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Overview of the drug development process

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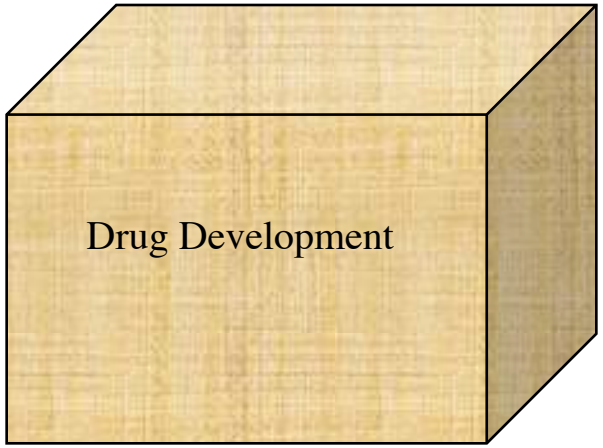

- Overview of drug development
  - Drug discovery
    - History
    - Compounds to candidates
  - Drug development
    - Preclinical
    - Clinical

"…knowledge belongs to humanity, and is the torch which illuminates the world."

Louis Pasteur

What is a drug?

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- Aim of drug development: To find a compound that will have therapeutic benefits and develop it into an approved drug that can help people improve the quality of their lives
- What is a drug?
  - Any chemical substance that affects the functioning of living things and the organisms (such as bacteria, fungi, and viruses) that infect them
  - Substance used to diagnose, cure, treat, or prevent disease

What is a drug? (cont.)

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- Europe – medicinal product:
  - (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
  - (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

What is a drug? (cont.)

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- US – drug:
  - 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.

Numbers

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- 250 of 5 000–10 000 screened compounds enter preclinical testing
- Only 5–10 eventually make it to human testing
- Only 1 safe and effective to be approved
- On average, 9–13 years of study before it can be approved and made available for the general public
- Cost: $350M, but can be much more

Main phases

- **Drug discovery**
  - New compounds from basic research and identification of drug targets
  - Lead compounds → new chemical entity (NCE) → patent application
- **Drug development**
  - Preclinical phase
    - Animal studies
    - Investigational New Drug (IND) Application
  - Clinical phase
    - Phase I Trials
    - Phase II Trials
    - Phase III Trials
  - New Drug Application (NDA)
  - Approval

History

- Relied on intuition, trial and error in search for specific medicinal properties in herbs, plants, etc.
- Oldest written evidence of plants for medicinal preparations = 5 000 years
- Nature's pharmaceuticals only relief for man's pain and suffering
- Advancements in science last 500 years enabled scientists to study natural remedies more systematically
- First pharmacopoeia appeared in 1546 in Germany
- Chemist studied the preparation of medicines rather than experimenting with alchemy

History (cont.)

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- In the 1800s, chemists isolated compounds from plants for the first time, e.g., morphine isolated from opium around 1804
- Identifying and isolating active ingredients from traditional remedies:
  - more accurate doses
  - less of potentially harmful plant material
  - better understanding of chemical structure of pure drugs → laboratory synthesis of structurally related compounds
  - mechanism of drug action analyzed in physiological terms
- Second half of the 19th century = pharmaceutical industry and the production of synthetic drugs

History (cont.)

- Late 19th, early 20th centuries: social, cultural, and technical changes of importance to pharmaceutical discovery, development, and manufacturing
- For example: universities began to encourage their faculties to form a more coherent understanding of existing information
- Chemists: developed ways to separate chemicals from minerals, plants, and animals and to synthesize novel compounds
- Biologist: research to improve understanding of the processes fundamental to life in species of microbes, plants, and animals
- Rapid developments in science, education of pharmacists and physicians changed

History (cont.)

