Intro to Drug Development

Oct. 22, 2024

Definitions: What is a drug?

Slide courtesy of Prof. Jacquin NIles

- A substance recognized by an official pharmacopoeia or formulary.
- A substance *intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease*.
- A substance (*other than food*) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine, but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical *versus* biological).

FDA Website:
https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#:~:text=or%20an%20injectable.-,Drug,any%20function%20of%20the%20body.

How were drugs previously discovered?

Slide courtesy of Prof. Jacquin NIles

- Extracts from natural products (usually plants)

Poppy
ca. 1500 BC
“pain relief; sedation”

Opiates

Willow tree extract
ca. 3000-1500 BC
“pain reliever”

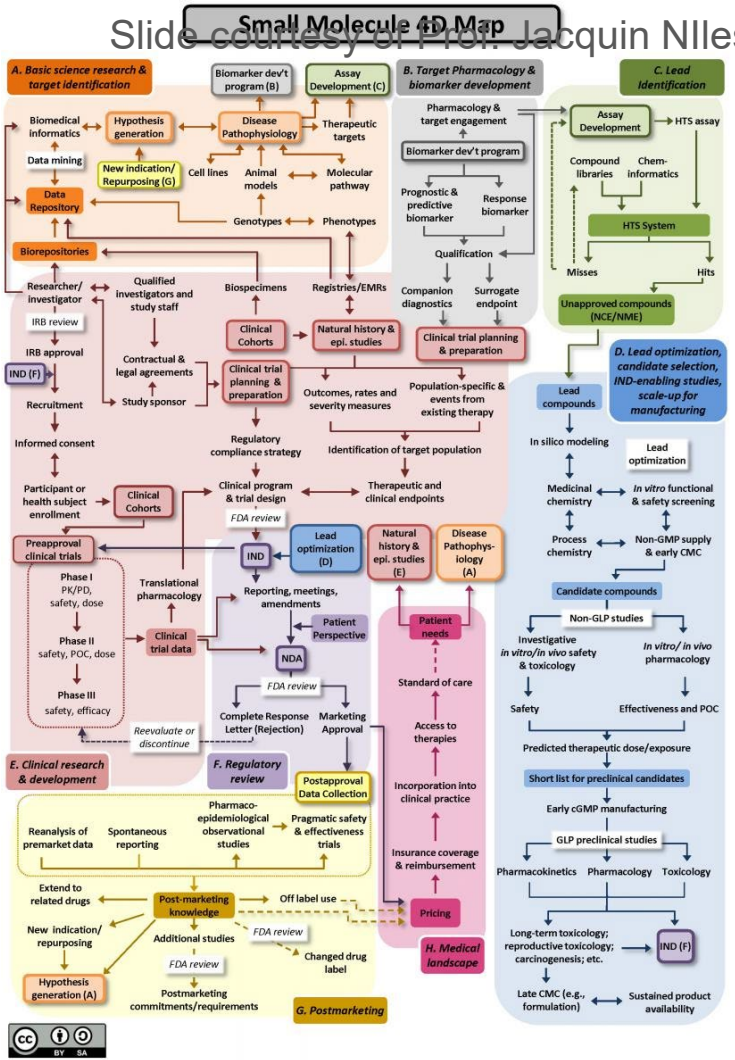
Aspirin

Artemisia annua
L.
ca. 168 BC
“fever”

Artemisinin

Modern framework for drug discovery and development

A. Basic science research and target identification
B. Target pharmacology and biomarker development
C. Lead identification
D. Lead optimization and candidate selection
   - Improving pharmacologic, metabolic, safety profiles of lead toward use in humans
E. Clinical research & development
   - Clinical trials to establish efficacy and safety
F. Regulatory review (FDA approval)
G. Post-marketing
   - Surveillance (adverse effects)
   - Repurposing
   - Off-label use
H. Medical landscape



Slide courtesy of Prof. Jacquin NIles

References:
1) Wagner et al; Nature Reviews Drug Discovery; 2018;
2) https://ncats.nih.gov/translation/maps
3) 4D Map (interactive): https://4dmap.ncats.nih.gov/#/

Modern framework for drug discovery and development

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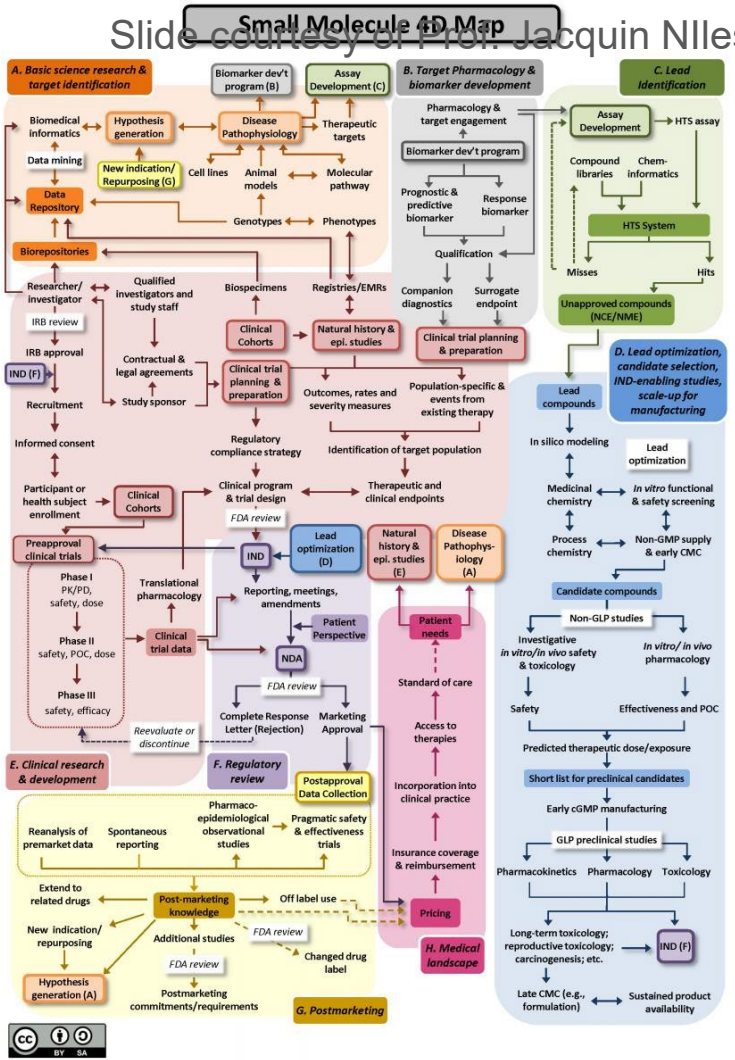

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Contrasting old with modern framework for drug discovery and development

- Intentional and broad search for therapeutic agents
- Engages fundamental understanding of disease biology and mechanism
- Highly multidisciplinary
  - biologists, chemists, engineers, bioinformatics, clinicians, business, legal, …
- High burden-of-proof to establish safety and efficacy

- Business model:
  - Incentivized process (profits) for innovating therapeutic solutions to diverse diseases impacting health
  - Potential skewing of disease areas preferentially prioritized for investment in drug discovery activities

Slide courtesy of Prof. Jacquin NIles

Types of drugs

- **Key Categories:**
  - Small Molecule Drugs
  - Biologics
  - Live Biotherapeutic Agents
  - Cell Therapies
- Each type has unique characteristics, manufacturing processes, and regulatory pathways.

Small molecule drugs

- **Definition:** Low molecular weight compounds, typically less than 900 Daltons.
- **Characteristics:**
  - Easily synthesized through chemical processes.
  - Typically administered orally, but can also be given intravenously or via other routes.
  - Often designed to interact with specific molecular targets (e.g., enzymes, receptors).
  - Capable of diffusing across cell membranes.
- **Examples:** Aspirin (pain relief), Metformin (diabetes), Statins (cholesterol control).
- **Advantages:** Oral bioavailability. Generally easier and cheaper to manufacture. Can be stored and distributed more easily.
- **Disadvantages:** May cause off-target effects and toxicity. Often subject to drug resistance (e.g., antibiotics).

Biologics

- **Definition:** Large, complex molecules derived from living cells, typically proteins or antibodies.
- **Characteristics:**
  - Produced through biological processes (e.g., fermentation, cell culture).
  - Large molecular weight (e.g., monoclonal antibodies, enzymes).
  - Typically administered via injection or infusion (due to poor oral bioavailability).
  - Highly specific to biological targets (e.g., receptors, signaling molecules).
- **Examples:** Monoclonal antibodies (e.g., Herceptin for breast cancer), insulin (diabetes), vaccines.
- **Advantages:** Highly specific and targeted action. Reduced risk of off-target effects compared to small molecules. Effective for conditions that small molecules cannot target (e.g., autoimmune diseases, cancers).
- **Disadvantages:** Expensive to manufacture and administer. Complex production requiring strict regulation. Immunogenicity concerns (risk of immune reactions).

Live Biotherapeutics Agents (LBAs)

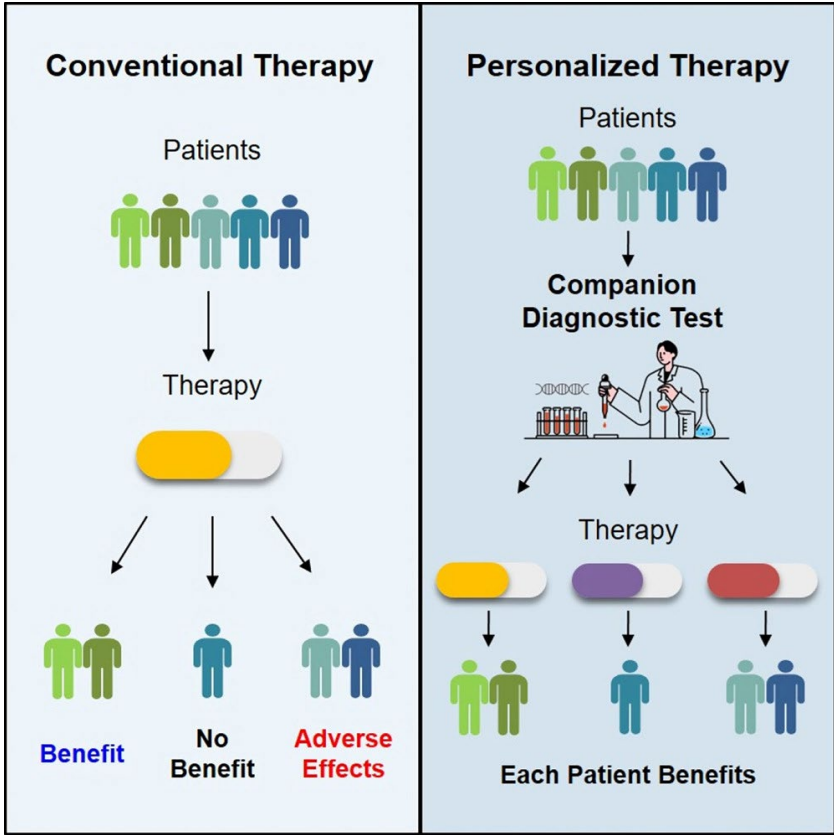
- **Definition:** Medicinal products containing live organisms, such as bacteria, that are used to prevent, treat, or cure diseases.
- **Characteristics:**
  - Typically consist of commensal or engineered microorganisms (e.g., probiotics).
  - Mechanism of action is based on restoring or modifying the gut microbiome, producing beneficial metabolites, or directly interacting with the host immune system.
  - Administered orally, sometimes topically or via other routes.
- **Examples:** Probiotics (e.g., Lactobacillus, Bifidobacterium) for gut health. Fecal Microbiota Transplantation (FMT) for recurrent C. difficile infections. Emerging microbial therapies for inflammatory bowel disease (IBD) and metabolic disorders.
- **Advantages:** Natural component of the human microbiome → low toxicity. Potential for long-lasting effects through colonization or modulation of the microbiome.
- **Disadvantages:** Complex to regulate and standardize. Potential for unforeseen interactions with the host immune system or microbiome. Challenges in scaling production and ensuring product consistency.

