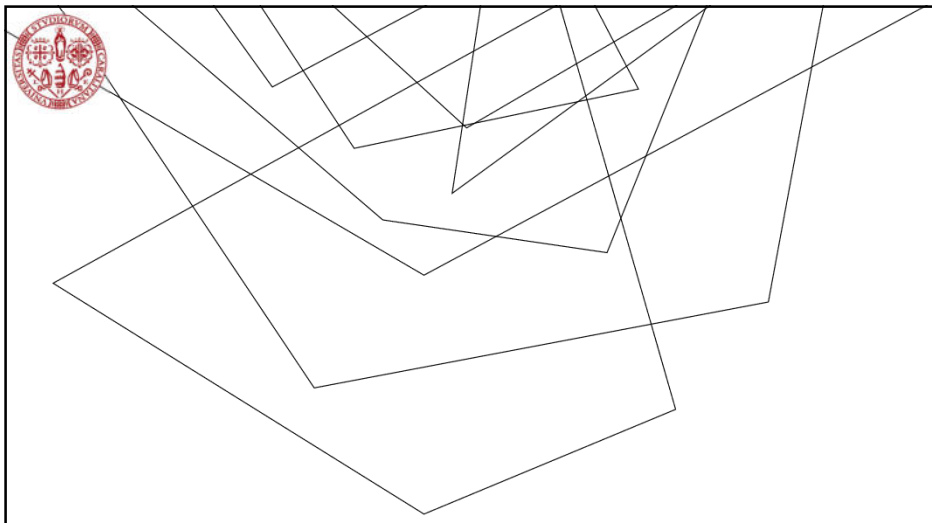

BASIC PRINCIPLES OF DRUG DISCOVERY AND DEVELOPMENT

Prof. Enrico Sanna, Prof. Simona Distinto, Prof. Maria Letizia Manca
DEPARTMENT OF LIFE AND ENVIRONMENTAL SCIENCES – FACULTY OF BIOLOGY AND PHARMACY
University of Cagliari

1

PROF. ENRICO SANNA

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Email esanna@unica.it

Phone +39-0706754139 (Office) - +39-0706754200 (Laboratory)

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PROF. MARIA LETIZIA MANCA

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4

SOMETHING ABOUT YOU

Mailing list

A course mailing list ensures clear and timely communication, allowing professor and students to share announcements, materials in one reliable channel.

https://forms.office.com/e/3bwTSzTYCM

5

INFO AND PROGRAMS

6

ADVANCED BIOTECHNOLOGY

The Master's in Advanced Biotechnology (LM-9) provides students with in-depth knowledge of modern biotechnology, focusing on areas like drug discovery, molecular biology, nanotechnology, and biomedical research. The program includes topics such as drug development, green chemistry, omics, regenerative medicine, and advanced screening methods. Graduates will be prepared for careers in biopharma, diagnostics, and research, with skills to drive innovation and tackle global health and sustainability challenges..

https://web.unica.it/unica/it/crs_60_80.page

7

OVERVIEW OF ADVANCED BIOTECHNOLOGY PROGRAMME

I year

1 sem

1. **Basic principles of drug discovery and development**

2. Green chemistry and bioconjugation

3. Cellular and molecular bases of cancer and tissue regeneration

2 sem

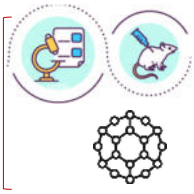
4. Biotechnology of fermentations and biochemical methods

5. Advanced methods for drug screening in infectious diseases

https://web.unica.it/unica/protected/505264/0/def/ref/DOC505255/

8

II year



6. Advanced methodologies for preclinical drug studies

7. Nanomaterials applied to biotechnological and diagnostics compounds and methods

8. Omics sciences

9. Manufacturing of biotechnological medicines

10. Structural bioinformatics and CADD

11. Bioethics, clinical trial design and pharmacovigilance

I and II Year

Optional Teaching Activities 12 (including seminars)
Internship 15
Thesis 11

9

10

BASIC PRINCIPLES OF DRUG DISCOVERY AND DEVELOPMENT

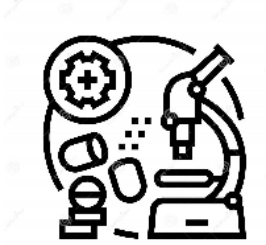
11

BASIC PRINCIPLES OF DRUG DISCOVERY AND DEVELOPMENT

AIM OF THE COURSE/COURSE OBJECTIVES

To provides an in-depth understanding of the drug discovery process, from the identification of potential biological targets to the development and optimization of biotechnology-based therapies, such as monoclonal antibodies, proteins, peptides and gene therapies.

Students will explore key aspects of medicinal chemistry, pharmacokinetics, and pharmaceutical technologies, learning how to design, formulate, and evaluate both conventional and biotechnological drugs.