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- Medical schools established science departments; large chemical and pharmaceutical companies employing university-trained scientists
- During 20th century, general public and politicians began to appreciate benefits of medical, chemical, and biological research, prompting governments to develop mechanisms to provide support for university research
- Government agencies own research, or supported research and discovery at universities to be used for pharmaceutical development
- Nonprofit organizations were developed to support research

Drug discovery

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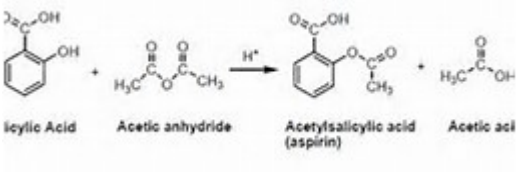
Process by which new candidate medications are discovered

➢ New Chemical Entity (NCE)

- Identification of a target → target validation (TV) → assay development → high-throughput screening (HTS) → hit to lead (H2L) → lead optimization (LO) → NCE → Preclinical drug development → Clinical drug development

New compounds

- Compounds from natural products or made naturally by microscopic organisms
- Synthesis
- Computer simulations
- Genetic engineering
- Serendipity



sĕrėndĭp′ĭtў *n.*
faculty of making happy discoveries by accident.

Drug screening

- Drugs discovered through identifying the active ingredient from traditional remedies
- Classical (forward) pharmacology basis for the discovery of new drugs – compounds screened in cellular/animal disease models to identify compounds that cause a desirable effect or show characteristics that might be therapeutically beneficial
- Early 20th century: potential drugs screened in live animals (in vivo), later replaced with test tubes
- Compounds screened one by one, added to the substance of interest in test tube, ascertain which additions show chemical effect
- Require one-by-one testing of hundreds of compounds → time consuming
- Late 20th century: automated in vitro screening techniques → tens of thousands of chemical compounds screened in a single day

Drug targets

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- More recently: develop hypothesis that biological target is disease modifying, screen for compounds that modulate the activity of this target, then compounds are tested in animals → Reverse pharmacology or target based drug discovery (TDD)
- Target: “A biological target is anything within a living organism to which some other entity (like a drug) is directed and/or binds, resulting in a change in its behavior or function.”
- “A biomolecular target (e.g., a protein or nucleic acid) is a key molecule involved in a particular metabolic or signaling pathway that is associated with a specific disease condition or pathology.”

High-throughput screening (HTS)

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- Since the sequencing of the human genome, it has become common practice to use HTS of large compounds libraries against isolated biological targets.

- HTS: method for scientific experimentation using robotics and microtiter plates to quickly conduct millions of chemical, genetic, or pharmacological tests → individual chemicals are mixed with drug targets in test-tube-like wells of the microtiter plates → can rapidly identify active compounds, antibodies, or genes that modulate a particular biomolecular pathway

- Many molecular interactions cannot be predicted: thus, the wider the chemical space sampled by the chemical library, the better the chance HTS will find a "hit"

Hit → Lead → Candidate

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- Hit to lead (lead generation):
  - Perform follow-up assays, “cherrypick” possible hits, re-run the experiment
- Lead compound:
  - “Leads”: chemical compounds with pharmacological or biological activity likely to be therapeutically useful, subjected to further developmental tests and some optimization
  - Suboptimal leads: additional chemicals with slightly altered structures may be synthesized in the lead optimization phase to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to increase the half-life), and oral bioavailability
  - Compound fulfilling all of these requirements = drug candidate

Candidate drug: “New chemical entities (NCEs) or compounds that have promising activity against a particular biological target that is important in a disease.” → Patent

Main phases

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Drug discovery

Drug development

- Preclinical
  - CNC
  - Animal testing
- Clinical

Preclinical

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- Chemistry, Manufacturing, and Control (CMC)
  - Physicochemical properties of new chemical entities (NCEs) must be established
  - Manufacturers need to optimize the process they use to make the chemical
  - Examine product for suitability to package as capsules, tablets, aerosol, intramuscular injectable, etc.
  - These processes = CMC

- NCEs have promising activity against a particular biological target – however safety, toxicity, pharmacokinetics, and metabolism in humans are unknown
- Many aspects of drug development focused on satisfying regulatory requirements of drug licensing authorities
  - Number of tests to determine the major toxicities, e.g. major organ toxicity
  - In vitro methods
  - Test on experimental animals

