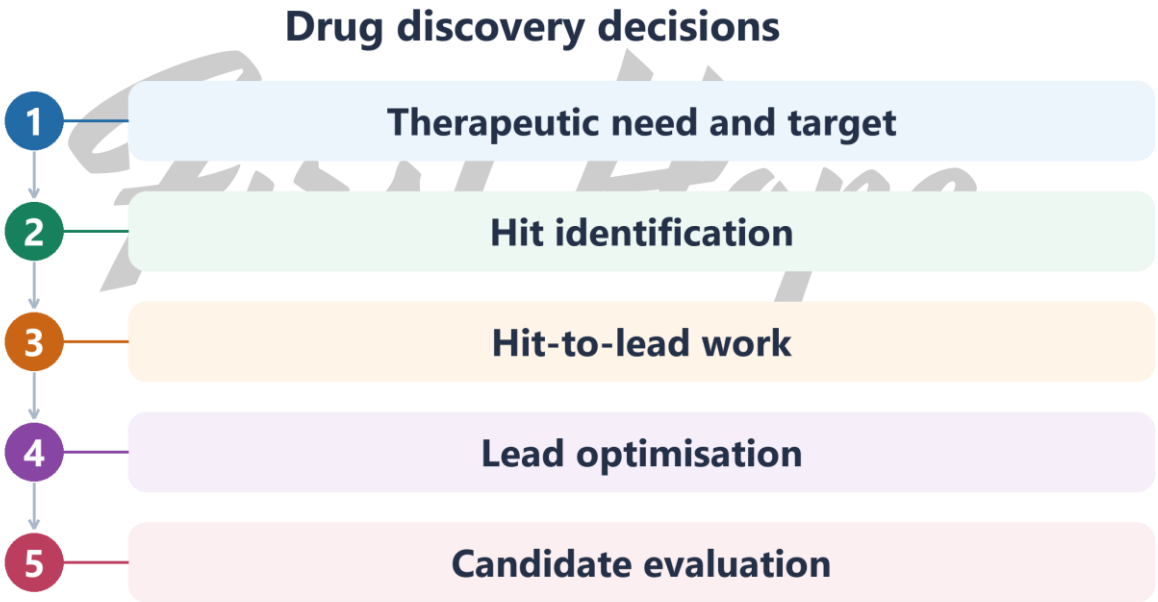
Drug Discovery

Stages of Drug Discovery

- **Drug discovery** is the process of identifying and improving a candidate that can modify a disease-related biological process with useful selectivity and exposure.
- **Medicinal chemistry** connects molecular structure with biological activity, physicochemical behaviour and the practical requirements of a useful medicine.
- A biologically active compound becomes a useful lead only when its activity is reproducible and its chemical identity is established.
- Discovery teams optimise potency together with selectivity, exposure, safety, chemical stability and the ability to prepare a consistent material.
- A compound that binds strongly to an isolated protein may still fail because it cannot reach the relevant tissue or has an unacceptable off-target effect.
- Drug discovery is iterative, so biological experiments can change the target hypothesis and synthesis plans can change the chemical series.



Sequence of Discovery Stages

1. Define the Therapeutic Problem

- The starting question identifies an unmet medical need, a relevant disease process and the type of intervention that might produce benefit.
- A target product profile translates the therapeutic aim into practical properties such as route, duration and the required biological effect.
- The desired profile guides later choices without guaranteeing that every proposed property can be achieved simultaneously.

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2. Identify and Validate the Target

- **Target identification** selects a biological component whose modulation may influence the disease process.
- **Target validation** tests whether changing that component produces the intended effect in relevant biological systems.
- Genetic perturbation, selective chemical tools, patient-derived observations and appropriate disease models provide complementary evidence.
- A correlation between target abundance and disease does not establish that inhibiting the target will improve the disease.
- On-target effects in normal tissue must also be considered because a biologically important target may create mechanism-based toxicity.

3. Discover and Confirm Hits

- A **hit** is a compound that gives a reproducible response in a defined screening assay after suitable confirmation.
- High-throughput screening tests many compounds, while fragment screening starts with smaller molecules that may bind only weakly.
- Phenotypic screening selects a desired cellular or organism-level response and may identify the molecular target later.
- Structure-based and ligand-based computational methods can prioritise compounds for testing, but predictions require experimental confirmation.
- Counterscreens help detect assay interference, nonspecific aggregation, reactive compounds and effects unrelated to the intended mechanism.

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4. Develop a Lead Series

- **Hit-to-lead work** confirms the chemical series, explores initial structure-activity relationships and improves the properties that limit usefulness.
- A **lead** is a sufficiently characterised starting point for systematic optimisation rather than a compound selected only by a low assay concentration.
- Analogue synthesis tests which structural features control potency, selectivity, solubility and metabolic stability.
- Early measurements of permeability, protein binding and clearance help prevent excessive investment in a series with unsuitable exposure.