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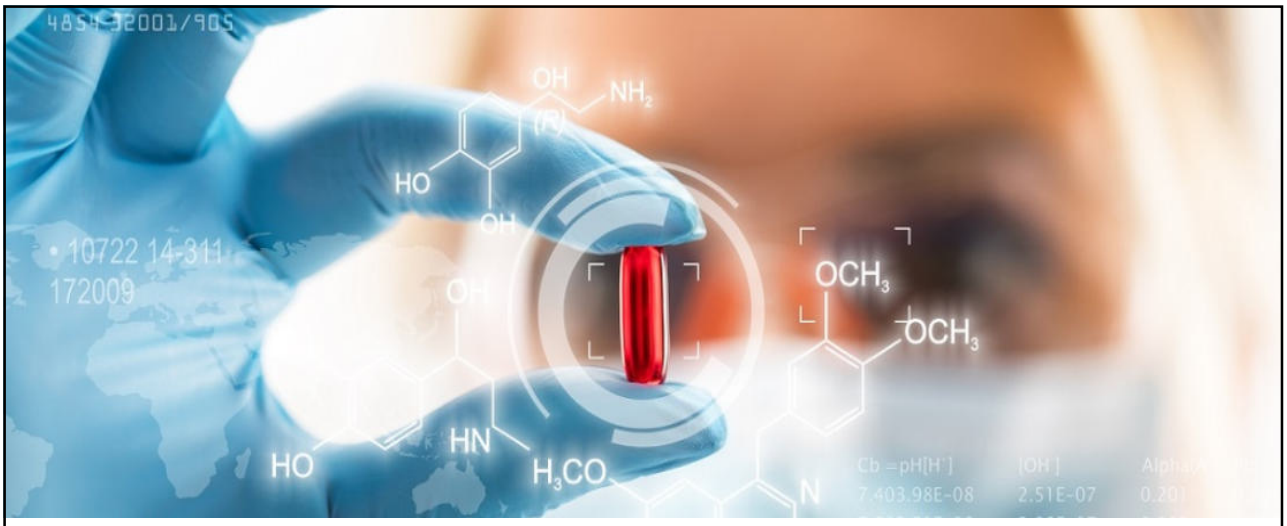

MEDICINAL CHEMISTRY PROGRAM

13

PROGRAM

The **Medicinal Chemistry (MC)** section will cover the following topics:

1. Introduction to MC and Biotechnology:
-The drug discovery process and the role of Computer-Aided Drug Design (CADD).
-Biologics versus small molecules: key differences in structure, function, and applications.
-Integration of MC and biotechnology in modern drug discovery.
2. New perspectives in drug discovery and MC: Emerging strategies, challenges, and future trends in drug discovery.
3. Basic concepts of MC: Molecular principles of molecular recognition.
-Non-covalent and covalent interactions in drug-target binding.
-Functional groups, physicochemical properties, and their influence on drug activity.
4. Structure-activity relationships (SAR) and pharmacophores.
-Strategies for optimizing drug activity through structural modification.
-Pharmacophore concepts, QSAR methods, and computational approaches.
5. Pharmacokinetics (PK): ADME and drug design.
6. Pharmacodynamics (PD): From Structure to Function: MC strategies in drug action.
7. Biotechnological drugs: Peptides, proteins, and nucleic acids in therapy. Drug design strategies, and structural aspects.

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PHARMACOLOGY

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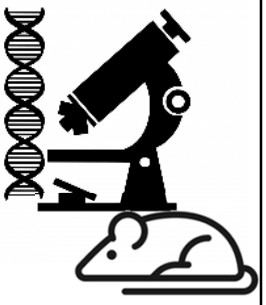
PROGRAM

The pharmacology part will be divided into the following topics:
1. Principles of pharmacodynamics: quantitative aspects of drug-receptor interaction.
2. Classic and innovative molecular targets in drug discovery. Enzymes, GPC receptor signaling pathways, transmembrane receptors linked to intracellular enzymes, ion channels, membrane transporters, nuclear receptors, RNA, DNA.
3. In vitro systems for drug screening.
Biochemical and cellular assays; radioligand assays, ELISA, fluorescence-based systems, gene-reporter FRET assays, electrophysiological systems (patch-clamp).
4. Biotechnological drugs.
Monoclonal antibodies. Structural and pharmacokinetic properties. Oligonucleotides modulating gene expression. Gene editing.
5. The foundations of clinical trials.
Phase 1 – 4 clinical trials. The design of clinical trials, meta-analysis of clinical trial data.
6. Principles of pharmacogenetics and pharmacogenomics.
7. Principles of gene therapy.
8. Safety and toxicity of drugs.



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PHARMACEUTICAL TECHNOLOGY

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PROGRAM

The pharmaceutical-technology part will focus on:

1. Introduction to pharmaceutical technology
- Combination of different materials to prepare drug carriers;
- Importance in therapeutic programs.
2. From conventional to Biotechnological drugs
- Types of therapeutic molecules
- Stability concerns
- Challenges in biotechnology
3. Dosage forms for biotechnological drugs
- From conventional to controlled-release dosage forms
- Mechanism of Action
- Factors Influencing Release
4. Nanotechnology for biotechnological drugs: Focus on the most promising dosage forms for the delivery of biotechnological molecules
5. Pharmaceutical dosage forms and routes of administration
- Promising route of administration for biotechnological molecules
- Parenteral delivery
- Combination of the ideal administration and promising carrier to obtain the therapeutic effect.
6. Role of excipients of a pharmaceutical dosage form
- Combination of various excipients to obtain the ideal dosage form
- Ability of the excipients to influence the release of the active molecules
7. Current regulations for the production of biotechnological drugs
- Main normative criteria
- Outline of the regulatory process for the production of biotechnological drugs.
8. Production of biotechnological medicines
- Industrial production and main requisites needed for a biotechnological company.

