PHM302B: Drug Discovery, Design, and Development

OVERVIEW OF DRUG DISCOVERY, DESIGN, AND DEVELOPMENT

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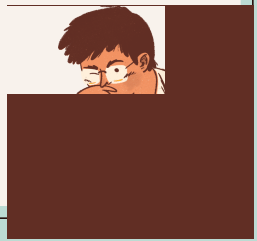


MEDICINAL CHEMISTRY: AN INTERDISCIPLINARY SCIENCE

- Therapeutic agents are chemical entities that prevent disease, assist in restoring health to the diseased, or alleviate symptoms associated with disease conditions.
- Medicinal Chemistry is the scientific discipline that makes such drugs available either through discovery or design processes.

MEDICINAL CHEMISTRY: AN INTERDISCIPLINARY SCIENCE

Four Natural Discovery Milestones

Morphine	Hyoscyamine	Quinine	Digitalis
• isolated from opium poppy recognized as the foundational blueprint for analgesic pain relief.	• Classification: Tropane alkaloid extracted from Solanaceae essential for anti-cholinergic	• Isolated from Cinchona bark. Historically revolutionized the clinical treatment of global malaria.	• Classification: Cardiac glycosides - critical for treating cardiac insufficiency and heart failure.

MEDICINAL CHEMISTRY: AN INTERDISCIPLINARY SCIENCE

The Twentieth Century Paradigm Shift

- The 20th century saw the mass chemical modification of biologically active natural products to optimize pharmacology, potency, and drug parameters.
  - **Advanced Synthesis:** Escalated synthetic capabilities enabled production of novel compounds independent of natural plant supply.
  - **Rational Design:** Cellular understanding led directly to rational synthesis targeting specific biological mechanisms.

MEDICINAL CHEMISTRY: AN INTERDISCIPLINARY SCIENCE

- Modern medicinal chemistry draws upon many scientific disciplines, with organic chemistry, physical chemistry, and pharmacology being of fundamental importance.
- Other disciplines such as biochemistry, molecular biology, toxicology, genetics, cell biology, biophysics, physiology, pathology, and computer modeling approaches play important roles.
- **Research objective:** to investigate relationships between chemical structure and biological effects.

SAR - structure activity relationship

MEDICINAL CHEMISTRY: AN INTERDISCIPLINARY SCIENCE

A drug candidate must satisfy a complex; multifaceted set of biological criteria before safe patient trials can begin. These are critical filters in preclinical development:

- ADME
- toxicology studies in animals

DRUG DISCOVERY: A HISTORICAL PERSPECTIVE

The Empirical Era of Medicine

Progress in ancient times was purely empirical, operating without biological insights.

- **Historical Actives:** Traditional therapeutics utilized plants like ephedra, digitalis, coca, salicylic acid, and opium.
- **Ecosystem Utility:** These compounds were biosynthesized by plants to assist their own ecological survival, not for human medicinal convenience

DRUG DISCOVERY: A HISTORICAL PERSPECTIVE

- The presence of biologically active substances in nature, notably in certain plants, was in medieval times interpreted more teleologically. In the early sixteenth century, the Swiss Austrian medical doctor and natural scientist Paracelsus formulated the "Doctrine of Signatures":

"Just as women can be recognized and appraised on the basis of their shape; drugs can easily be identified by appearance. God has created all diseases, and he also has created an agent or a drug for every disease. They can be found everywhere in nature, because nature is the universal pharmacy. God is the highest ranking pharmacist"

"Just as we honor the brilliant diversity, resilience, and inherent dignity of women, we can admire the intentional design found throughout the nature world. creation serves as a vast, natural pharmacy, perfectly balanced to heal and support life"

DRUG DISCOVERY: A HISTORICAL PERSPECTIVE

Macromolecular Complementarity

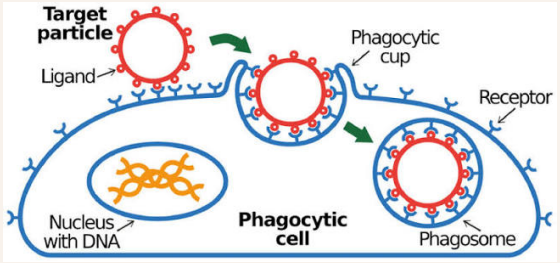
Over 100 years ago, chemist Emil Fischer proposed that ligand binding mimics a key fitting into its corresponding lock, later refined by John Langley and Paul Ehrlich composed "compound 606, magic bullet, salvarsan" = syphilis.