Cell Therapies

- **Definition:** Treatments where live cells are introduced into a patient to treat or cure diseases.
- **Characteristics:**
  - Cells are used as therapeutic agents to repair or replace damaged tissues, modulate the immune system, or directly attack cancer cells.
  - Cells can be autologous (from the patient) or allogeneic (from a donor).
  - Commonly administered intravenously, via tissue injection, or through surgical implantation.
- **Types of Cell Therapies:**
  - Stem cell therapy: Using pluripotent or multipotent stem cells for tissue regeneration (e.g., bone marrow transplants, mesenchymal stem cells).
  - CAR-T cell therapy: Genetically engineered T cells designed to recognize and destroy cancer cells.
- **Examples:** CAR-T therapy (e.g., Kymriah, Yescarta) for certain blood cancers. Bone marrow transplants for leukemia and other blood disorders. Stem cell therapies for tissue repair (e.g., heart disease, spinal cord injuries).
- **Advantages:** Potential for personalized, regenerative therapies. Long-lasting therapeutic effects (e.g., immune system modification, tissue regeneration). High specificity for diseased cells (e.g., CAR-T targeting cancer cells).
- **Disadvantages:** Expensive and complex manufacturing. Immune rejection or adverse immune responses (e.g., graft-vs-host disease). Difficult logistics (e.g., transportation, storage, and handling of living cells).

Companion Diagnostics

- **Definition:** Tests that provide essential information for the safe and effective use of a specific drug.
- Purpose:
  - Enables personalized medicine by identifying patients most likely to benefit from or be harmed by a treatment.
  - Guides therapy decisions based on genetic, protein, or biomarker profiles.
- Examples:
  - HER2 testing for breast cancer (Herceptin).
  - EGFR mutation testing for lung cancer (gefitinib).
  - PD-L1 expression for immunotherapy (Keytruda).
- Advantages:
  - Optimizes efficacy: Targets the right patients for the right drug.
  - Reduces toxicity: Minimizes exposure to ineffective treatments.
  - Cost-effective: Prevents unnecessary treatments and improves outcomes.
- Challenges:
  - Development complexity: Co-development with drugs is required.
  - Regulatory approval: Must be approved alongside the drug (FDA).
  - Access: Limited availability and high cost can restrict use.
- Emerging Trends: Multi-gene panels and liquid biopsies for broader and non-invasive testing.



Pharmacokinetics (PK)

- **What the body does to drugs**
- Important for understanding dosage, frequency, and potential side effects.
- Fundamental concepts of dose and response
- Absorption, transporters and toxicity
- Distribution, protein binding and toxicity
- Metabolism, the liver and portal circulation
- Excretion pathways

Overview of ADME

- **ADME:** Key processes in pharmacokinetics
- **Absorption:** How drugs enter the bloodstream
- **Distribution:** How drugs are dispersed throughout the body
- **Metabolism:** How drugs are chemically modified
- **Excretion:** How drugs and metabolites are eliminated

Absorption

- Movement of the drug from the site of administration into the bloodstream
- Affected by:
- Route of administration (oral, intravenous, etc.)
- Drug solubility and formulation
- pH and blood flow at the absorption site
- Influences bioavailability (how much drug reaches systemic circulation)

Distribution

- Dispersion of the drug through the body's tissues and fluids
- Factors influencing distribution:
- Blood flow to tissues and organs
- Drug binding to plasma proteins (e.g., albumin)
- Ability to cross biological barriers (e.g., blood-brain barrier)
- Volume of distribution (Vd): A measure of how extensively a drug spreads in the body

Blood Brain Barrier

- Definition: The Blood-Brain Barrier (BBB) is a highly selective, semipermeable barrier that separates the circulating blood from the brain's extracellular fluid, protecting the brain from harmful substances while allowing essential nutrients to pass through.
- Structure:
  - Composed of endothelial cells tightly joined by tight junctions, along with support from:
    - Astrocytes: Provide structural support and influence permeability.
    - Pericytes: Regulate blood flow and maintain barrier integrity.
- Function:
  - Protects the brain from toxins, pathogens, and fluctuations in blood composition.
  - Allows selective passage of necessary molecules such as:
    - Nutrients (e.g., glucose, amino acids) via specialized transport systems.
    - Lipid-soluble molecules (e.g., oxygen, carbon dioxide) through passive diffusion.
- Challenges for Drug Delivery:
  - The BBB restricts the entry of large molecules and hydrophilic drugs, making drug delivery to the brain difficult.
- Strategies to overcome the BBB include:
  - Lipophilic drug design.
  - Nanoparticles for targeted delivery.
  - Intranasal administration to bypass the BBB.

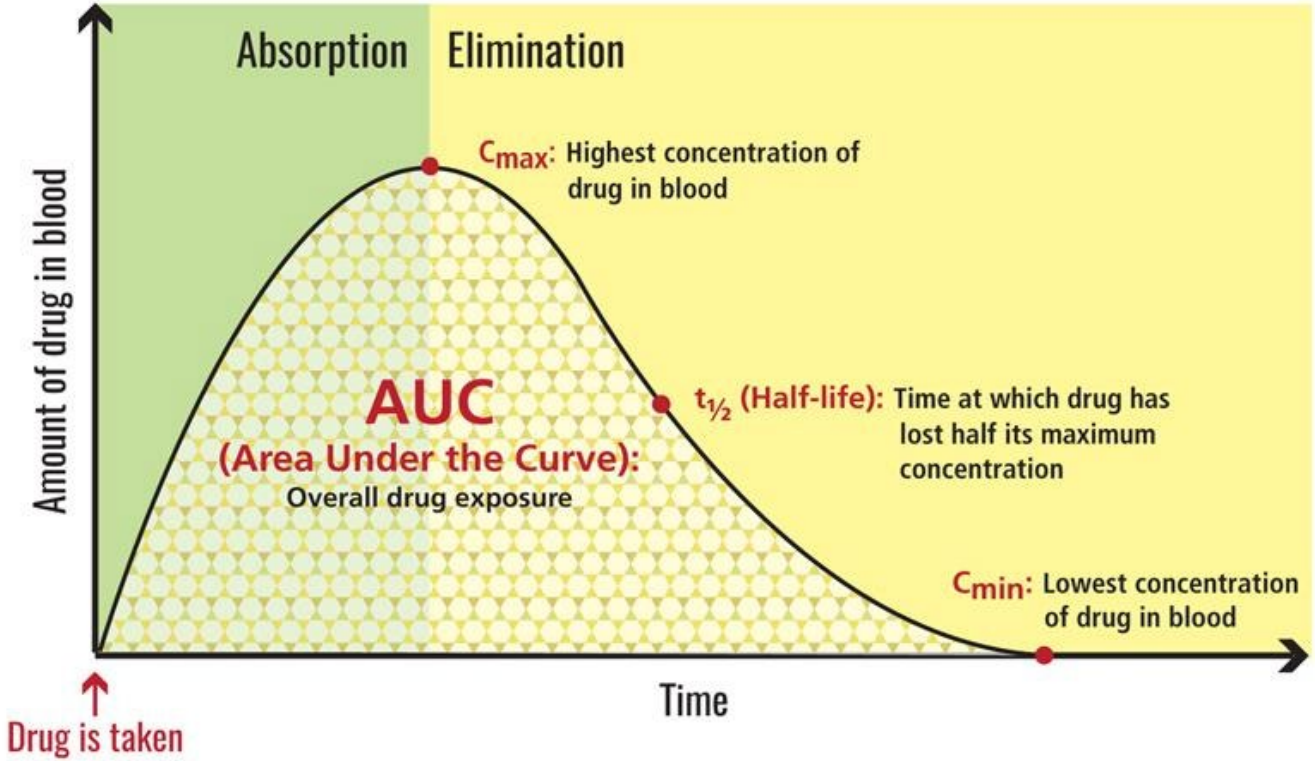
Metabolism

- Chemical transformation of the drug, mainly in the liver
- Two phases of metabolism:
  - Phase I: Modification (e.g., oxidation, reduction, hydrolysis) by enzymes (e.g., cytochrome P450)
  - Phase II: Conjugation (e.g., glucuronidation) to make drugs more water-soluble
- Produces active or inactive metabolites
- Metabolites can be toxic (e.g., acetaminophen)

Excretion

- Elimination of drugs and their metabolites from the body
- Primarily through kidneys (urine) or liver (bile/feces)
- Other routes:
  - lungs
  - sweat
  - breast milk
- Key factors:
  - Renal function (glomerular filtration, secretion, reabsorption)
  - Hepatic function (bile excretion)
  - Half-life: Time required for the drug concentration to reduce by 50%

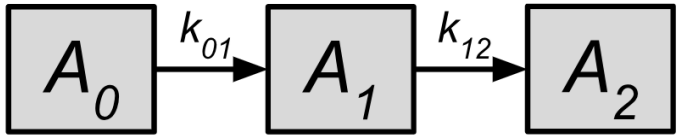
Pharmacokinetics



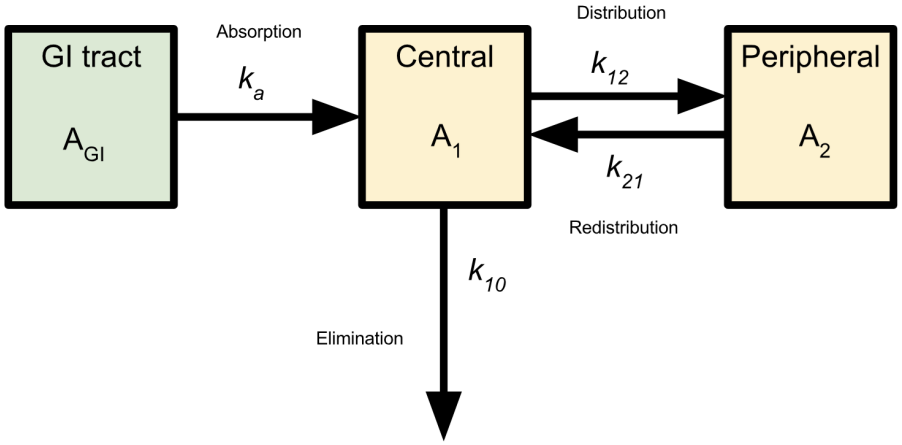
hivinfo.nih.gov
https://docs.google.com/presentation/d/1visAn0sDo_NvTYlRmooZ_d9JLqlnNS4D/edit#slide=id.g2d48e9b40e0_0_136