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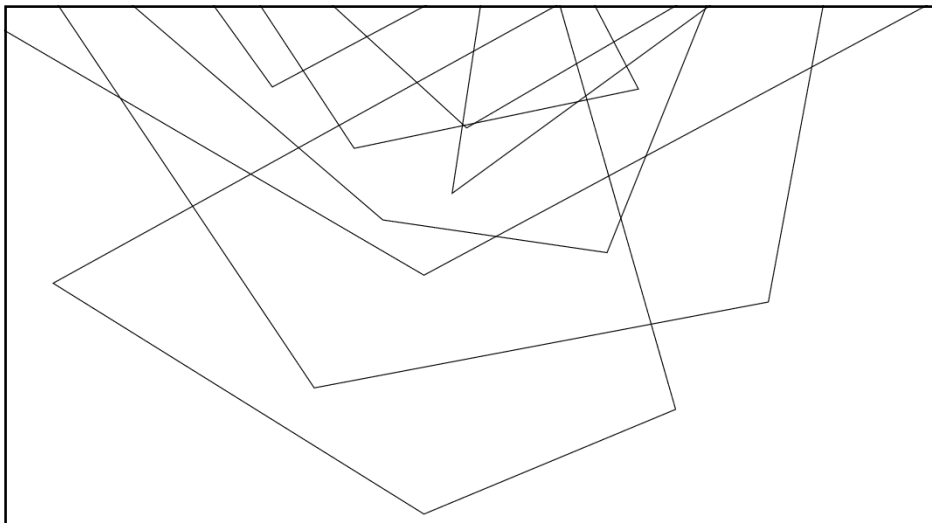

SUGGESTED BOOKS AND TEACHING MATERIAL

19

SUGGESTED BOOKS

B.E. Blass. Basic principles of drug discovery and development. 2nd edition. Academic Press, Elsevier, 2021.

D.J.A. Crommelin, R.D. Sindelar, B. Meibohm. Pharmaceutical Biotechnology, Fundamentals and Applications Springer

A.R. Leach. Molecular Modelling, Principles and Applications - Pearson College Div.

L.L. Brunton, B.C. Knollmann. Goodman & Gilman's The Pharmacological Basis of Therapeutics. McGraw Hill, 14° ed. 2023.

TEACHING MATERIAL

Medicinal Chemistry
https://web.unica.it/unica/en/ateneo_s07_ss01_sss03.page?contentId=SHD30332

Pharmacology
PowerPoint presentations and other teaching materials will be made available via e-mail using the common e-mail address for the class.

Pharmaceutical Technology
PowerPoint presentations and other teaching materials will be made available via e-mail or Teams

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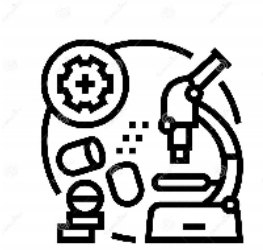
GOALS



Student will be able to:

- hypothesize a rational design of a new bioactive molecule;
- choose the most suitable dosage form for the selected route of administration;
- critically elaborate on the concepts presented during the course and to identify the most appropriate technique to address a specific problem in the design and development of a drug;
- independently and critically ponder the needed components capable of enhancing the effect of a biotechnological active, especially in view of its possible use in therapy;
- analyze, from a chemical-pharmaceutical, technological and pharmacological point of view, the most suitable solutions for the formulation of an effective dosage form, characterized by high standards of quality.

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EXAM

It is highly recommended to take the exam at the end of the semester

Written exam using Forms.
Covers all three sections of the course.
Structure:

1 open-ended question (4 points)
3 multiple-choice and short-answer questions (2 points each)

Designed to assess both factual knowledge and the ability to integrate concepts.
Length: 12 questions total, 90 minutes.
This written exam option will be offered only in **January and February**.
From **March onwards**, assessment will take place exclusively through a longer **oral exam**.

Oral exam

- Each student presents a **short seminar** on a topic assigned by the professors the last week of the course.
- The seminar must integrate **medicinal chemistry, pharmacology, and pharmaceutical technology** aspects.
- The oral exam evaluates **critical thinking, integration of knowledge, and communication skills**.
- Professors may also ask **additional questions** to verify the student's preparation, especially if the written exam was not fully satisfactory.

The final grade considers both written and oral exam

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VERIFICATION OF LEARNING

You can find details about how we will evaluate your preparation in the link below:

https://unica.coursecatalogue.cineca.it/insegnamenti/2025/22418/2024/9999/11110?coorte=2025&schemaid=5161

23

SAVE-THE-DATES

CALENDARIO ESAMI A.A. 2025/2026

I ANNO

			2026										2027		Commissioni			
Insegnamento	Titolare e co-docenti	Semestre	GEN	FEB	MAR	APR	MAG	GIU	LUG	SET	OTT	NOV	DIC	GEN	FEB	Presidente	Componente	Componente	Componente
CELLULAR AND MOLECULAR BASES OF CANCER AND TISSUE REGENERATION	MARONGIU FABIO	1°																	
BASIC PRINCIPLES OF DRUG DISCOVERY AND DEVELOPMENT	SANNA ENRICO - DISTINTO SIMONA - MANCA MARIA LETIZIA	1°	20	4,18				16	23	16				20	4,18	SANNA ENRICO	DISTINTO SIMONA	MANCA MARIA LETIZIA	

The written exam will be held **on January** 12th 14th, then you can decide to take the exam on Jan 20th or Feb 4th

and on **February** (second week, probably 9th or 10th or 11th)

According to Room 209 - A Building availability.