Animal testing

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- Effort to use as few animals possible
- 2 or more species
- Test toxicology, safety
- ADME
  - Absorption, Distribution, Metabolism, Excretion
- IND

Drug development phases

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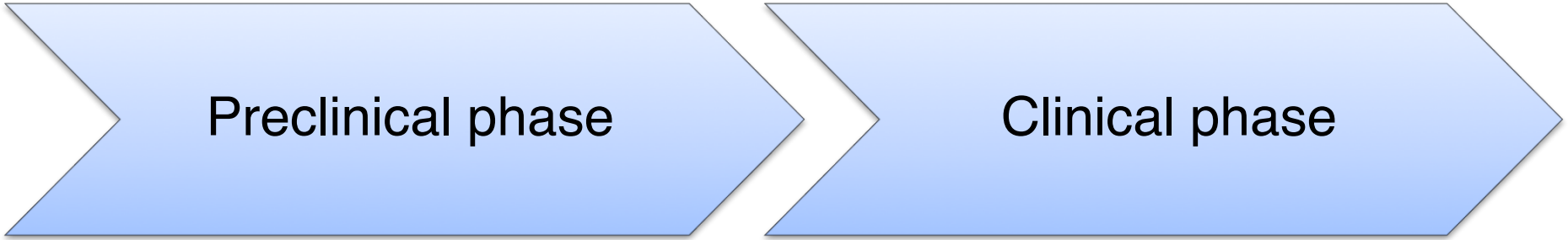

- Animal studies
- Investigational New Drug Application

- Phase I Trials
- Phase II Trials
- Phase III Trials
  - New Drug Application
  - Approval

Clinical trial/study

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- Test potential treatments in human volunteers
- Drug, medical device, or biologic, like a vaccine or blood product
- In past, often white males only
- Important to test it on the people who have the condition being studied
- Wide variety of people
  - Drugs can work differently in people of different age, race, gender, ethnicity
  - Trial guidelines / eligibility requirements
  - Inclusion / exclusion criteria
    - help identify appropriate participants and help to exclude those who may be put at risk by participating in a trial
- Carefully designed to answer specific research questions
- A protocol maps out what study procedures will be done, by whom, and why

Phase 0 – Microdosing

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- Speed up the development of promising drugs
- Administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (what the body does to the drugs)
- Gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect
- Rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development
- Enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data

Phase I – First time in humans

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- Healthy volunteers
- Determine dosing
- Study the activity: how the drug is metabolized and excreted
- Identify side effects and monitor potential toxicity
- Small study – 2–100 subjects
- Few weeks to about 1 year

Phase II – Exploratory

- More participants who have the disease or condition being studied
- Gather further safety data
- Determine the drug's effectiveness – check for evidence of beneficial effects
- 100–300 subjects
- About 2 years
- If risks are acceptable given the efficacy, drug moves to next phase

Phase III – Confirmatory

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- Given to even larger number of volunteers with the specific disease
- Physicians monitor patients closely to determine effects of the drug: the effectiveness and any side effects
- This phase confirms whether the drug is effective and safe
- Can also compare the drug's effect to an existing drug
- Up to 3 000 patients
- Can take up to three years or more

Marketing Authorization

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After all three phases, pharmaceutical company submit NCE portfolio of evidence for marketing approval

- The pharmaceutical company:
  - must clearly demonstrate effectiveness and safety of the drug
  - must provide all scientific information it has collected

In US, the FDA can take up to six months or more to review the application

- If approved, then made available for physicians to prescribe to patients
- Pharmaceutical company responsible for periodic reports to the FDA, e.g. side effects

- Phase IV Clinical Trials – Post Marketing:
  - serve to determine long-term side effects
  - other benefits
  - optimal use
  - test product in different populations (elderly, children…)

The future

- Mobile technology
- Wearables, sensors, smart devices
- Big data

➢ New ways of drug discovery ad development

Final thoughts

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The continual evolution and advancement of the pharmaceutical industry is fundamental in the control and elimination of disease around the world.

Thank you!