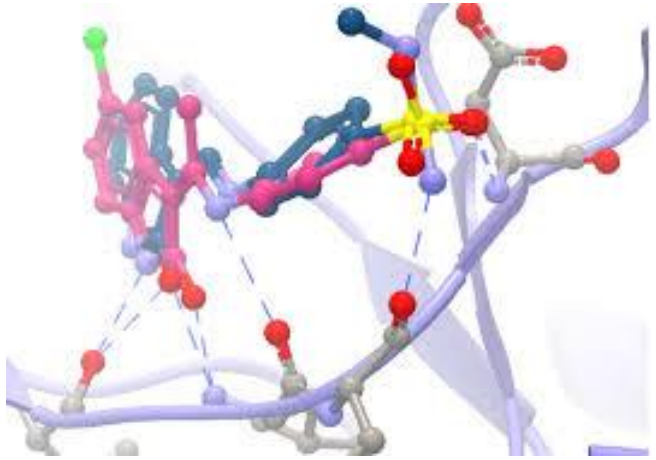
Screening of drug activities at molecular levels: Rational drug discovery

Tues 17th Nov 2015



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What is the highest ambition or the ultimate goal of a pharmacist?

CEO of a mega pharma company

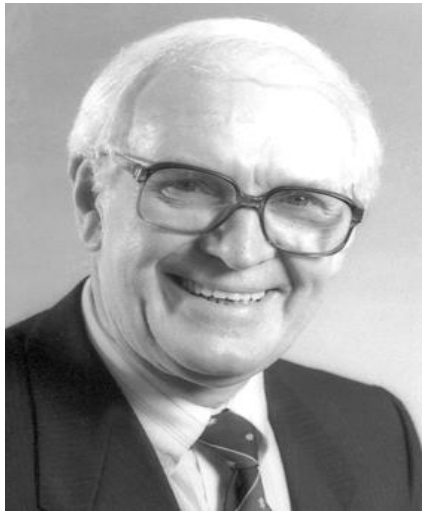
Dean of faculty

Assistant Minister of Health for Pharmaceutical Affairs

Owner of a chain of pharmacies

What is the highest ambition or the ultimate goal of a pharmacist?

Drug discovery



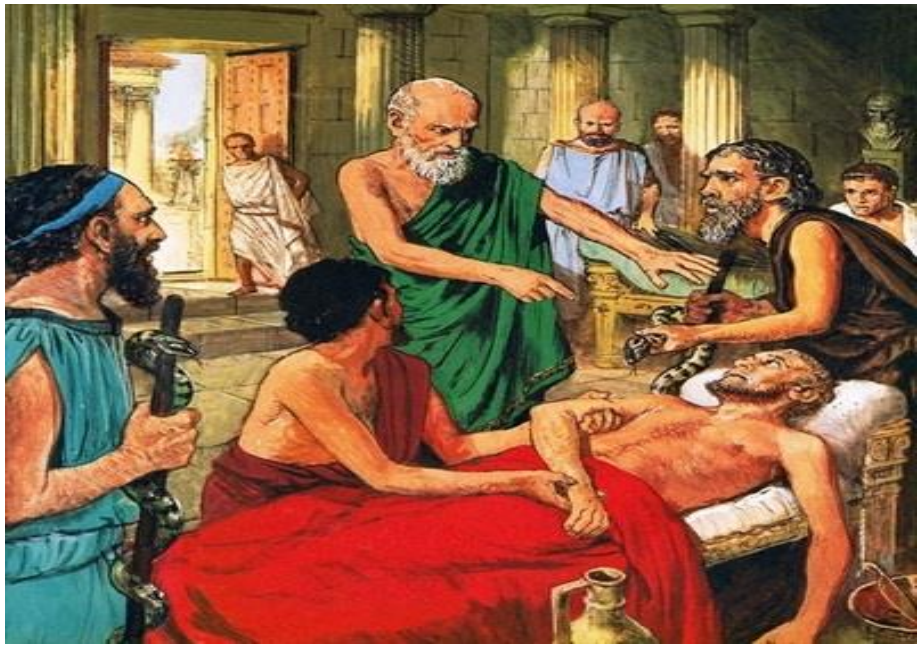
Sir James Black
Nobel prize in 1988
Propranolol
Cimetidine

Sir John Vane
Nobel prize in 1982

Identified the mechanism of action of aspirin as inhibition of cyclooxygenase in 1971

History of drug discovery

Nature has been a generous source for drugs throughout history. Communities were familiar with the toxic or therapeutic properties of certain plants and minerals long before they knew the target or mechanism of action.