From March onwards, the exam
will take place exclusively through a longer oral exam.

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MODULES ORGANIZATION

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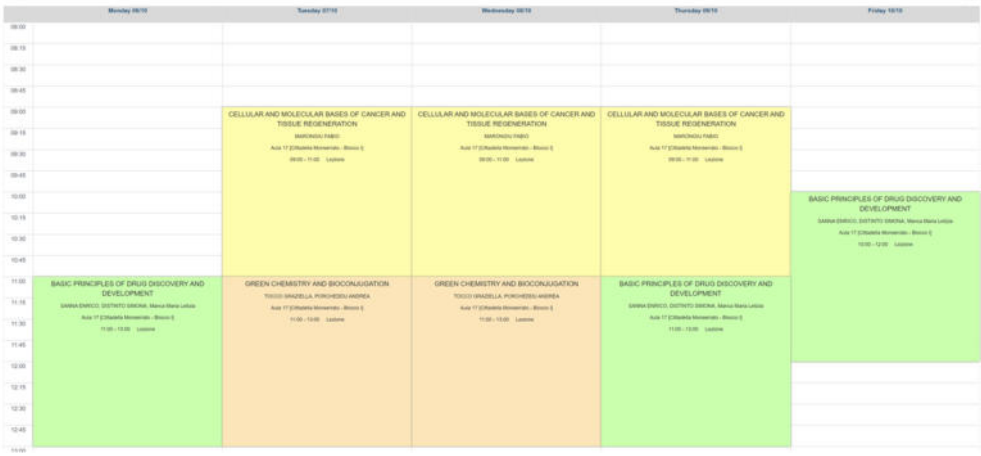
EASY LESSON PORTAL

https://unica.easystaff.it/AgendaWeb/index.php?view=easycourse&include=corso&_lang=en



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TIMETABLE FOR MEDCHEM MODULE

Option 1: starting at 11 a.m.

Date	N of h
03/10/2025	2
06/10/2025	2
13/10/2025	2
20/10/2025	2
27/10/2025	3
03/11/2025	2
10/11/2025	2
17/11/2025	Probably cancelled
24/11/2025	2
01/12/2025	3
15/12/2025	2
22/12/2025	2

Option 2: starting at 10 a.m.

Date	N of h
03/10/2025	2
06/10/2025	2
13/10/2025	3
20/10/2025	3
27/10/2025	3
03/11/2025	3
10/11/2025	3
17/11/2025	Probably cancelled
24/11/2025	3
01/12/2025	2

On 17th November, I will probably have to attend a conference, so the lesson will be cancelled.

You can think about it and give me your answer next Monday

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SOME IMPORTANT GENERAL ADVICES

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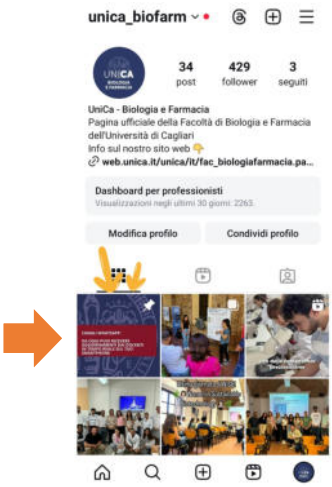
INFORMATION ABOUT WHATSAPP COURSE CHANNEL



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BASIC PRINCIPLES OF DRUG DISCOVERY AND DEVELOPMENT:

A MULTI-DISCIPLINARY CHALLENGE

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PHARMACEUTICAL R&D: A MULTI-DISCIPLINARY CHALLENGE

The drug discovery process involves many different scientific fields

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DRUG DISCOVERY AND DEVELOPMENT (DD&D) - A SYNERGIC EFFORT

- Pharmacology
- Medicinal Chemistry
- Pharmaceutical Technology
- Biology
- Clinical Research
- Toxicology
- Biostatistics
- Quality Assurance
- Pharmacoeconomics
- Project Management
- ….

A successful outcome is achieved through the integration of multiple areas of expertise

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BASIC DEFINITIONS

"The **drug** is an organic chemical compound which, when introduced into a living system, produces a change in physiological functions through chemical actions."

The word 'drug' derives possible origin is the Medieval Latin word "droga," used to describe medicinal substances, particularly those that were dried.
Today, the term "drug" encompasses a wide variety of substances, including those used for medical treatment (pharmaceuticals) as well as recreational and illicit substances.

Often the drug is call **medicament**, but we have to pay attention that this is different from **medication.**
A medicament is specifically a drug that has been prepared, formulated, and authorized for therapeutic use.

An **excipient** is an inactive substance that is combined with the drug in the formulation. Excipients do not have a therapeutic effect but serve several important roles, such as:
•Aiding in the drug's delivery to the body (e.g., helping it dissolve).
•Stabilizing the formulation (preventing the drug from degrading).
•Improving the taste, texture, or appearance.
•Facilitating absorption by the body.