Modeling pharmacokinetics

One compartment model



Two compartment model



http://www.turkupetcentre.net/petanalysis

ADME and toxicity

- Poor absorption: Low therapeutic effect
- Extensive distribution: Drug accumulation in tissues (e.g., fat, liver)
- Metabolism: Production of toxic metabolites (e.g., liver toxicity)
- Incomplete excretion: Drug accumulation leading to toxicity, especially in patients with renal or hepatic impairment

Pharmacodynamics (PD)

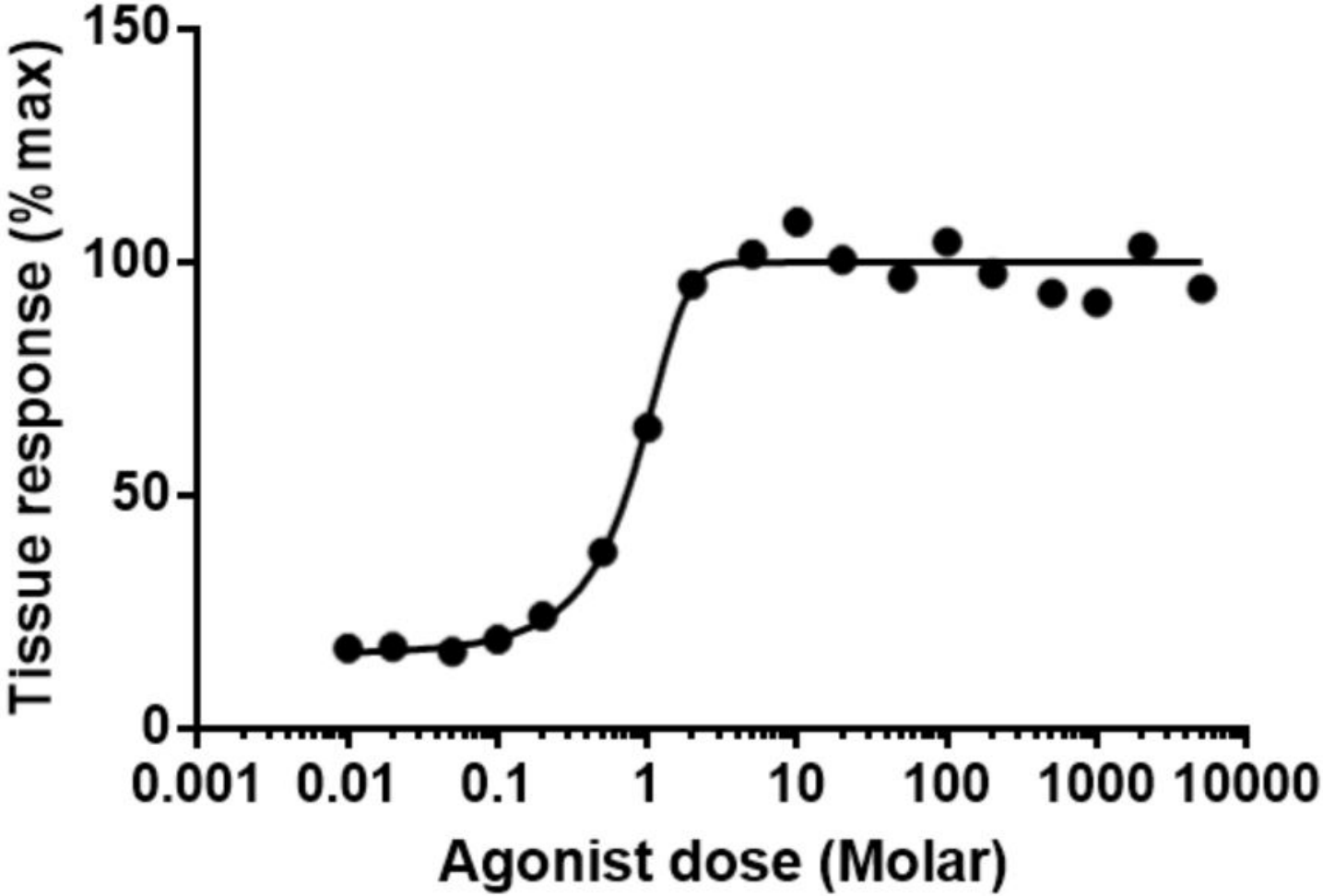
- **What drugs do to the body**
- Drug-receptor interactions
- Dose-response relationships
- Mechanism of action (MOA)
- Therapeutic and toxic effects

Drug-Receptor interactions

- **Receptors:** Proteins that drugs bind to initiate their effects
- **Types:** G-protein-coupled receptors, ion channels, enzymes, nuclear receptors
- **Agonists:** Drugs that activate receptors to produce a response
- **Antagonists:** Drugs that block receptor activation (no response)
- **Partial Agonists:** Activate receptors but with less efficacy than full agonists
- **Affinity:** Strength of the drug-receptor interaction

Dose-Response relationship

- **Dose-Response Curve:** Relationship between drug dose and the magnitude of effect
- **EC50:** Dose that produces 50% of the maximum effect (measure of potency)
- **Emax:** Maximum effect a drug can produce, regardless of dose
- **Potency:** Amount of drug needed to produce a specific effect
- **Efficacy:** Maximum effect a drug can achieve
- **Therapeutic Window:** Range of doses that produce a therapeutic effect without causing toxicity



https://en.wikipedia.org/wiki/Dose%E2%80%93response_relationship

Mechanism of Action (MOA)

- **MOA:** How a drug produces its effects at the molecular level
- **Example:** Beta-blockers reduce heart rate by blocking β-adrenergic receptors
- **Specificity:** How selectively a drug interacts with its target (higher specificity = fewer side effects)
- **Therapeutic effects:** Desired clinical outcomes (e.g., pain relief, lowered blood pressure)
- **Adverse effects:** Unintended, often harmful effects (e.g., nausea, liver toxicity)

Signal transduction and drug action

- Drugs often act through signal transduction pathways:
- Second messengers (e.g., cAMP, calcium ions) amplify the drug's signal inside the cell
- Signal transduction can lead to:
  - Gene expression changes (e.g., steroids)
  - Enzyme activation/inhibition
  - Cellular responses (e.g., contraction, secretion)

Pharmacodynamic tolerance and sensitization

- **Tolerance:** Reduced response to a drug after prolonged use, requiring higher doses
- **Desensitization:** Reduced receptor sensitivity due to repeated exposure
- **Downregulation:** Decreased number of receptors
- **Sensitization:** Increased response to a drug after repeated use
- **Example:** Sensitization to certain stimulants

Toxicology

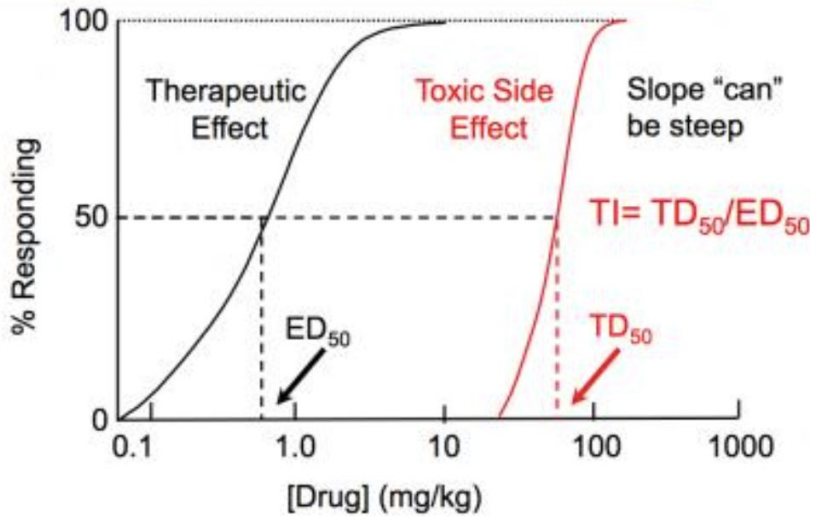
- **Goal:** Identify potential toxicity, side effects, and the safe dose range.
- **Types of Toxicology Studies:**
  - **Acute toxicity:** Single-dose studies to assess immediate toxic effects.
  - **Sub-chronic and chronic toxicity:** Repeated-dose studies to evaluate longer-term effects.
  - **Genotoxicity:** Assess potential for DNA damage (mutagenicity).
  - **Carcinogenicity:** Determine the likelihood that the drug might cause cancer.
  - **Reproductive toxicity:** Assess risks to reproductive health and offspring development.
- **Outcome:** Establishment of the no observed adverse effect level (NOAEL) and maximum tolerated dose (MTD).

Safety pharmacology

- **Goal:** Investigate potential adverse effects on vital organ systems.
- **Core Areas:**
  - **Cardiovascular system:** Effects on heart rate, blood pressure, and ECG (QT interval).
  - **Central nervous system (CNS):** Impact on behavior, motor coordination, and neurological functions.
  - **Respiratory system:** Effects on breathing rate and function.
- **Methods:** Use of animal models to assess effects on these vital systems.