- Serendipity (unexpected discovery) and good observational skills played an important role in the discovery of those early drugs.

History of drug discovery

Medicines made from willow tree were used in Ancient Egyptian and Greek civilizations 2000 and 400 BC.

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In 1897, Felix Hoffmann at Bayer prepared a pure form of acetylsalicylic acid (aspirin)

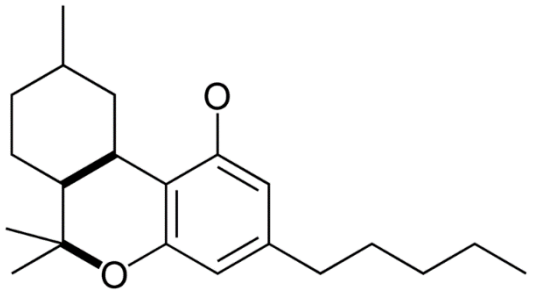
Only in 1971, Sir John Vane identified the mechanism of action of aspirin as inhibition of cyclooxygenase

- Serendipity (unexpected discovery) and good observational skills played an important role in the discovery of those early drugs

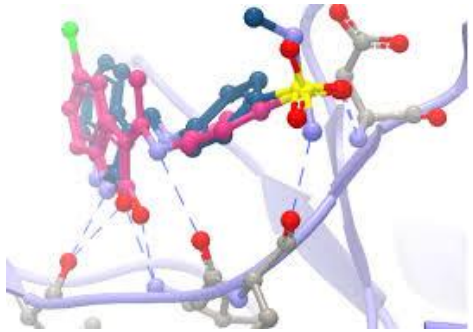
- Developing a new drug from the original idea to a marketed product takes 12–15 years and costs billions of dollars

- New **small molecules** that can **potently** and **selectively** modulate the functions of **key proteins e.g. enzymes, receptors, or transporters** that play important roles in the pathogenesis of diseases

- **Genomics** and **bioinformatics** are facilitating the dissection of the genetic basis of diseases to identify potential **drug targets** for future medicines in what is known as **rational drug discovery**



Small molecules



Drug target

This lecture will look at contemporary techniques for drug screening at molecular levels from initial target identification and validation, through assay development, high throughput screening, hit identification, lead optimization to obtain a candidate drug for clinical development

Rational drug discovery

Unmet clinical need

Target identification

Scientists identify a molecular target e.g. **enzyme, receptor or transporter** that influences a disease

Target validation

Scientists confirm the function of the chosen molecular target and examine the effect of its **manipulation on disease pathogenesis**

Assay development

Non-functional/biochemical assays Functional/cell-based assays.

Rational drug discovery, continued

High throughput screening

Hits identification

Lead selection and optimization

Potency, selectivity, pharmacokinetic parameters (absorption, distribution, metabolism and excretion) and **physiochemical** properties (solubility, stability and permeability) to select the best candidates

Drug candidate

Examine efficacy and safety profile using whole animal models

Drug development phase

Drug development phase (clinical trials)

Phase I

First time a new drug or regimen is tested on humans

Few participants (say <30), healthy volunteers

aim to find a dose with an acceptable level of safety, and examine the biological and pharmacological effects

Phase II

Not too large (say 30–70 people), patients

Aim is to obtain a *preliminary* estimate of efficacy and safety also

Not designed to determine whether a new treatment works

Phase III

Must be randomised and with a comparison (control) group

Relatively large (usually several hundred or thousand people), patients

provide a *definitive* answer whether a new treatment is better the control group, or is similarly effective but there are other advantages

FDA approval

Phase IV, post marketing survillance

Relatively large (usually several hundred or thousand people)

Used to continue to monitor efficacy and safety in the population once the new treatment has been adopted into routine practice.