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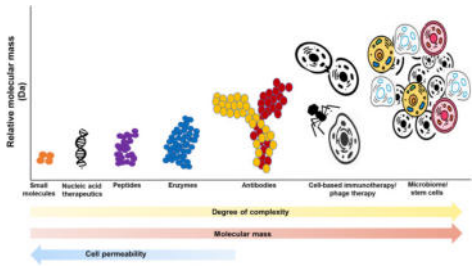
THE EVOLUTION OF DRUG DISCOVERY: BRIDGING PHARMACEUTICALS AND BIOTECHNOLOGY

Historically, medicinal chemistry focused on small molecules, optimizing compounds for therapeutic effects. However, as the limitations of small molecules in addressing complex diseases became evident, the biotechnology revolution of the late 20th century introduced new paradigms. Biotech companies began developing macromolecules, such as proteins, antibodies, and nucleic acids, which offered more precise and targeted therapies, particularly for conditions like cancer, autoimmune disorders, and genetic diseases.



https://doi.org/10.1016/B978-0-12-821972-0.00015-0

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Today, drug discovery has become a highly multidisciplinary field, with medicinal chemistry working alongside pharmacology and pharmaceutical technology to drive innovation.

Pharmacology provides critical insights into drug mechanisms, guiding the development of more effective therapies by clarifying how molecules interact with biological systems.

At the same time, advances in pharmaceutical technology have enabled the design and delivery of complex drugs, such as biologics and nanomedicines, with enhanced efficacy and reduced side effects.

In the modern drug discovery development several researchers collaborate closely to develop hybrid solutions, including antibody-drug conjugates (ADCs), gene therapies, and personalized medicines.

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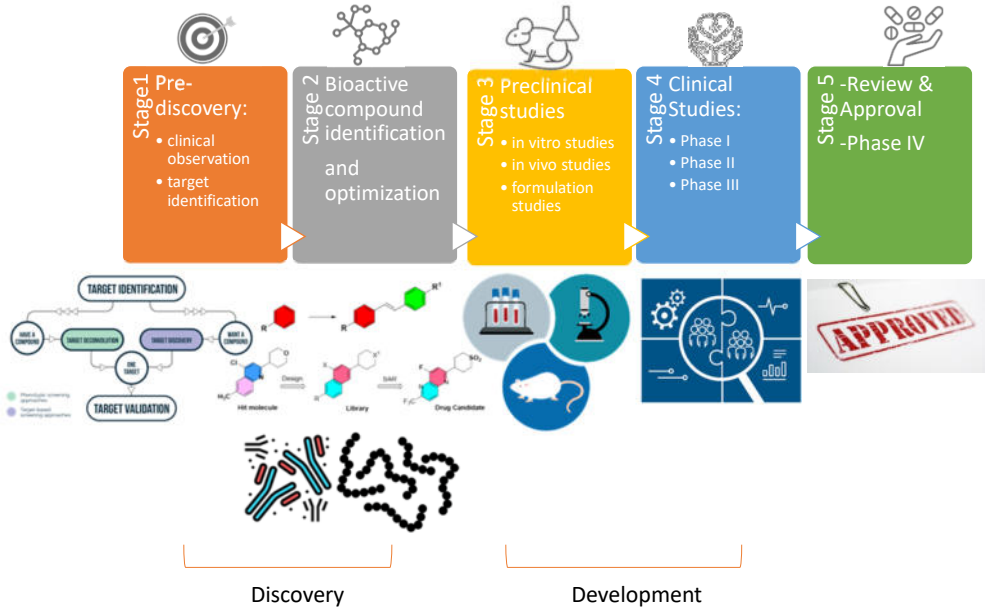
OVERVIEW OF DRUG DISCOVERY AND DEVELOPMENT



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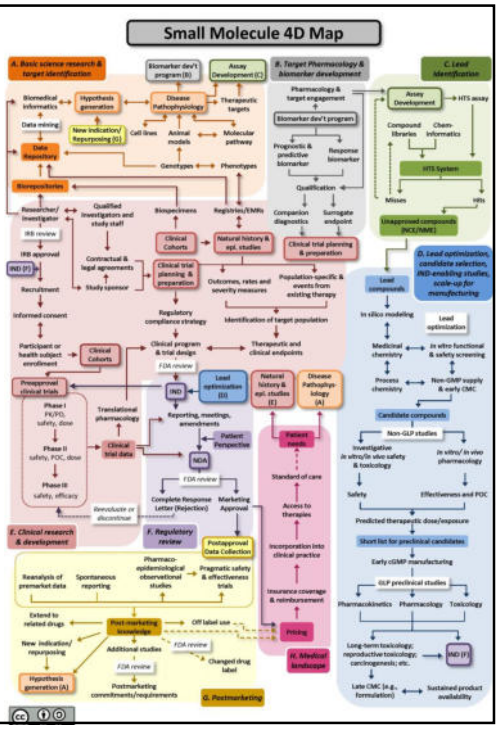
MORE COMPLEX DEPICTION

The map comprises neighbourhoods (panels **a**–**h**), each of which consists of a complex network of steps that interact with steps in other neighbourhoods. Steps identified in the mapping process as being characterized by the greatest cost, time or likelihood of failure are identified with a red outline; fewer problematic roadblocks are identified with a pink or orange outline. Dotted lines indicate possible alternative pathways between two steps.