Therapeutic Index (TI)

- Therapeutic Index: Measure of drug safety
- TI = TD50 / ED50
- TD50: Dose that causes toxicity in 50% of the population
- ED50: Dose that produces a therapeutic effect in 50% of the population
- Wide TI: Safer drugs (large margin between therapeutic and toxic dose)
- Narrow TI: Risky drugs (small margin between effective and toxic dose)



PD and drug interactions

Synergism: Two drugs produce a combined effect greater than the sum of individual effects

Example: Alcohol and sedatives

Antagonism: One drug reduces or blocks the effect of another

Example: Naloxone blocking opioid receptors

Additive effects: Combined effect is the sum of individual effects

Example: Two antihypertensive drugs lowering blood pressure

Key steps in drug discovery process

- **Target Identification:** Finding a biological target (e.g., protein, gene) associated with a disease
- **Target Validation:** Confirming the target's role in the disease process
- **Hit Identification:** Screening compounds that interact with the target
- **Hit-to-Lead (H2L):** Optimizing hits to generate high-quality lead compounds
- **Lead Identification:** Selecting promising compounds (hits) with drug-like properties
- **Lead Optimization:** Refining the leads to improve efficacy, safety, and pharmacokinetics

Target identification

- **Goal:** Identify a molecular target involved in the disease
- **Types of targets:** Proteins (e.g., enzymes, receptors), Genes/DNA/RNA
- **Approaches:** Genomics and proteomics studies, Disease pathway analysis, High-throughput screening (HTS), Bioinformatics and AI tools
- **Key Considerations:**
  - Relevance to disease
  - Druggability (can the target interact with small molecules or biologics?)
  - Availability of structural information

Druggability

- **Definition:** Druggability refers to the likelihood that a target (protein, enzyme, receptor, etc.) can be modulated by a small molecule or biologic to produce a therapeutic effect.
- **Undruggable Targets:** Some targets, like intrinsically disordered proteins or protein-protein interaction interfaces, lack traditional binding pockets, making them hard to target with small molecules.
- **Alternative Approaches:** For challenging targets, biologics (e.g., monoclonal antibodies) or gene-based therapies (e.g., CRISPR) may be explored.
- **Assessing druggability:**
    - Computational modeling
    - experiment

Factors influencing druggability

- **Binding Sites:** Presence of well-defined and accessible binding pockets or active sites. Preferably a hydrophobic pocket for small molecules.
- **Target Class:** Common druggable classes: GPCRs, kinases, ion channels, nuclear receptors.
- **Challenging classes:** Protein-protein interactions (PPIs), transcription factors (due to lack of defined binding pockets).
- **Biological Role:** The target should be central to disease pathology without critical off-target effects. Oncogenes, enzymes in metabolic pathways, and immune modulators are often druggable.
- **Target Expression:** Selective expression in diseased tissues increases druggability. Minimal expression in healthy tissues reduces the risk of side effects.
- **Structural Information:** Availability of 3D structural data from X-ray crystallography or cryo-EM aids in identifying potential binding sites and designing drugs.

Target validation

- **Goal:** Confirm the role of the target in the disease and its potential for drug development
- **Methods:**
  - Genetic knockdown/knockout (e.g., CRISPR, siRNA)
  - Overexpression studies
  - Animal models of disease
  - Biomarker identification
- **Importance:** Ensures that targeting the chosen molecule will have a therapeutic effect and minimizes the risk of failure in later stages

Hit identification

- **Goal:** Identify compounds (hits) that interact with the target and produce a desired biological effect
- **Methods:**
  - **High-throughput screening (HTS):** Test large libraries of compounds for activity against the target
  - **Fragment-based screening:** Using small chemical fragments to identify starting points for lead development
  - **Virtual screening:** Computational methods to predict potential hits
- **Natural products:** Screening compounds from natural sources (e.g., plants, microorganisms)
- **Criteria for hits:**
  - Sufficient binding affinity to the target
  - Evidence of biological activity

Hit to Lead (H2L)

- **Goal:** Convert hits into lead compounds with improved drug-like properties
- **Activities:**
  - **Hit validation:** Retesting hits to confirm activity
  - **Structure-activity relationship (SAR) studies:** Modifying chemical structures to understand how changes affect activity
  - **Early ADME (Absorption, Distribution, Metabolism, Excretion) screening:** Assessing pharmacokinetics and toxicity
  - **Optimization of potency:** Enhancing the ability to produce a therapeutic effect
- **Key metrics:**
  - Potency (IC50, EC50)
  - Selectivity for the target
  - Early safety profiles

Lead identification

- **Goal:** Select the most promising compounds (leads) from the pool of hits
- **Criteria for a lead compound:**
  - High affinity for the target
  - Selectivity (minimal off-target effects)
  - Drug-like properties (Lipinski's Rule of Five)
  - Preliminary in vivo efficacy (tested in animal models)
  - Acceptable ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profile
- **Methods:**
  - Iterative testing and optimization of chemical properties
  - Further refinement of Structure-Activity Relationships (SAR)
  - Initial toxicity screening

Lead optimization

- **Goal:** Refine lead compounds to enhance their efficacy, safety, and pharmacokinetics
- **Focus areas:**
  - **Potency:** Increasing target affinity and reducing the required dose
  - **Selectivity:** Minimizing interaction with unintended targets
  - **Pharmacokinetics:** Improving bioavailability, half-life, and distribution
  - **Safety:** Reducing toxicity and adverse effects
  - **Formulation:** Ensuring the compound can be delivered effectively (oral, IV, etc.)
- **Methods:**
  - SAR studies to optimize chemical structure
  - Preclinical in vivo studies (efficacy, toxicity, pharmacokinetics)
  - Early formulation and drug delivery considerations

Structure-Activity Relationship (SAR)

- **Definition:** SAR refers to the relationship between a drug's chemical structure and its biological activity.
- **Goal:** To understand how modifications to a molecule's structure affect its interaction with a target, efficacy, potency, and selectivity.
- **Importance:** Critical for drug design, optimization, and improving pharmacological properties.

SAR in Drug Discovery

- **Identify key molecular features:** Determine which parts of the molecule are essential for activity.
- **Optimize efficacy:** Modify chemical groups to increase the drug’s activity or potency.
- **Improve selectivity:** Enhance specificity for the target while minimizing off-target effects.
- **Reduce toxicity:** Eliminate or modify structural features that cause adverse effects.
- **Enhance pharmacokinetics:** Improve absorption, distribution, metabolism, and excretion (ADME) properties.

SAR Process

- **Lead Compound Identification:**
  - Start with a lead compound that shows biological activity.
  - Study its interactions with the target.
- **Systematic Modification:**
  - Modify chemical groups on the molecule (e.g., substitutions, chain extensions, ring alterations).
  - Analyze how changes affect activity and selectivity.
- **SAR Data Collection:**
  - Measure biological activity (e.g., IC50, EC50, Ki) after each modification.
  - Identify trends between structure changes and changes in potency or binding affinity.

Typical SAR Strategies

- **Functional group modification:** Changing substituents (e.g., methyl, hydroxyl, halogen) to study their impact on activity.
- **Chain length alteration:** Varying the length of side chains or linkers to optimize target binding.
- **Ring modifications:** Adding or removing rings, changing aromaticity, or introducing heteroatoms.
- **Isosteric replacements:** Substituting atoms or groups with similar electronic or steric properties to retain activity while improving properties (e.g., replacing hydrogen with fluorine).
- **QSAR:** computational methods used to quantify/predict the relationship between a chemical compound's structural properties and its biological activity.
- **Example:** Beta-lactam Antibiotics (Penicillin). Modifications to the R group attached to the beta-lactam ring alters spectrum of activity and resistance to beta-lactamases.

SAR Challenges

- **Complexity of biological systems:** Modifications may have unintended effects on off-target proteins or pathways.
- **Context-dependent effects:** SAR may vary between in vitro and in vivo environments.
- **Balancing multiple properties:** Achieving the right balance between efficacy, safety, and pharmacokinetics can be challenging.

Preclinical Development

- **Objective:** Evaluate the safety, efficacy, pharmacokinetics, and toxicity of a drug candidate before human testing.
- **Key Focus Areas:**
  - In vitro (lab-based) and in vivo (animal) studies
  - Toxicology and safety profiling
  - Pharmacokinetics (PK) and pharmacodynamics (PD)
  - Manufacturing and formulation optimization
- **Outcome:** Sufficient evidence to support an Investigational New Drug (IND) application for clinical trials.

Preclinical efficacy studies

- **Goal:** Demonstrate that the drug produces the desired therapeutic effect.
- **In vitro models:**
  - Use of cell-based assays to study drug-receptor interactions, enzyme inhibition, or cancer cell cytotoxicity.
- **In vivo models:**
  - Animal models of disease (e.g., cancer, autoimmune diseases, cardiovascular conditions).
  - Evaluation of drug effects in animal systems that mimic human disease conditions.
- **Endpoints:**
  - Reduction in disease markers, tumor size, inflammation, etc.
  - Validation of target engagement and pathway modulation.

Pharmacodynamics (PD) studies

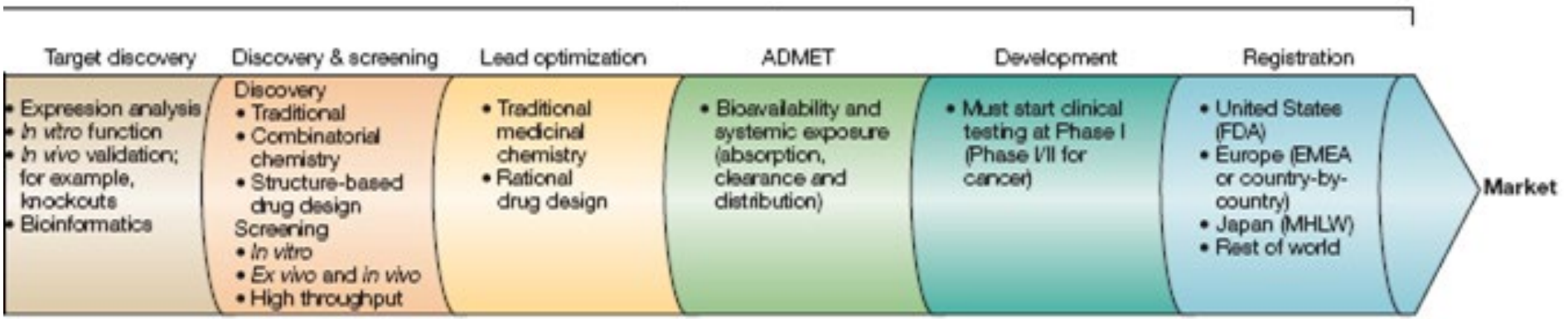
- **Goal:** Investigate the biological effects of the drug and the relationship between drug concentration and effect.
- **Key PD Studies:**
- **Dose-response relationship:** The effect of different doses on therapeutic outcomes.
- **Mechanism of action (MOA):** How the drug interacts with its target.
- **Therapeutic window:** Identifying the optimal dose range that balances efficacy and safety.
- **PD Markers:** Biomarkers or surrogate endpoints (e.g., blood glucose levels for diabetes drugs, tumor shrinkage for cancer).

