Prescription Drugs:
From Discovery to Approval

Hanan Alkaysi, R.Ph., Ph.D.

Prescription Drugs

Discovery

- Traditional
- Rational

Development

Approval

Discovery

1- Traditional Approach

- Based on
  - empirical observations of biological activity.
  - Serendipity
  - Trial and error

- 65% of the medications still in use are natural products or their derivatives.

History

Ötzi’s Kit

History

- Medical texts from Mesopotamia and Ancient Egypt.
- Indian Medicine and Chinese Medicine(900 BC).
- Greek *Materia Medica.*
- Muslim physicians, translation and research. (Avicenna)
- Medieval Apothecary.

History

OPIUM

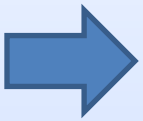
- First used by the Sumerians (3400 BC) and referred to as *Hul Gil*, the “joy plant”.
- The Greek named it Opium (Greek word for Juice, *Opion*) to describe poppy juice.
- Also used for constipating effect.
- Different preparations including tinctures and elixirs.

Heidelberg Apothecary

Chemistry

- Chemistry developed away from Alchemy to a well established science.
- Dalton atomic theory and the Periodic Table.
- Synthetic Chemistry (1830).
- Synthetic dye –William Henry Perkins (1856).

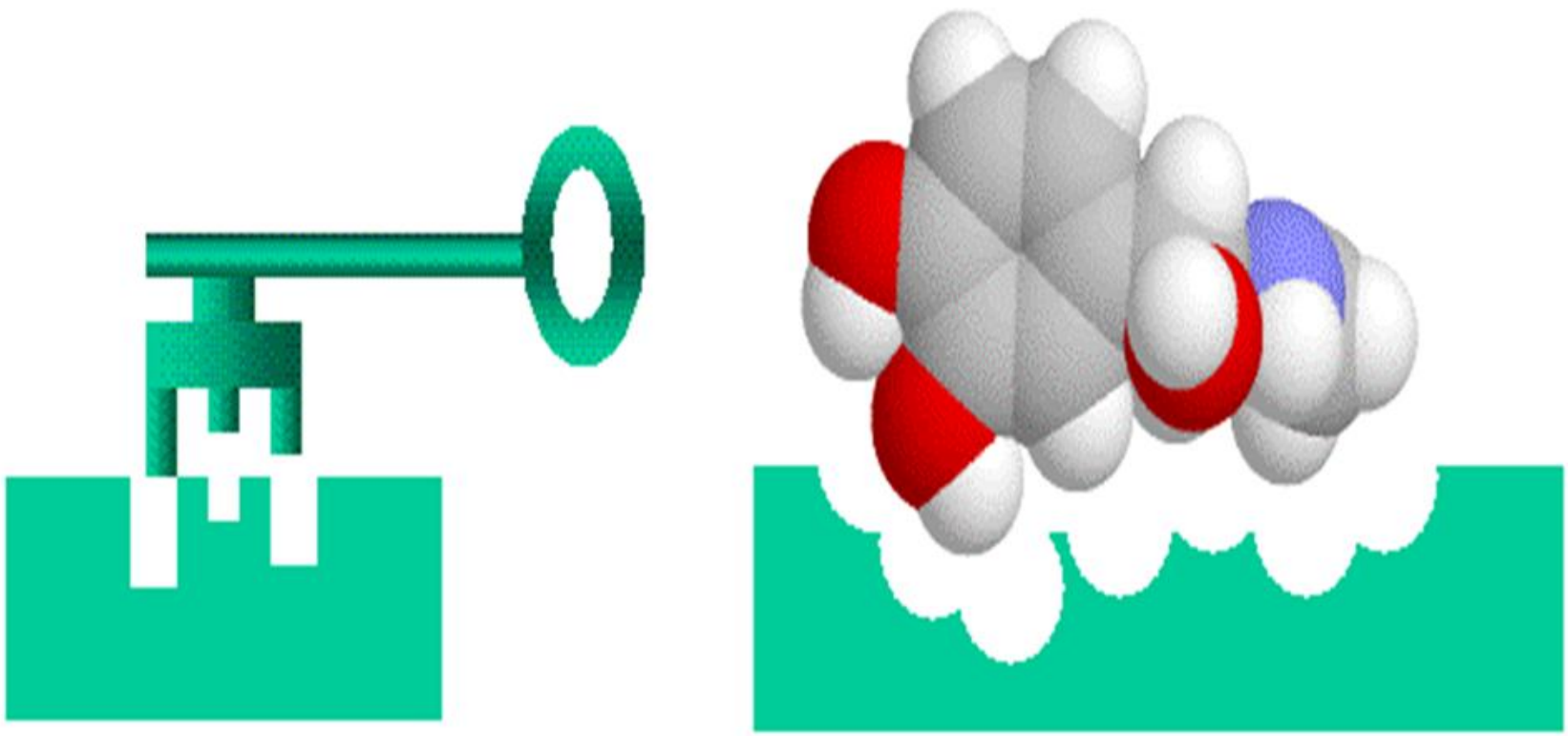
Chemistry

- Synthetic dyes Industry  Pharmaceutical Industry.
- Isolation and purification of plant's active ingredient(s).
- Preparation of synthetic derivatives of plant's active ingredient(s).
  - Bayer Aspirin (1899)

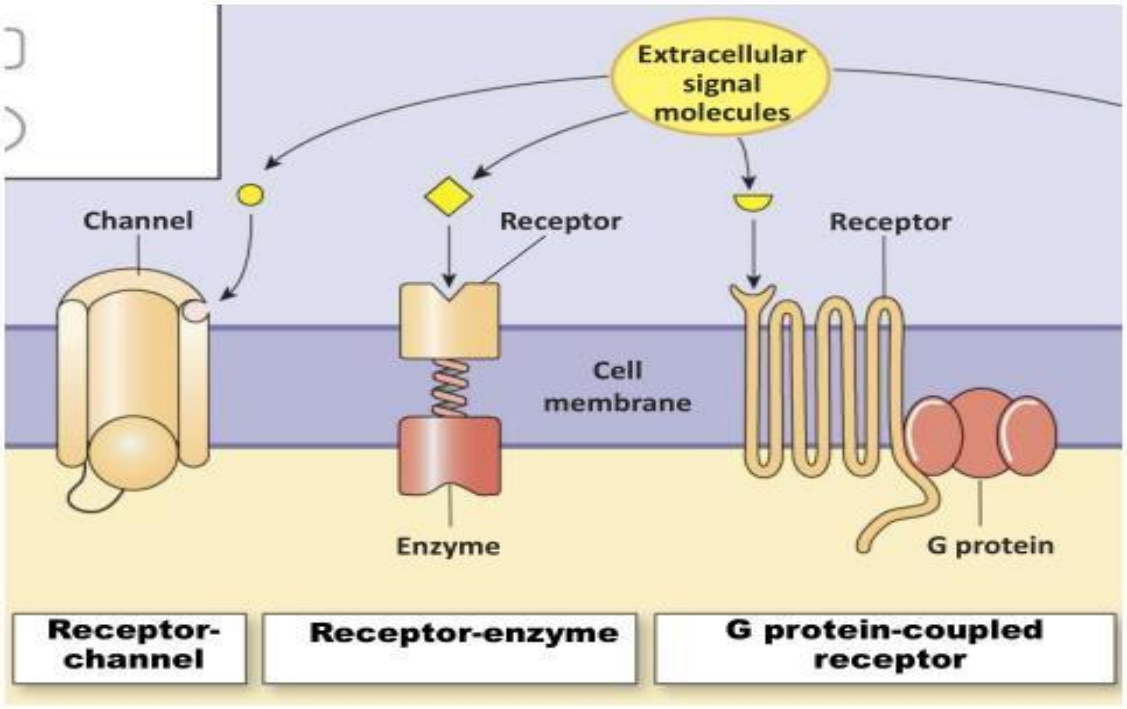
Receptors

- Paul Ehrlich *(receptor theory*)
  - Noticed that chemical dyes stain certain proteins in the cell. (1874)
  - Discovered the concept of the Chemoreceptor.
  - Lock and Key theory –As mechanism of drug action. (Pharmacology)