5. Optimise and Select a Candidate

- Lead optimisation balances several properties through repeated design, synthesis, testing and interpretation.
- A change that increases lipophilicity may improve binding in one assay but reduce solubility, increase nonspecific binding or accelerate an unwanted metabolic pathway.

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- Candidate selection considers the total evidence, including reproducible pharmacology, exposure, safety signals and a workable preparation route.
- A robust impurity profile and a suitable solid form become increasingly important as the required quantity of material increases.

6. Evaluate Preclinical and Clinical Performance

- Preclinical studies characterise pharmacology, disposition and safety before and during the transition to human investigation.
- Early clinical development studies human tolerability and exposure, while later studies evaluate benefit-risk in appropriate patient populations.
- Phase I, II and III are useful general stage descriptions, but trial designs and populations vary with the medicine and disease.
- Approval does not end evaluation because manufacturing control, pharmacovigilance and additional clinical evidence continue throughout use.

Progression from Discovery to a Medicine

1. Preclinical Development

- A selected candidate must be studied for pharmacology, exposure, metabolism and toxic effects before an appropriate first study in humans.
- The proposed formulation and manufacturing process must provide material with a defined identity, strength and impurity profile.
    - A promising animal result supports further investigation but does not establish safety or efficacy in people.

2. Clinical Development

A. Early Human Studies

- Phase I studies usually examine initial human safety, tolerability and pharmacokinetics.
- The study population depends on the product and disease; healthy volunteers are not suitable for every medicine.

B. Exploratory and Confirmatory Studies

- Phase II studies investigate activity in patients and help define a useful treatment approach.
- Phase III studies provide larger confirmatory comparisons intended to establish the balance of benefit and harm.

3. Regulatory Review and Continued Monitoring

- The submitted evidence includes quality, nonclinical and clinical information.
- Monitoring continues after approval because uncommon adverse effects and long-term outcomes may not be fully characterised before marketing.

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Decision Making During Development

- A project may stop because its biological hypothesis fails, its exposure is inadequate or its safety margin is unacceptable.
- Early negative findings can prevent a weak chemical series from consuming resources in later development.
- Each stage therefore has a scientific question and a decision criterion, rather than serving only as a chronological label.

Lead Discovery

Natural Products and Existing Medicines

- Natural compounds can reveal biologically productive scaffolds, although complex structures and limited supply may require semisynthesis or a simpler analogue.
- An existing medicine can provide a starting pharmacophore for improved potency, selectivity or a different delivery profile.
- A known scaffold should not be assumed to transfer all of its safety and efficacy properties to a new analogue.

Screening Libraries and Fragments

- A screening library should contain verified compounds with useful chemical diversity rather than only a large number of closely related structures.
- Fragments often require sensitive biophysical methods because their binding can be weak at the beginning of optimisation.
- Fragment growing, linking or merging can increase affinity when the resulting molecule preserves the productive binding geometry.

Biological Knowledge and Rational Design

- Knowledge of an endogenous ligand, an enzyme substrate or a transition-state arrangement can suggest a starting inhibitor or receptor ligand.
- A crystal or cryo-EM structure may reveal an accessible pocket, but the experimental structure represents only part of a dynamic biological system.
- Rational design combines structural reasoning with testing rather than replacing experiments with a convincing picture.

Confirm Chemical Identity

- Establish the compound's identity, purity and stability before interpreting a biological result.
- An active impurity or a decomposed sample can create a misleading structure-activity relationship.

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Repeat Activity in an Independent Format

- Repeat the concentration-response experiment and use an orthogonal assay when possible.
- An assay that detects a different physical signal helps separate true target activity from interference with a reporter.

Test Selectivity and Cellular Relevance

- Compare the intended target with relevant related targets and measure whether the compound reaches and engages the target in cells.
- A biochemical hit with poor cellular exposure may require permeability optimisation or a different chemical series.

From an Initial Hit to a Credible Lead

Chemical Confirmation

- An initial signal is checked with a compound of established identity and purity.
- Freshly prepared or independently obtained material helps determine whether an impurity caused the apparent activity.
- A concentration-response experiment should demonstrate a reproducible relationship between concentration and biological response.

Biological Confirmation

- An orthogonal assay measures the same biological question by a different detection method.
- A counterscreen asks whether the compound interferes with the assay or acts through an unwanted mechanism.
- Activity in a cell requires suitable permeability, stability and access to the target, so biochemical potency alone is insufficient.

Initial Medicinal Chemistry

- A small set of related compounds is used to establish whether structural changes produce interpretable changes in activity.
- A tractable lead also needs positions that can be modified without destroying the essential binding features.
- Patent position, synthetic accessibility and early solubility or metabolic problems influence selection between otherwise similar leads.

Identification of Drug Targets

- **Target identification** establishes which biological molecule or process might be modulated to influence a disease.

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