Timeline for new drug discovery process

Slide courtesy of Prof. Jacquin NIles

De novo drug discovery and development

- ***10-17 year process!***



A	B	C	D	E	F	G
2-3 years	0.5-1 years	1-3 years	1-2 years	5-6 years	1-2 years	Lifetime

Preclinical phase ("discovery")

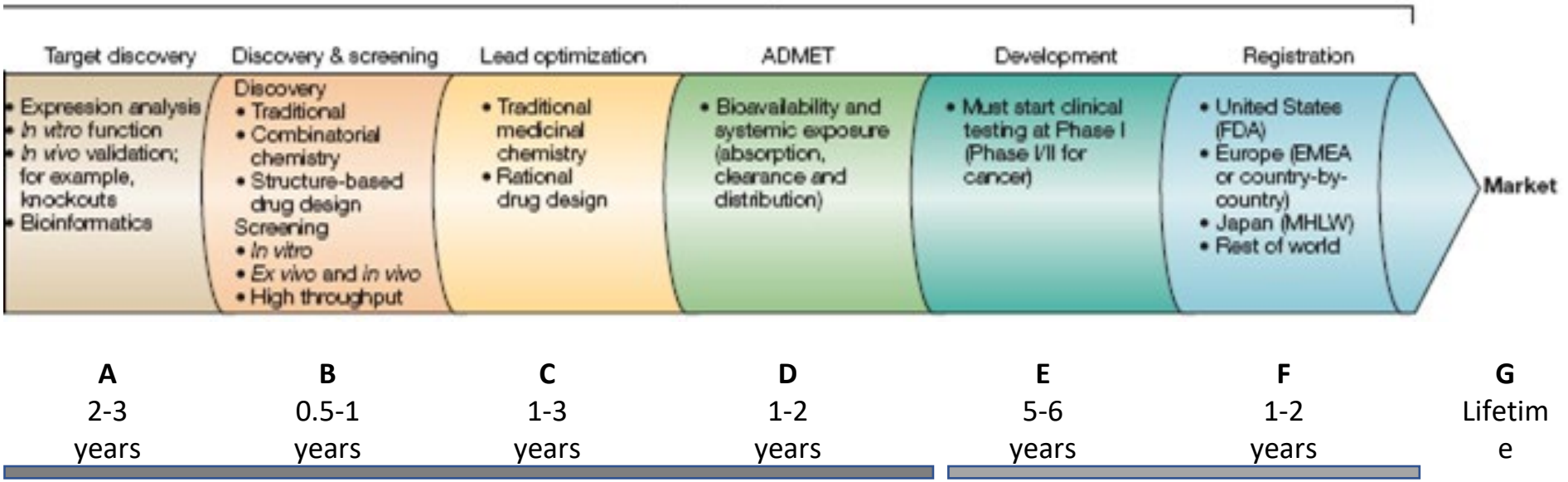
Clinical phase ("testing")

Ashburn, T.T. & Thor, K.B. (2004). Drug Repositioning: Identifying and Developing New Uses for Existing Drugs. *Nature Reviews Drug Discovery*. **3,** 673-683.

Probability of successfully developing a new drug that comes to market

De novo drug discovery and development

- ***10-17 year process!***



Ashburn, T.T. & Thor, K.B. (2004). Drug Repositioning: Identifying and Developing New Uses for Existing Drugs. *Nature Reviews Drug Discovery*. **3,** 673-683.

Preclinical phase attrition/ streamlining

Slide courtesy of Prof. Jacquin NIles

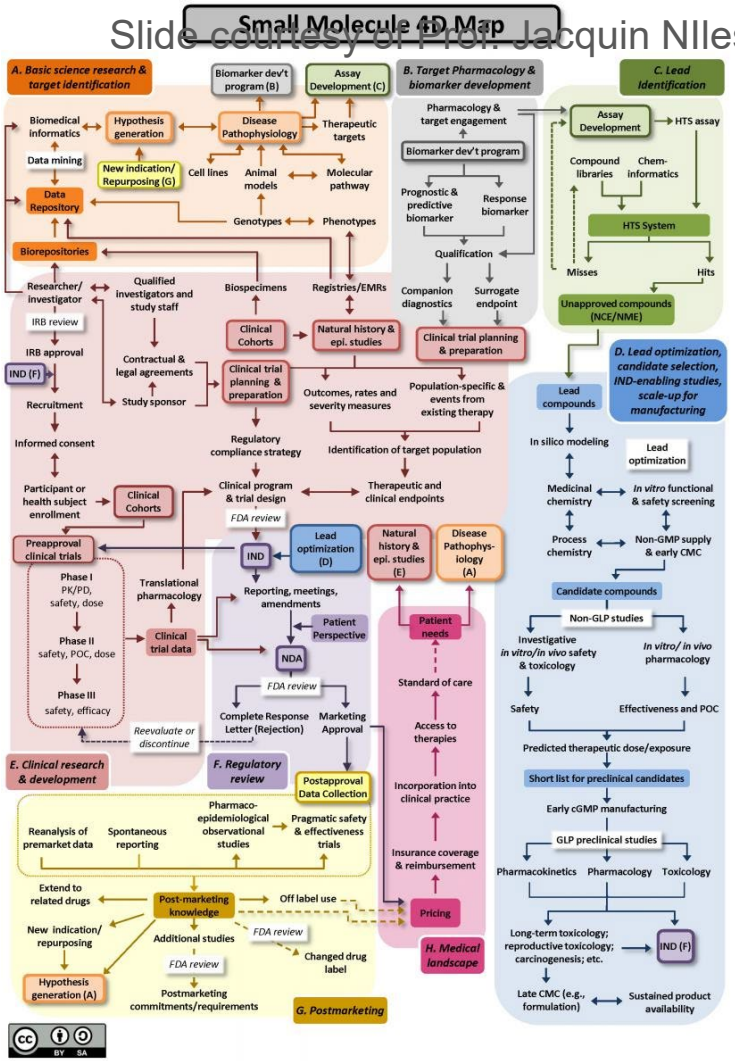
A. Basic science research and target identification
B. Target pharmacology and biomarker development
C. Lead identification
D. Lead optimization and candidate selection
   - Improving pharmacologic, metabolic, safety profiles of lead toward use in humans

E. Clinical research & development
   - Clinical trials to establish efficacy and safety

F. Regulatory review (FDA approval)

G. Post-marketing
   - Surveillance (adverse effects)
   - Repurposing
   - Off-label use

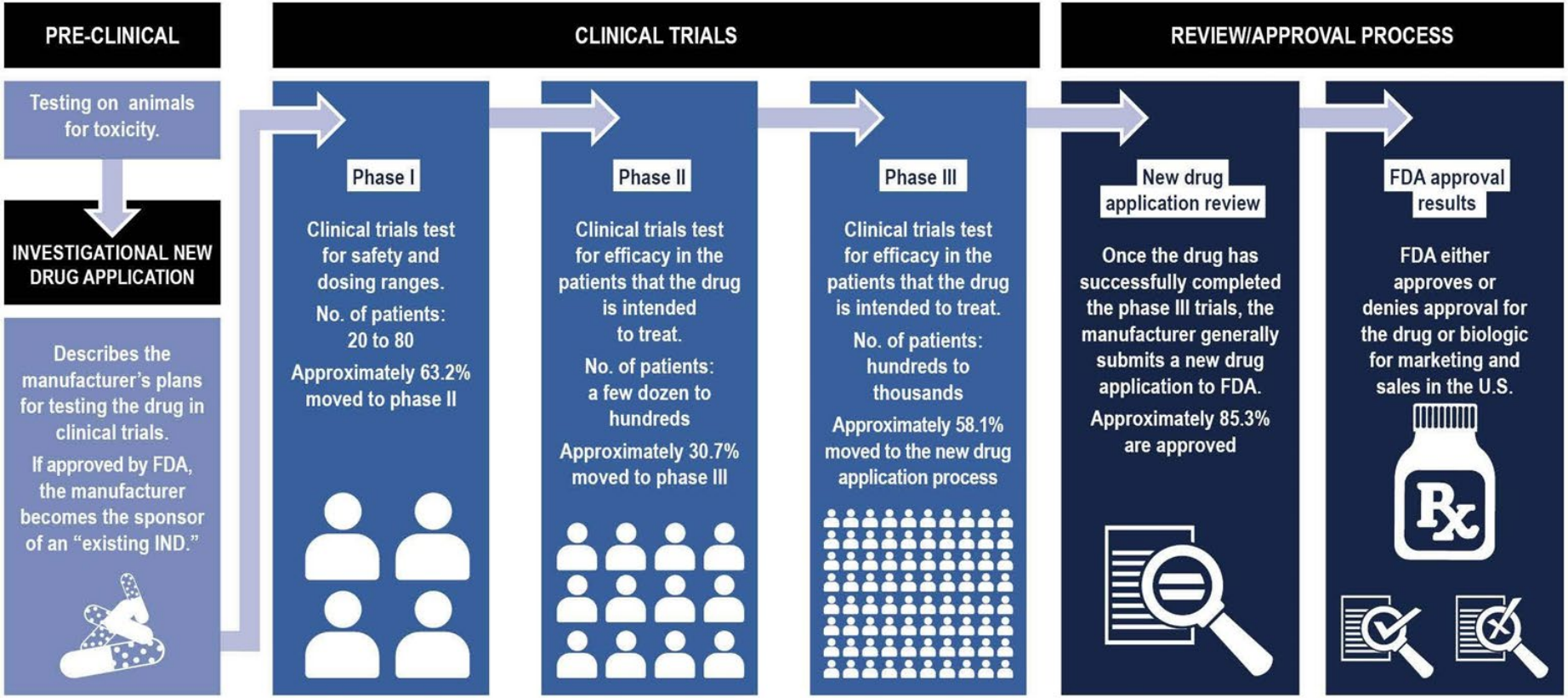
H. Medical landscape



References:

Clinical phase:
Brief overview of clinical research and development

Slide courtesy of Prof. Jacquin NIles



Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion.[a] | GAO-17-564

Attrition along the drug discovery pipeline

Slide courtesy of Prof. Jacquin NIles

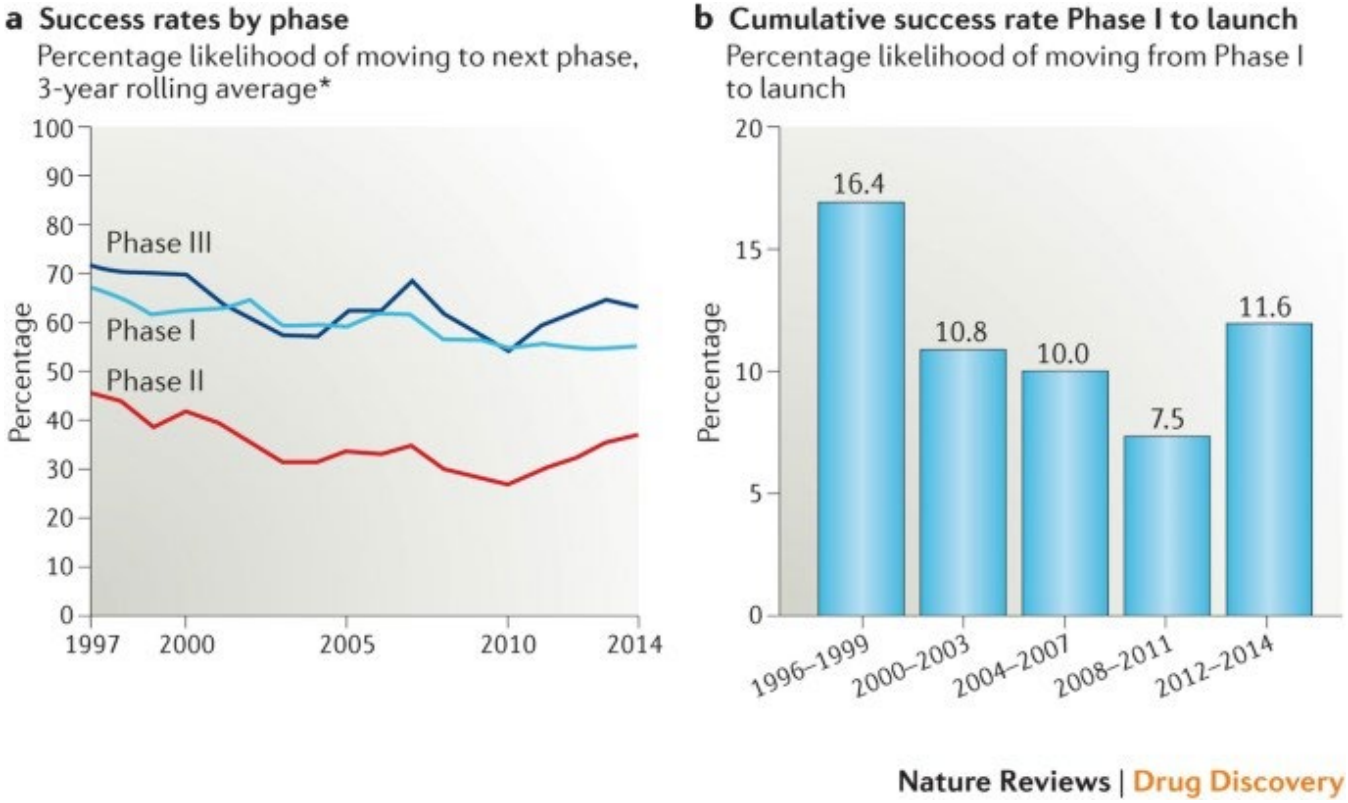
	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic group	Total paths	$POS_{1,2}$, % (SE, %)	Total paths	$POS_{2,3}$, % (SE, %)	$POS_{2,APP}$, % (SE, %)	Total paths	$POS_{3,APP}$, % (SE, %)	POS, % (SE, %)
Oncology	17 368	57.6 (0.4)	6533	32.7 (0.6)	6.7 (0.3)	1236	35.5 (1.4)	3.4 (0.2)
Metabolic/ Endocrinology	3589	76.2 (0.7)	2357	59.7 (1.0)	24.1 (0.9)	1101	51.6 (1.5)	19.6 (0.7)
Cardiovascular	2810	73.3 (0.8)	1858	65.7 (1.1)	32.3 (1.1)	964	62.2 (1.6)	25.5 (0.9)
CNS	4924	73.2 (0.6)	3037	51.9 (0.9)	19.5 (0.7)	1156	51.1 (1.5)	15.0 (0.6)
Autoimmune/ Inflammation	5086	69.8 (0.6)	2910	45.7 (0.9)	21.2 (0.8)	969	63.7 (1.5)	15.1 (0.6)
Genitourinary	757	68.7 (1.7)	475	57.1 (2.3)	29.7 (2.1)	212	66.5 (3.2)	21.6 (1.6)
Infectious disease	3963	70.1 (0.7)	2314	58.3 (1.0)	35.1 (1.0)	1078	75.3 (1.3)	25.2 (0.8)
Ophthalmology	674	87.1 (1.3)	461	60.7 (2.3)	33.6 (2.2)	207	74.9 (3.0)	32.6 (2.2)
Vaccines (Infectious Disease)	1869	76.8 (1.0)	1235	58.2 (1.4)	42.1 (1.4)	609	85.4 (1.4)	33.4 (1.2)
Overall	41 040	66.4 (0.2)	21 180	48.6 (0.3)	21.0 (0.3)	7532	59.0 (0.6)	13.8 (0.2)
All without oncology	23 672	73.0 (0.3)	14 647	55.7 (0.4)	27.3 (0.4)	6296	63.6 (0.6)	20.9 (0.3)

- 185,994 unique trials of over 21,143 compounds from Jan 2000 through Oct 2015
  - 13.8% of drug programs make it from Phase I to approval
    - 20.9% if cancer excluded
  - (Higher than the often-touted estimates of 5% or 10%)
- Probability of success varies by disease area
  - **Why might this be**?

Reference Wong et al; Biostatistics, Volume 20, Issue 2, April 2019, 273–286
https://academic.oup.com/biostatistics/article/20/2/273/48175243

Attrition along the drug discovery pipeline

Slide courtesy of Prof. Jacquin NIles

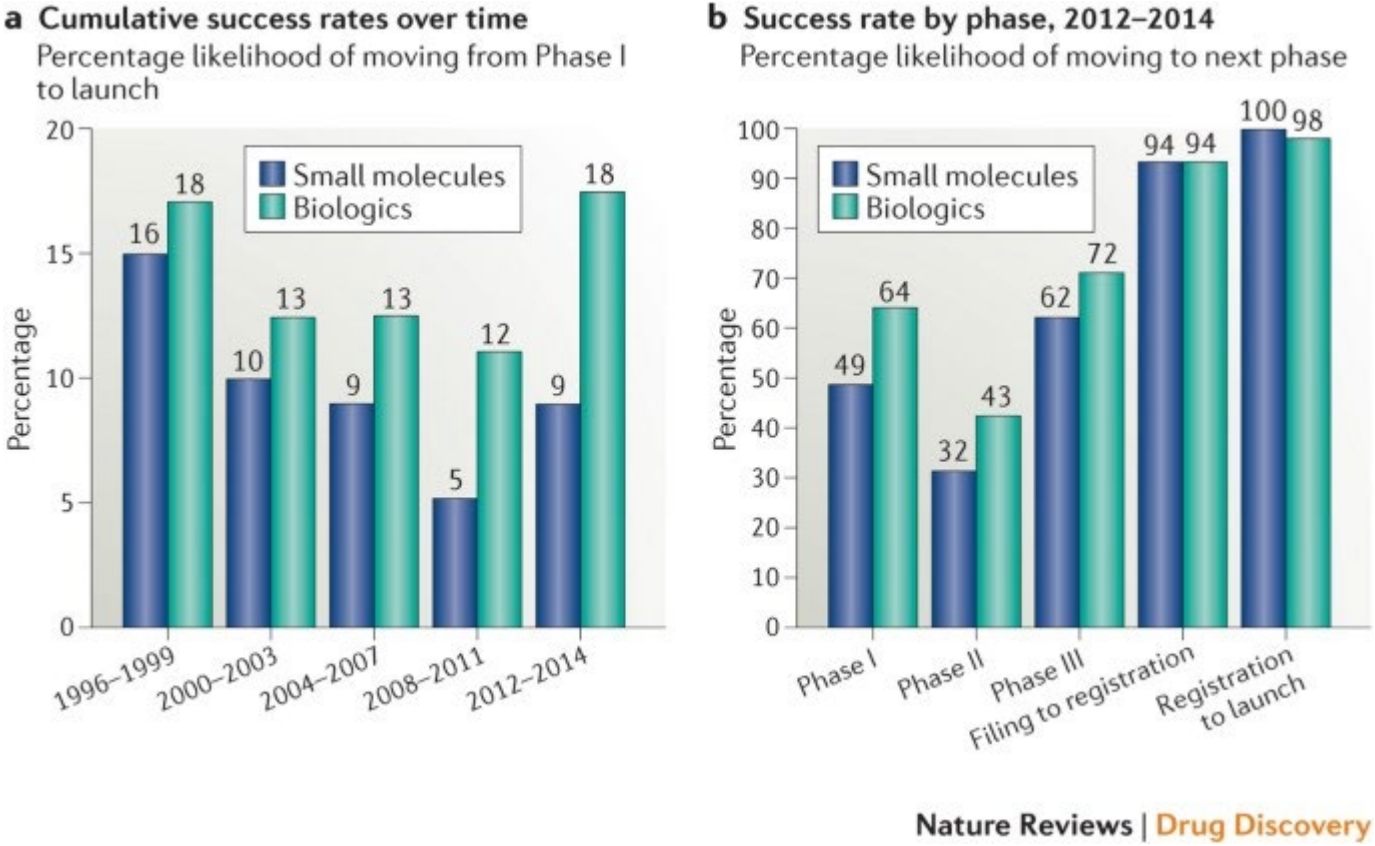


- Phase II success rates lowest
  - Why might this be so?
- Overall success rates steadily declining 1996-2011, but improved since 2012

Reference Katarzyna Smietana et al; Nature Reviews Drug Discovery volume 15, pages379–380(2016)

Attrition along the drug discovery pipeline

Slide courtesy of Prof. Jacquin NIles



- **Biologics are being approved at rates that rival those for small molecules**
- **Questions**
- What could be some reasons for this?
- Should we switch emphasis to biologics instead of small molecules?

Reference Katarzyna Smietana et al; Nature Reviews Drug Discovery volume 15, pages379–380(2016)

Regulation of drug approval in the U.S.