Receptors

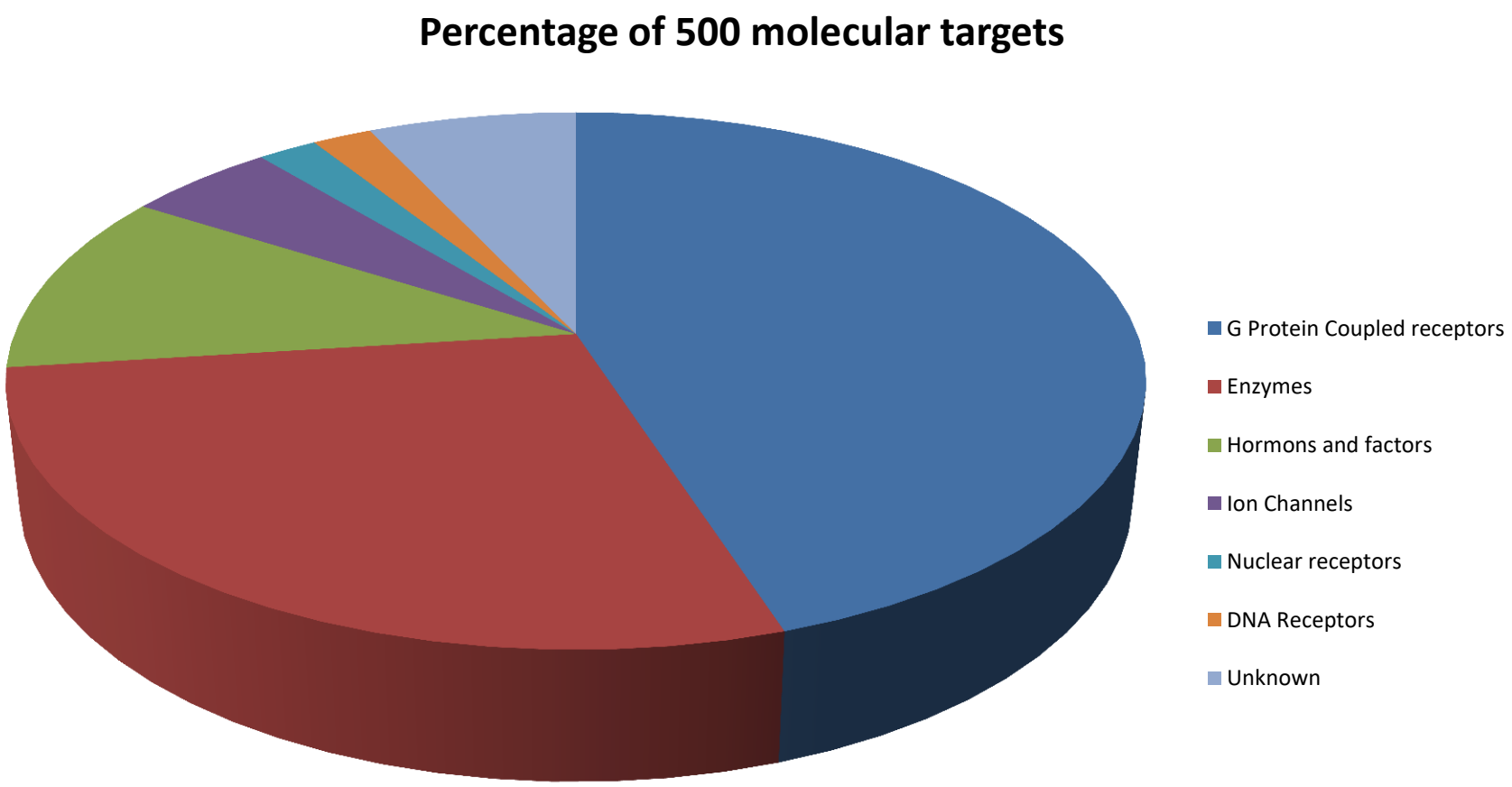


Membrane receptor types



Targets and Ligands

Targets


Percentage of 500 molecular targets
G Protein Coupled receptors
Enzymes
Hormons and factors
Ion Channels
Nuclear receptors
DNA Receptors
Unknown

Rational Drug Design