CMC, chemistry, manufacturing and controls; EMR, electronic medical record; FDA, Food and Drug Administration; GLP, good laboratory practice; GMP, good manufacturing practice; HTS, high-throughput screening; IND, investigational new drug; IRB, institutional review board; NCE, new chemical entity; NDA, new drug application; NME, new molecular entity; PK/PD, pharmacokinetics/pharmacodynamics; POC, proof of concept.

Small molecules

Wagner JA, Dahlem AM, Hudson LD, Terry SF, Altman RB, Gilliland CT, DeFeo C, and Austin CP. Drug Discovery, Development and Deployment Map (4DM): Small Molecules. Available at https://ncats.nih.gov/translation/maps. Last updated November 2017.



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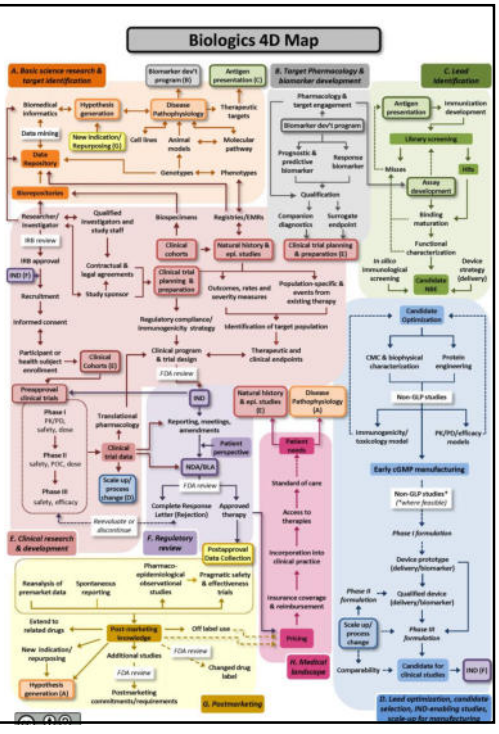
The "Map" offers a comprehensive, visual representation of the therapeutic development process for biologic drugs, such as monoclonal antibodies. This map serves as a strategic tool to identify the entire lifecycle of biologic drug development.

•**Multidimensional Framework:** The map is organized into eight interconnected "neighborhoods," each representing a critical phase in the development process, from target identification and assay development to clinical trials and regulatory approval.
•**Integration of Disciplines:** It highlights the collaborative nature of modern drug development, emphasizing the roles of pharmacology, biomarker development, and pharmaceutical technology in advancing biologic therapies.
•**Focus on Complex Therapies:** By using monoclonal antibodies as a representative example, the map underscores the unique challenges and considerations in developing large, complex molecules compared to traditional small molecule drugs.

Biologics



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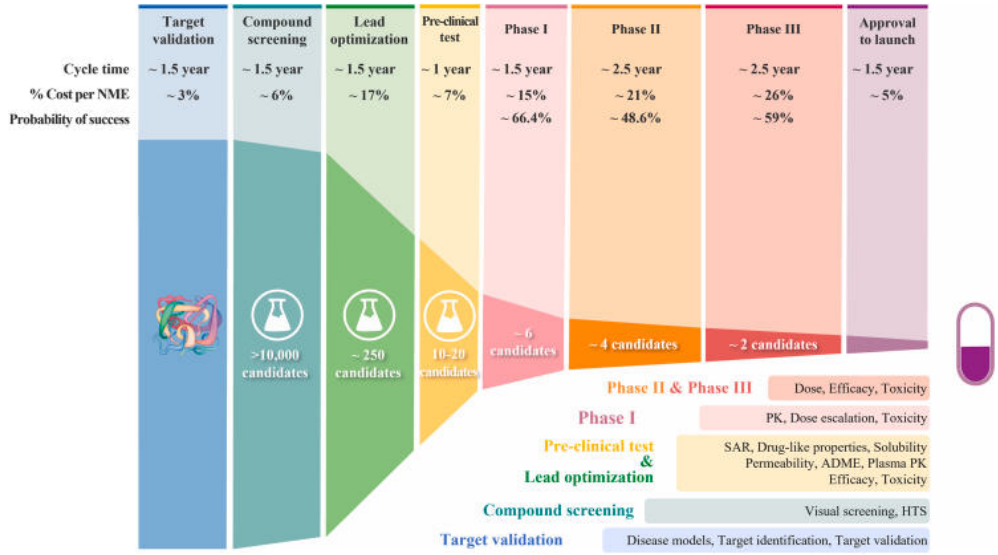

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9293739/

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SMALL MOLECULES VS BIOLOGICS

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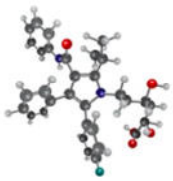
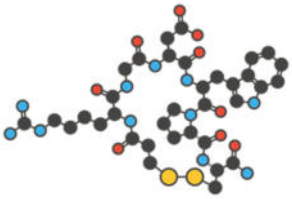
SM

LM



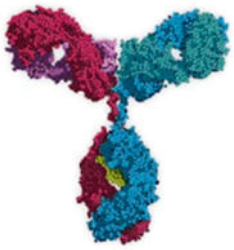
Small molecules (SM)