A. Basic science research and target identification
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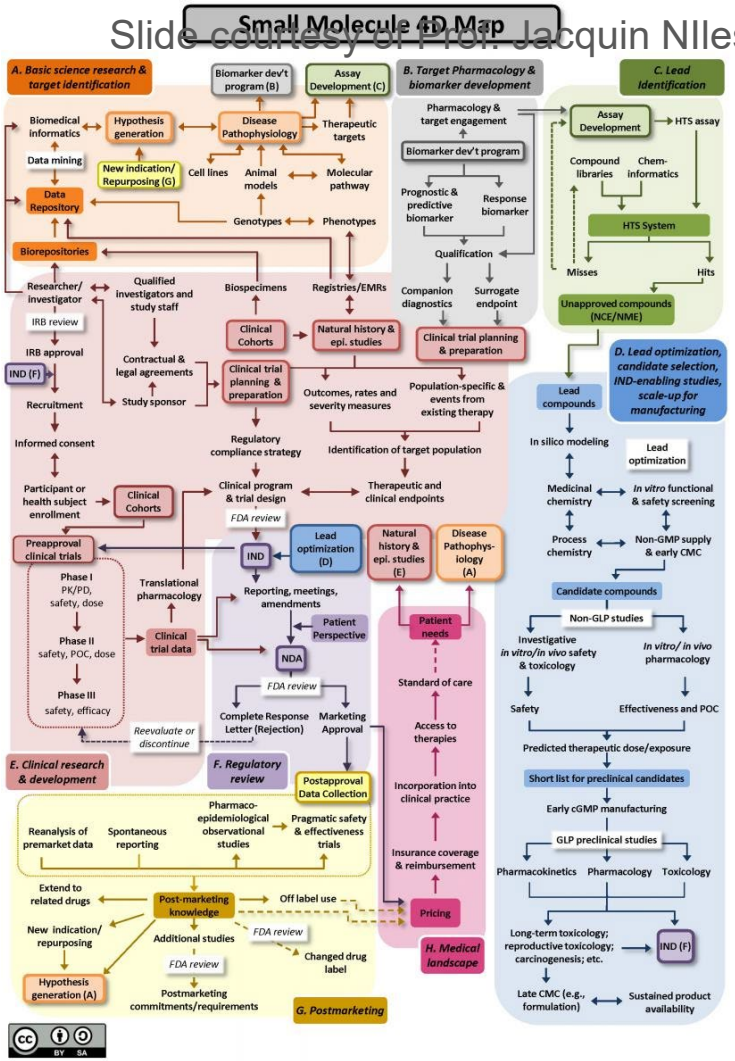
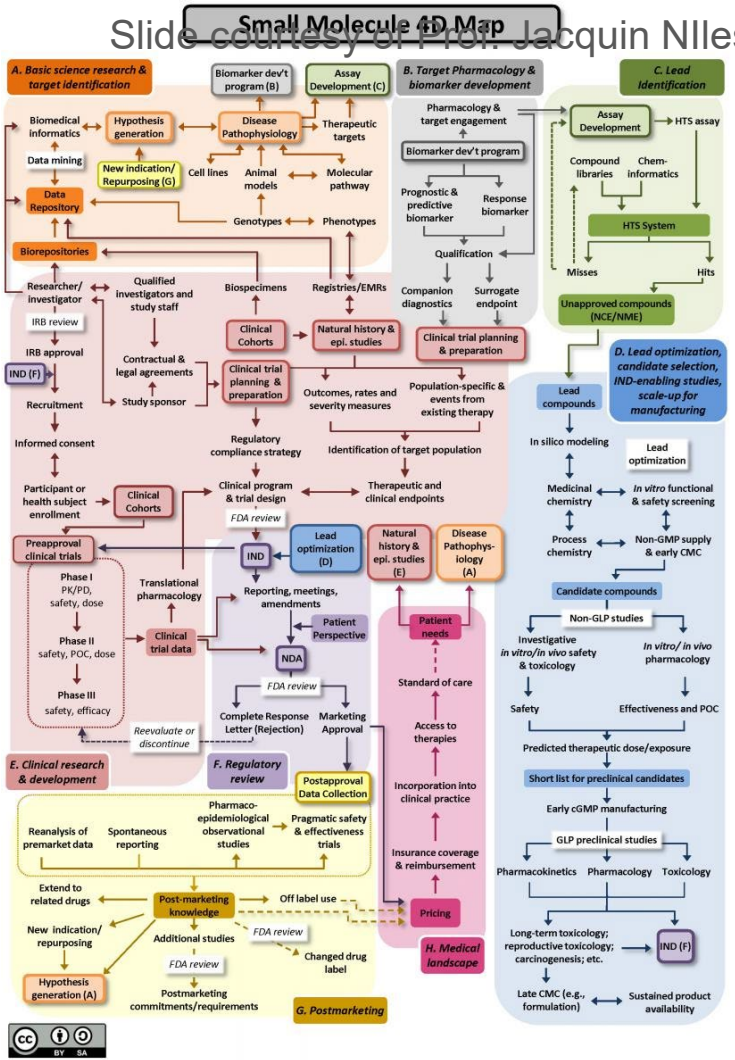


Regulation of drug approval in the U.S.

- What needs to be regulated?
- How is this regulation achieved?
  - FDA
  - United States Pharmacopeia-National Formulary (USP-NF)
- What are some implications of this regulation for the drug discovery and marketing process?

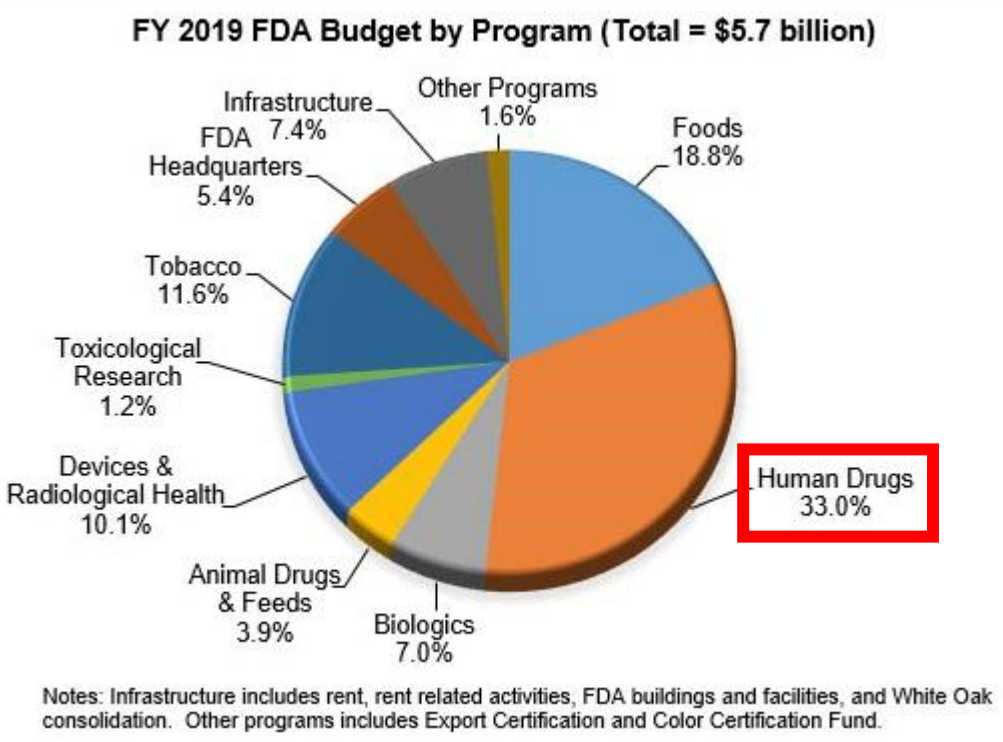
FDA Website



Food and Drug Association (FDA)

Slide courtesy of Prof. Jacquin NIles

- FDA is an agency within the U.S. Department of Health and Human Services
- Protects public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices.
- Over **20,000 FDA-regulated** prescription drug products approved for marketing
  - 1,600 FDA-approved animal drug products
  - 400 FDA-licensed biologics products
- FDA budget sources
  - ~ 55 percent ($3.1 billion) from federal government
  - ~45 percent ($2.6 billion) from industry fees.

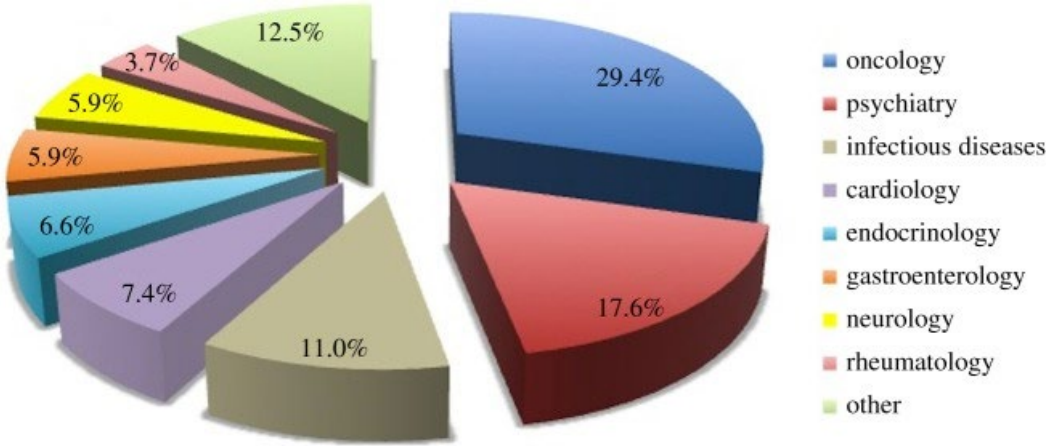


Reference:

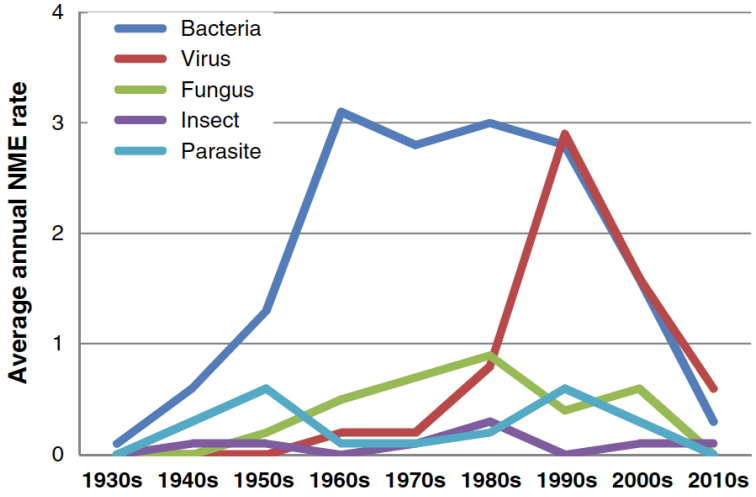
1) FDA at a Glancet: https://www.fda.gov/media/131874/download

FDA approved drugs and distribution across disease indication areas

Slide courtesy of Prof. Jacquin NIles



Breakdown of new infectious disease drugs



Antibacterial: 55%

Antiviral: 22%

Antifungal: 12%

Antiparasitic: 8%

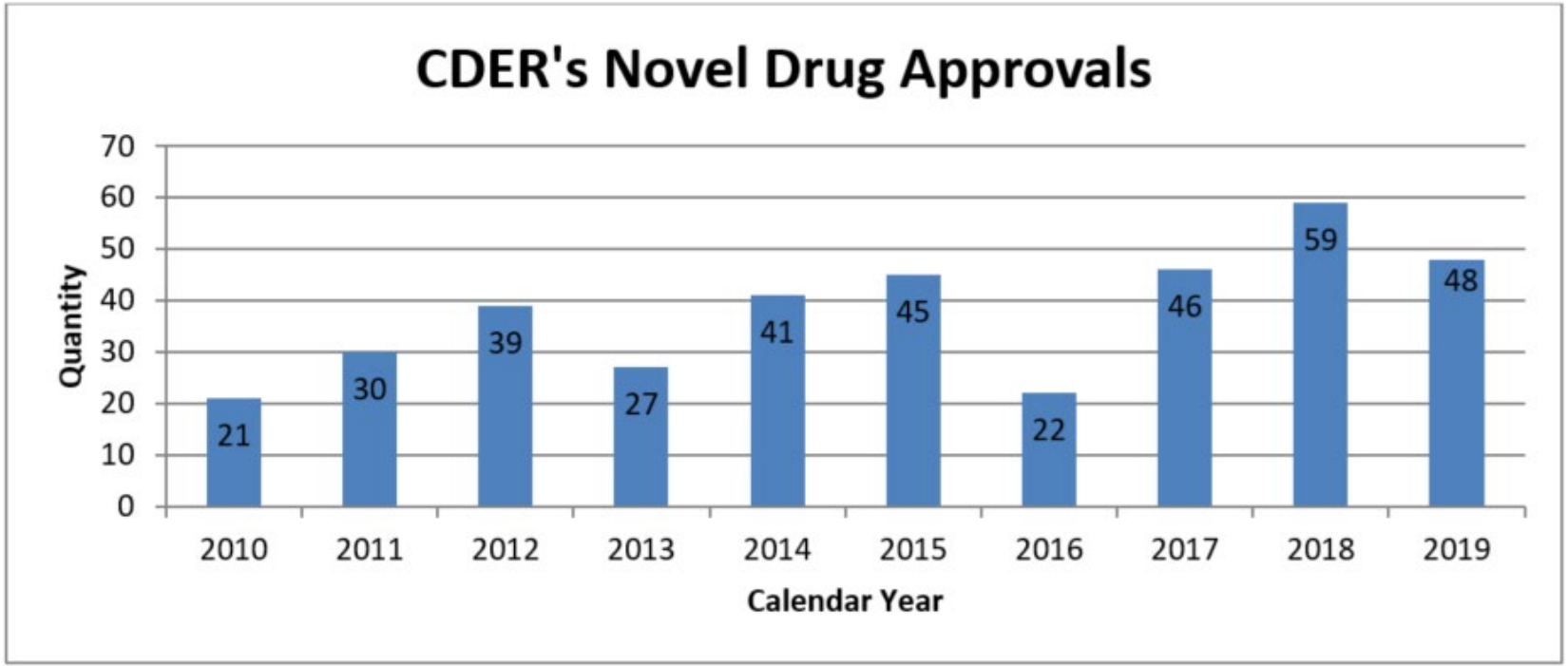
Insecticidal: 3%

References:

1) FDA at a Glancet: https://www.fda.gov/media/131874/download
2) Kinch et al; Drug Discovery Today; 2012

Annual new FDA drug approvals

Slide courtesy of Prof. Jacquin NIles



- In 2019, 20/48 FDA approved drugs were “first in class”
  - Possess distinct mechanisms of actions from previously approved drugs

FDA Website:
https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2019

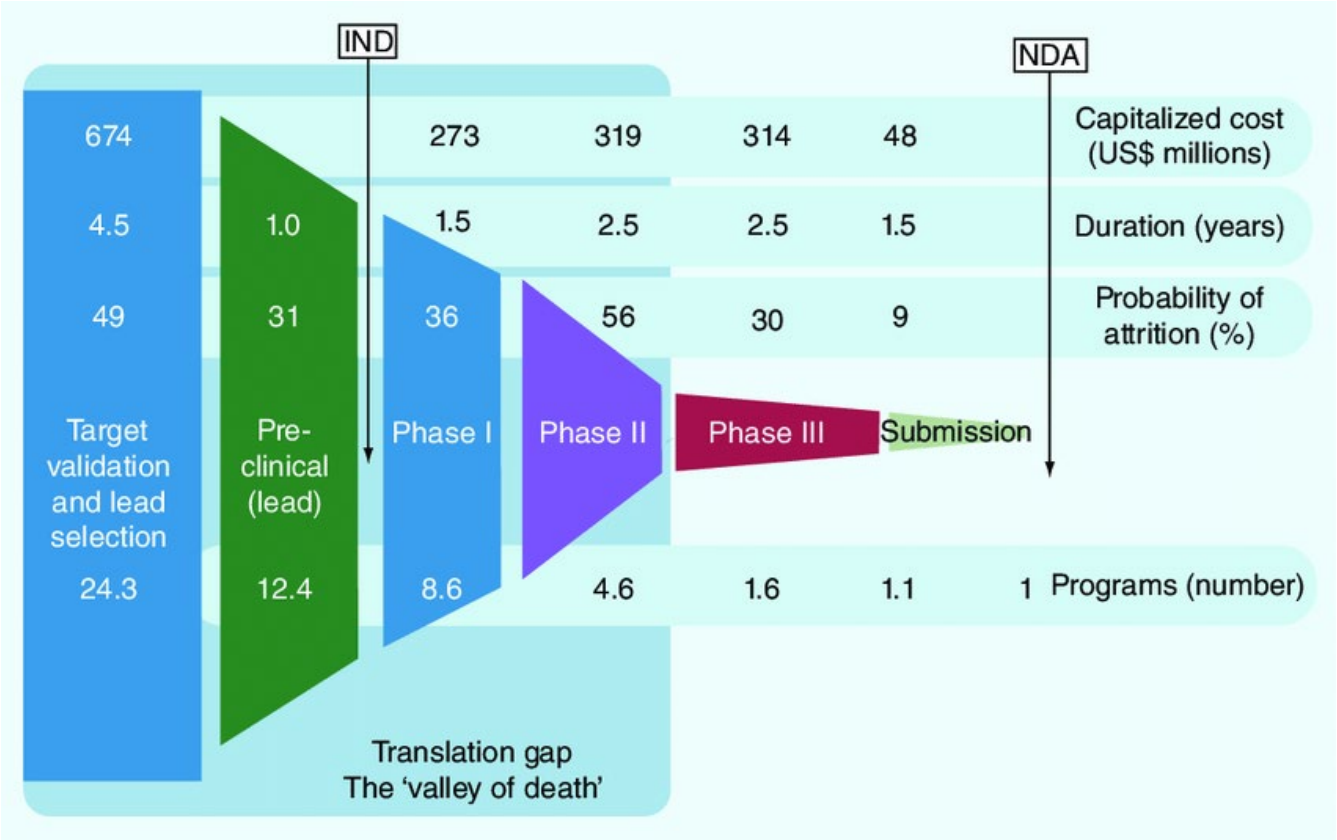
United States Pharmacopeia – National Formulary (USP-NF)

Slide courtesy of Prof. Jacquin NIles

References:
https://qualitymatters.usp.org/pharma-co-what

New drug discovery is expensive … with no guarantee of success!

Slide courtesy of Prof. Jacquin NIles

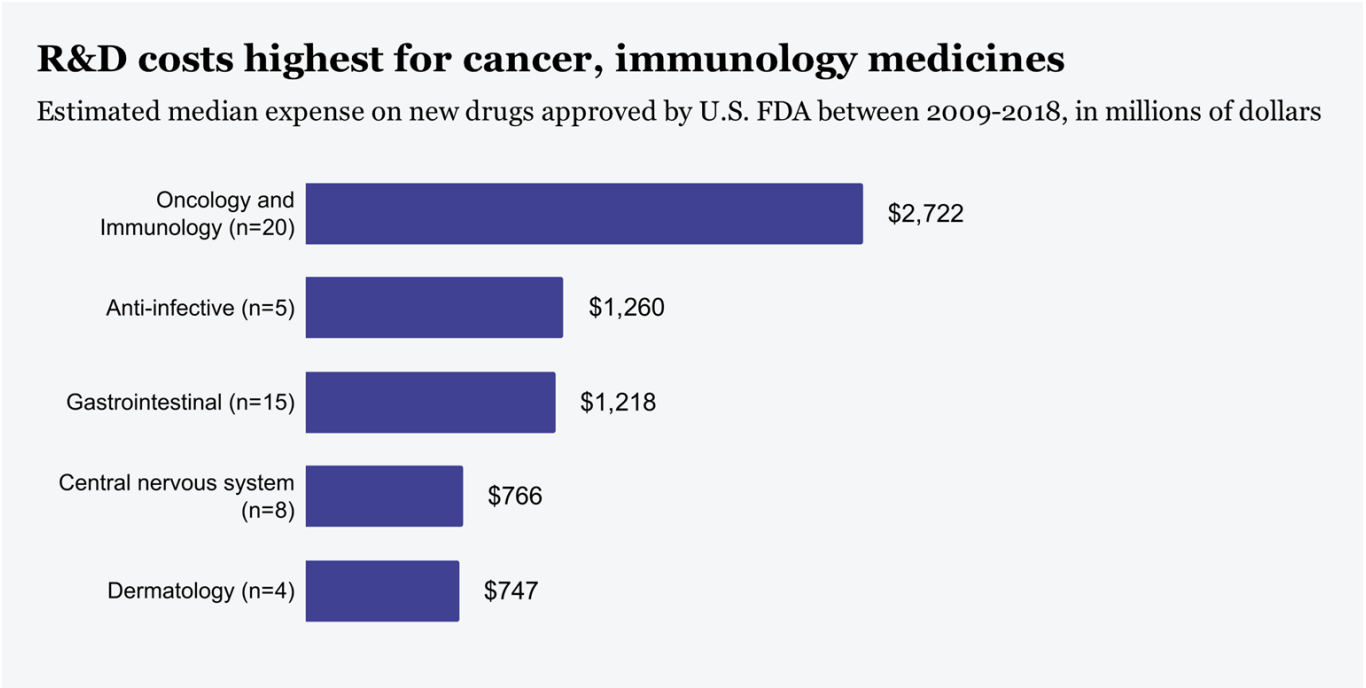


Between 2009 –2018, the median cost of developing a new drug was $985 million, while the average total was $1.3 billion!

Reference: Jesus Zurdo; Pharm. Bioprocess. (2013) 1(1)
DOI: 10.4155/PBP.13.3

New drug discovery is expensive … with no guarantee of success!

Slide courtesy of Prof. Jacquin NIles



Cost of developing a new drug (2009 –2018 data):

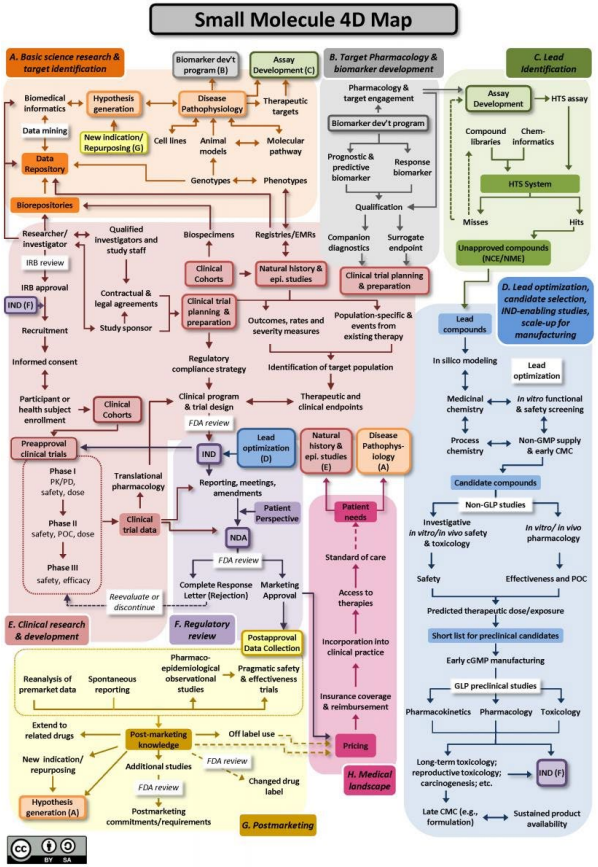
Median: $985 million
Average: $1.3 billion

Reference:
Wouters et al; JAMA. 2020;323(9):844-853. doi:10.1001/jama.2020.1166

Summary

Slide courtesy of Prof. Jacquin NIles

- Drug discovery and development is a highly complex, multidisciplinary process
- The goal is to develop safe and effective medicines across a broad portfolio of health needs
- Stringent regulation and monitoring during and after new drug approval by federal and independent organizations are vital to ensuring safety, product authenticity and efficacy
- Both the preclinical and clinical phases of drug development are very costly AND success is not guaranteed (failure is the norm?)!



Slide courtesy of Prof. Pete Dedon