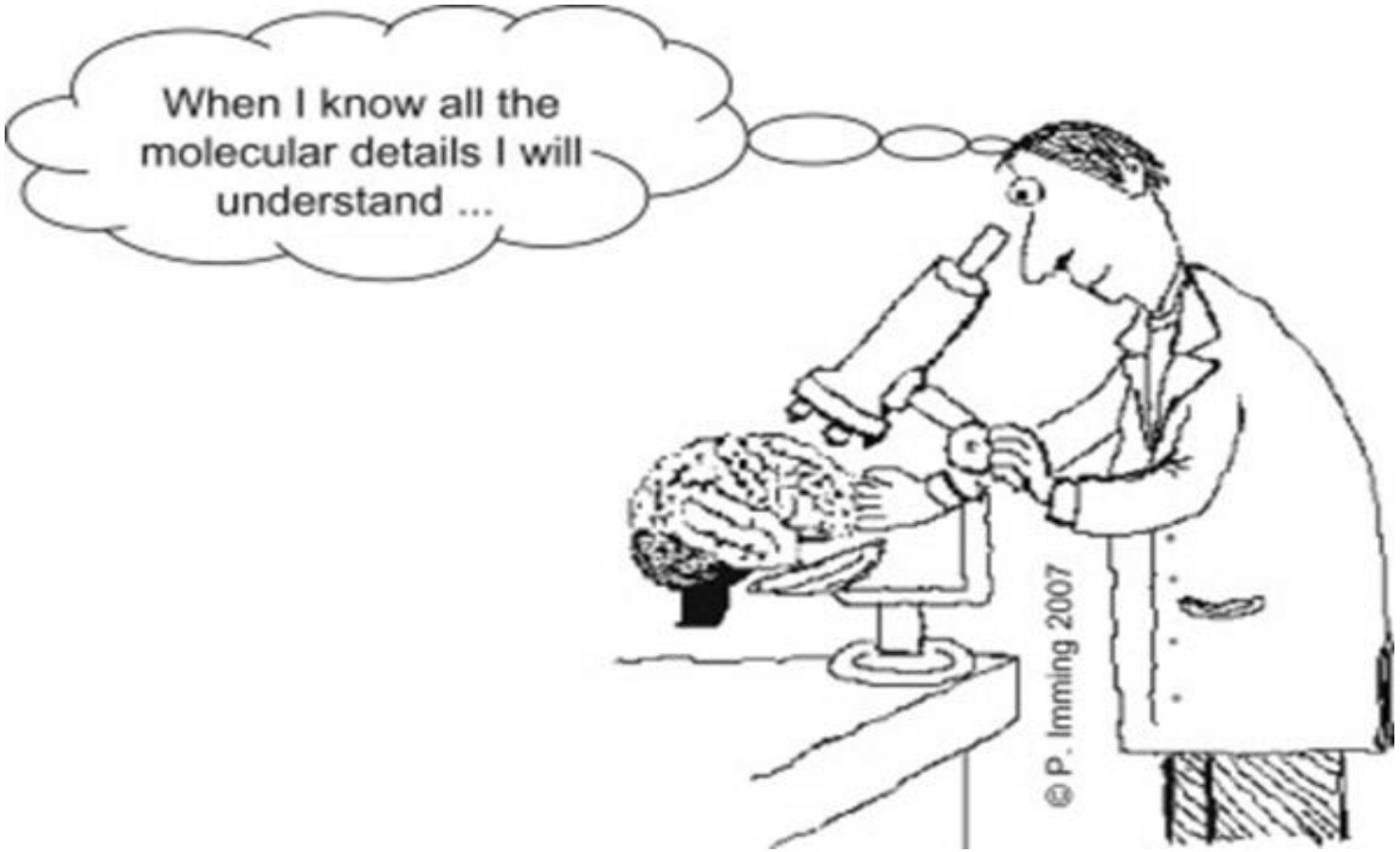
- Advances in Biochemistry, molecular biology and genetics led to:
  - Isolation and purification of Target molecules and the identification of their receptor sites.
- The use of bioinformatics to build structural models of the Target and it's Ligand.
- Rational drug design.