<900 Daltons

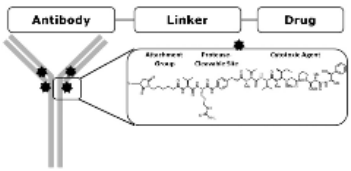


peptides

<100 aminoacids



proteins



ADC
Antibody–drug conjugate

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COMPARISON SM VS LM

Item	Small Molecule Drugs	Biologics
Size	Smaller with lower molecular mass	Larger with higher molecular mass
Structure	Chemical compounds	Biological structures
	Simple, definable, stable	Complex, heterogenous, degradable
	Consistent across manufacturing processes	Highly impacted by manufacturing processes
Mechanism of Action (MOA)	Interfere with biochemical reactions (e.g., receptor proteins, ion channels, kinases)	Impact biologic cellular and genetic processes (e.g., protein-protein interactions, protein production, gene expression)
	Exact MOA sometimes unknown	Thorough understanding of MOA necessary
Disease Target	Acute and chronic conditions (e.g., pain, fever, infection, psychiatric conditions, allergies, cardiovascular health)	Complex and hard-to-treat diseases (e.g., cancer, autoimmune disease, metabolic disease, genetic disorders)
Examples	Antibiotics, proton-pump inhibitors, beta blockers, calcium channel blockers, opioids, benzodiazepines, selective serotonin reuptake inhibitors, antihistamines, synthetic steroids, kinase inhibitors, etc.	Nucleic acids (e.g., RNA), peptides, enzymes, proteins, antibodies (e.g., monoclonal antibodies), cell therapies (e.g., CAR-T), vaccines, hormones, blood products

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COMPARISON SM VS LM

Selectivity	Lower selectivity	Higher specificity
	Off-target binding more likely	Off-target effects unlikely
		Lower toxicity overall
Safety	Potential toxicity due to off-target effects	Greater likelihood of immune response (immunogenicity)
	Higher likelihood drug-drug interactions (due to ADME processes)	Less prone to drug-drug interactions (due to ADME profile), though some potential to impact drug-metabolizing enzymes
Production	Straight forward chemical synthesis	Requires cell line production and live organisms
	Standardizable	Variable complex processes
	Processes easier to reproduce and quality control (QC)	Processes harder to reproduce and QC
	Replicating exact structure across different manufacturing processes is probable	Process greatly impacts structure
		Difficult to attain exact copies from batch to batch
Structural Assessment	Highly determinable via traditional analytic methods	Elusive and typically not fully determinable
		Structural determination and quantification challenging

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COMPARISON SM VS LM

Permeability	Higher permeability, easier to reach intracellular targets	Less permeable, more challenging to reach targets
		Injection or infusion in a care setting typically needed
		PK and PD difficult to predict
Administration	Oral administration possible	Impacted by size, structure, folding, and surface charge
	Predictable PK and PD	Modifications can improve profile (e.g., amino acid substitution, glycosylation, PEGylation, albumin binding, delivery vehicles, etc.).
	Animal and assay models well established	Animal and assay models less developed
	Faster time to peak concentration via blood distribution	Slower time to peak concentration via lymphatic and blood distribution
	Shorter half-life	Longer half-life
		Generally polar
Stability	Polarity varies	Heat sensitive
	Heat stable	Degradable
	Stable	Modifications (e.g., peptide stapling) can help improve degradation
Storage	Room temp	Refrigeration
	Well-established generic market	Burgeoning biosimilar market
	Easier to replicate due to stable structures and processes	More difficult to replicate due to complex processes and structures

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COMPARISON SM VS LM

Exclusivity / Generics	Straight-forward requirements for establishing generic equivalence and interchangeable prescription substitution	More complex requirements for establishing biosimilarity and attaining interchangeable prescription substitution
	5-year exclusivity before generic competition for new chemical entities (despite similar development timelines)	12 years exclusivity before generic competition (despite similar development timelines)
	Generic cost reduction ~80%	Biosimilar cost reduction ~20-30%
Price	Generally lower cost	Generally higher cost (contributing to its rapid increase in market share)

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CAN SMALL MOLECULES AND MACROMOLECULES BE FRIENDS?

Small molecules and biologics differ in structure, mechanism, and development challenges. Small molecules excel at intracellular targets, oral bioavailability, and cost-effective production. Biologics (such as antibodies, enzymes, and nucleic acids) offer high specificity, novel mechanisms, and therapeutic potential in previously “undruggable” targets.

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RATIONALE FOR COMBINATION

Enhanced Efficacy: Combining the broad action of small molecules with the specificity of biologics can lead to more effective treatments.

Reduced Resistance: Using both types of agents can help prevent or overcome drug resistance, a common issue in treatments like cancer therapy.

Targeted Delivery: Small molecules can be used to enhance the delivery and uptake of biologics into specific cells or tissues.

Case Study:

Cancer Therapy: Combining a small molecule kinase inhibitor with a monoclonal antibody targeting a specific cancer cell receptor. This approach can inhibit cancer cell growth and enhance immune system recognition and destruction of cancer cells.

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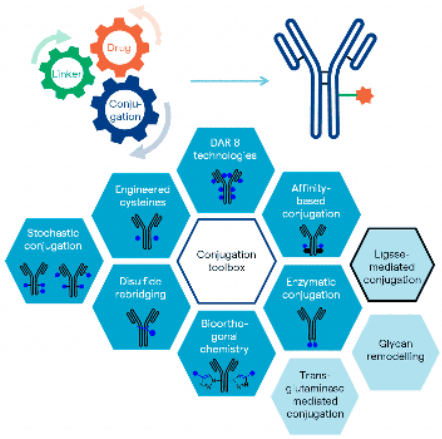
EXAMPLE OF COMBINATION

Mechanism of Action

•**Small Molecules**: Inhibitors of intracellular signaling pathways (e.g., kinase inhibitors or proteasome inhibitors). These molecules can easily enter cells and interfere with cancer-promoting processes, such as proliferation and survival signaling pathways.

