- **Clinical development** tests the candidate in people to establish how exposure, safety and therapeutic effects relate.
- The phases have different main questions, although real programmes may combine or overlap phases.



A. Phase I: Initial Safety and Pharmacokinetics

- Phase I studies primarily investigate safety, tolerability and pharmacokinetics; the participants depend on the disease and medicine.

B. Phase II: Exploratory Efficacy and Dose Selection

- Phase II studies examine activity in patients, dose selection and further safety information.

C. Phase III: Confirmatory Benefit–Risk Evaluation

- Phase III studies evaluate benefit and risk in larger relevant populations using an appropriate comparator and design.

3. Review and Continued Monitoring

- Regulatory review evaluates the submitted evidence, and monitoring continues after approval to identify effects not fully characterised earlier.
- **Post-marketing surveillance** continues to identify uncommon or delayed adverse effects and to reassess benefit and risk during wider use.

Lead Discovery

- **Lead discovery** identifies a chemically tractable starting point that can be improved into a potential medicine.

Sources of Leads

1. Screening of Compound Libraries

- **High-throughput screening** tests many compounds in a suitable assay.

Copyright by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

- Confirmed hits are checked in concentration–response studies and in additional assays that use a different measurement principle.

➢ An **orthogonal assay** tests the same biological question using a different measurement principle, helping to distinguish real activity from a misleading signal.

2. Natural Products

➢ Natural products provide complex structures and biological activities that may suggest new drug classes.

- Their potency can be useful, but supply, structural complexity and selectivity may require modification or semisynthesis.

3. Known Ligands and Existing Drugs

➢ An endogenous ligand or an established medicine can reveal the groups needed for target recognition.

- Analogue design can improve selectivity, duration of action or another property while retaining useful interactions.

4. Fragment-Based Discovery

➢ Small fragments are selected for measurable binding and efficient use of their atoms.

- They are grown, linked or merged using structural and biochemical evidence.
- A weak but well-characterised fragment can be valuable if its binding mode supports rational improvement.

➢ The purpose of **fragment growth** is to add interactions without losing the experimentally supported starting binding mode.

5. Structure-Based and Computational Approaches

➢ A target structure can reveal pockets and suggest molecules that complement them.

- Docking and virtual screening prioritise compounds for testing; a predicted pose is a hypothesis that needs experimental support.

6. Phenotypic Screening

➢ A phenotypic assay identifies compounds that change a cellular or organism-level response without requiring a known target at the start.

- Target identification may follow after a useful phenotype has been confirmed.

Qualities of a Useful Lead

- The activity should be **reproducible** and associated with a chemically identified compound.
- The structure should allow the preparation of informative **analogues**.
- Early **selectivity** and physicochemical data should suggest a realistic path to improvement.

First Hope

Copyright by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

First Hope

FREE PREVIEW

Click here to visit our website

PHARMACY PREMIUM NOTES

Complete subject and semesters are available on FirstHope app only.

Scan or click here

Click here to get the app >

Available on Google Play

JOIN THE FIRSTHOPE COMMUNITY

Join our Telegram channel

Click here to join Telegram >

Scan or click here

@FirstHopeNotes

Instagram

@firsthope.official

Click here to follow >

YouTube channel

FirstHope-Pharmacy / Live streams

Click here to watch >

WhatsApp channel

Follow FirstHope on WhatsApp

Click here to join >

FirstHope website

firsthope.co.in

Click here to visit >

B.Pharm / D.Pharm / M.Pharm / Pharm.D

Preview notes. Complete subjects and semesters in the FirstHope app.