Targets and Ligands

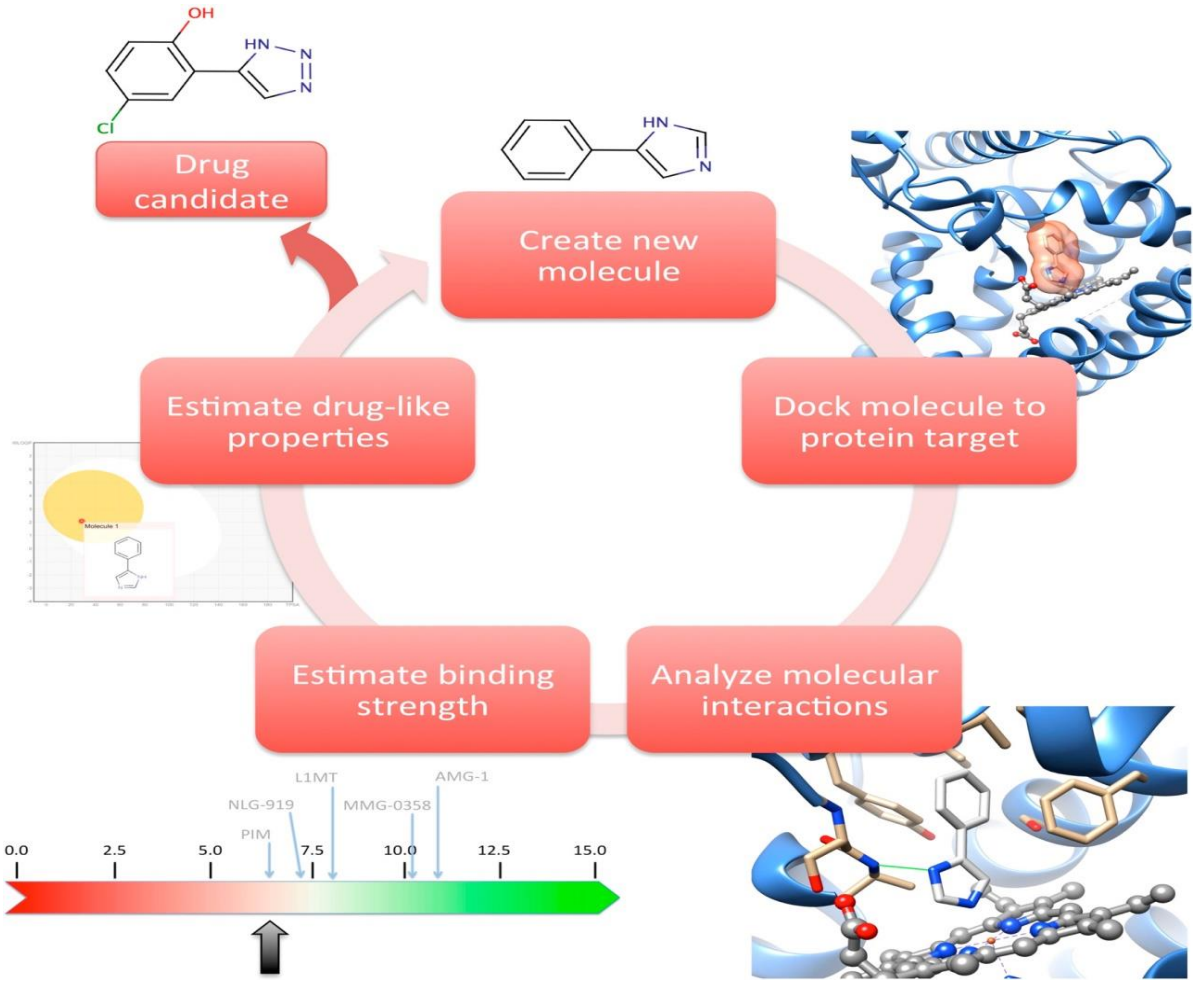
Drug Target

Definition: A native protein molecule or a cellular component whose biological activity is modified by a drug resulting in therapeutic effect.

- Isolation, Purification of the Target molecule