•**Biologics**: Monoclonal antibodies or antibody-drug conjugates (ADCs) designed to specifically target cancer cell surface markers, such as HER2, PD-L1, or CD20. These biologics can either block receptor signaling (antagonists) or mark cancer cells for destruction via immune-mediated mechanisms (e.g., antibody-dependent cellular cytotoxicity).



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COMBINATION STRATEGY

•**Targeted Delivery**: The biologic component can be an antibody that specifically binds to cancer cell surface receptors, delivering the attached small molecule directly to the tumor site. For example, an antibody-drug conjugate (ADC) can carry a cytotoxic small molecule payload that is released into the cancer cell upon internalization.

•**Synergistic Action**: The small molecule could inhibit an intracellular pathway, such as a kinase (e.g., EGFR or BRAF), while the biologic blocks extracellular signaling. This can reduce redundancy in cancer cell survival mechanisms and lead to better therapeutic outcomes.

•**Modulating Immune Response**: Biologics such as immune checkpoint inhibitors (e.g., anti-PD-1 or anti-CTLA-4) can be combined with small molecule inhibitors of immunosuppressive pathways (e.g., IDO or A2A receptor inhibitors) to enhance anti-tumor immune responses.

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CHALLENGES AND CONSIDERATIONS

Drug Delivery: Ensuring the correct dosing and co-localization of the small molecule and biologic can be challenging. When conjugation is not possible, nanoparticle or liposome-based drug delivery systems may be employed to co-deliver both components.

Pharmacokinetics and Toxicity: The pharmacokinetic profiles of small molecules and biologics differ greatly, which may complicate dosing schedules and require careful monitoring of toxicity and side effects.

Cost and Complexity: The production and development of biologics are generally more complex and expensive compared to small molecules, which could impact the overall cost of combination therapies.

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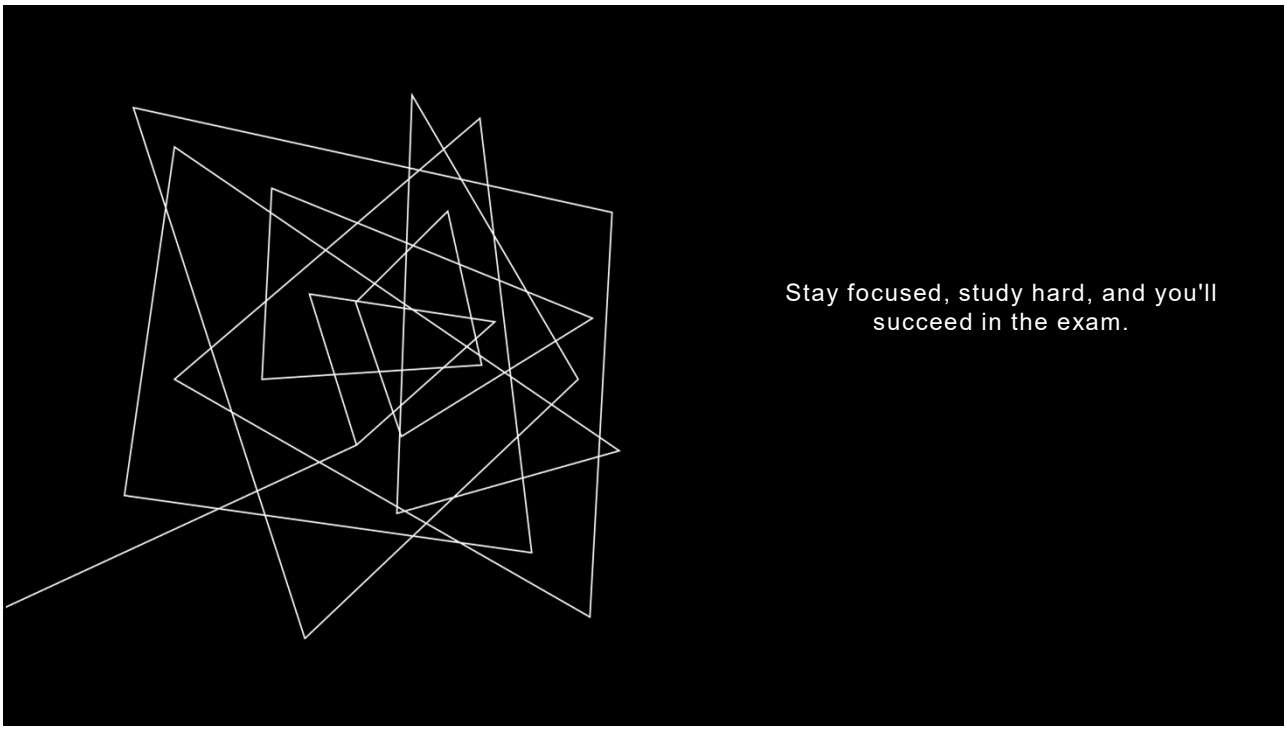

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