- **Super-Molecule:** The unified drug-receptor combination creates a brand-new thermodynamic complex leading directly to cellular signaling.
- **Agonist vs. Antagonist:** Successful key insertion prompts positive agonistic response; mismatched blocking molecules trigger antagonist inhibition

DRUG DISCOVERY: A HISTORICAL PERSPECTIVE

Evolution of Receptor Concept:

The Fischer Lock & Key **Rigid Conception:** Assumes receptors are static, rigid macromolecules built to fit specific, rigid drug structures. **Agonist/Antagonist:** Clean fit induces cellular activation; steric blockage halts standard mechanisms.	**The** Zipper Model In contrast, the Zipper Model views docking as a progressive, dynamic conformational wrap. **Mutual Adaptation:** Both ligand and receptor conform structurally during docking to optimize electrostatics. **Design Challenge:** Designing for flexible entities requires modeling dynamic complexes rather than resting-state ground state



DRUG DISCOVERY: A HISTORICAL PERSPECTIVE

Beyond classic enzymes and cell-surface receptors, modern design now successfully targets nuclear receptors (activated by steroids and lipophiles), membrane-ion channels, as well as genomic structures (DNA & RNA).

DRUG DISCOVERY

Procedures for Drug discovery

1. Random screening : tests new chemical for biological activity
   - methods: uses animal behavior, tissues, whole animals or disease models.
   - Drawbacks : expensive, slow, and low success rates
2. Molecular manipulation: alters existing chemical structures to optimize therapeutic profiles.
3. Molecular designing: rational method for creating a synthetic substances tailored for specific biological roles. Focuses on designing or replicating natural hormones and NT
4. Metabolites of drug
   - Some active metabolites offer benefits over the original drug.
5. Serendipity

v

means "happy chance" an accidental and fortunate discovery

ex- penicillin

insulin

DRUG DEVELOPMENT PROCESS: AN OUTLINE

Introducing a novel therapeutic agent to clinical deployment is an iterative, multi-phase timeline:

Discovery Phase 4 - 5 years Target identification & validation, chemistry assays, lead discovery, analog optimization, and patent protection filing Pre-clinical	**Development Phase** 6 - 10 years Large-scale synthesis, Phase I–III clinical evaluations, and regulatory review filing (NDA/Market Authorization). Clinical trial	**Post-Market & Patent** 17 - 25 years Phase IV pharmacovigilance, long-term safety, advertising, and the eventual transition to generic drug competition.

DRUG DEVELOPMENT PROCESS: AN OUTLINE

Steps involved in Drug development

Pre - Clinical Phase

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Clinical Phase

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FDA Review and Approval → NDA (New Drug Application)

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PMS (Post Marketing Surveillance)

nasa market na product

Pre-Clinical Evaluation (Animal Subject)

- **Drug Safety Testing:** Before human trials, drugs undergo tests to identify any harmful effects, focusing on toxicity to ensure safety.
- **Types of Preclinical Research:**
  - In vitro: Laboratory tests using cells or tissues to observe drug effects without involving live animals.
  - In vivo: Studies conducted on live animals to understand how the drug behaves in a whole organism.
- **Good Laboratory Practices (GLP):** These are strict guidelines set by the FDA to ensure reliability, consistency, and quality in preclinical studies, covering everything from study design to data reporting.
- **Study Size and Detail:** Although preclinical studies involve fewer subjects than clinical trials, they must provide precise information on drug dosage, toxicity thresholds, and side effects to guide further testing.

Pre-Clinical Evaluation (Animal Subject)

- **Animal Models:** Commonly used animals include rats, rabbit, guinea pigs, dogs, and occasionally monkeys.
- **Key Evaluation Areas:**
  - Toxicity studies: Assess immediate (acute), short-term (subacute), and long-term (chronic) toxic effects to understand potential risks.
  - Therapeutic index: Measures the safety margin by comparing effective doses to toxic doses, helping to determine safe dosage ranges.
- **Absorption, Distribution, and Elimination:** Studies how the drug is absorbed into the body, distributed to tissues, metabolized, and eventually excreted, which affects efficacy and safety.

Clinical Evaluation (Human Subject)

- **Animal studies:** Provide basic drug safety, effects, and processing data
- **Approval:** Submit to FDA (Food and Drug Administration) before human trials start.