- Demonstration that the interaction with the ligand leads to a reversal of disease symptoms.
- Interaction is reproducible and measurable.


When I know all the molecular details I will understand ...
© P. Imming 2007

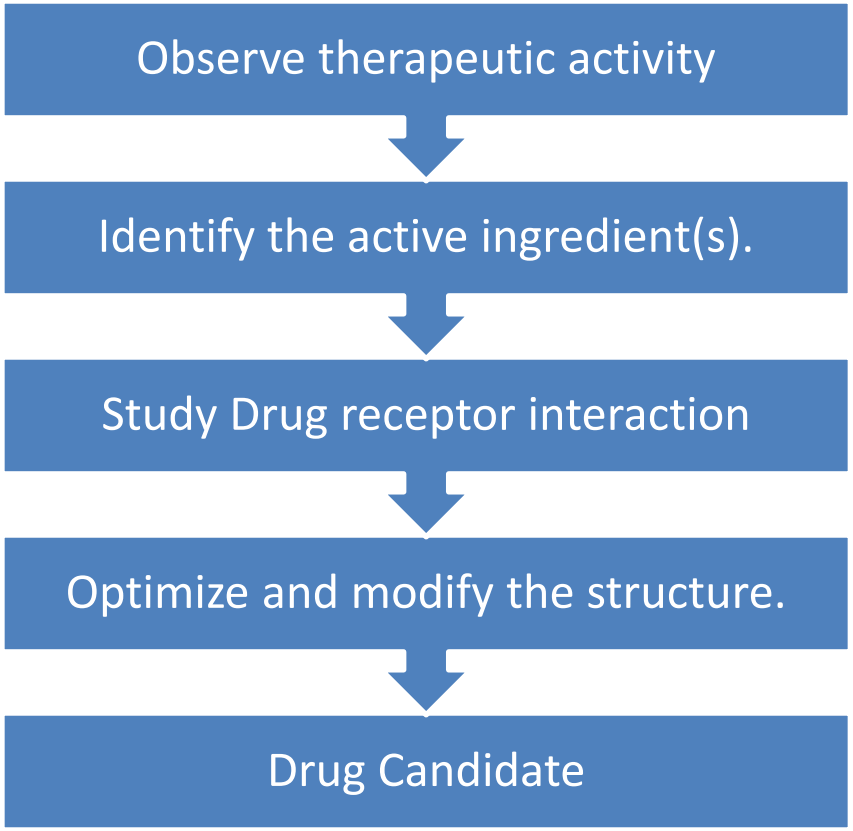
Computer Aided Drug Design



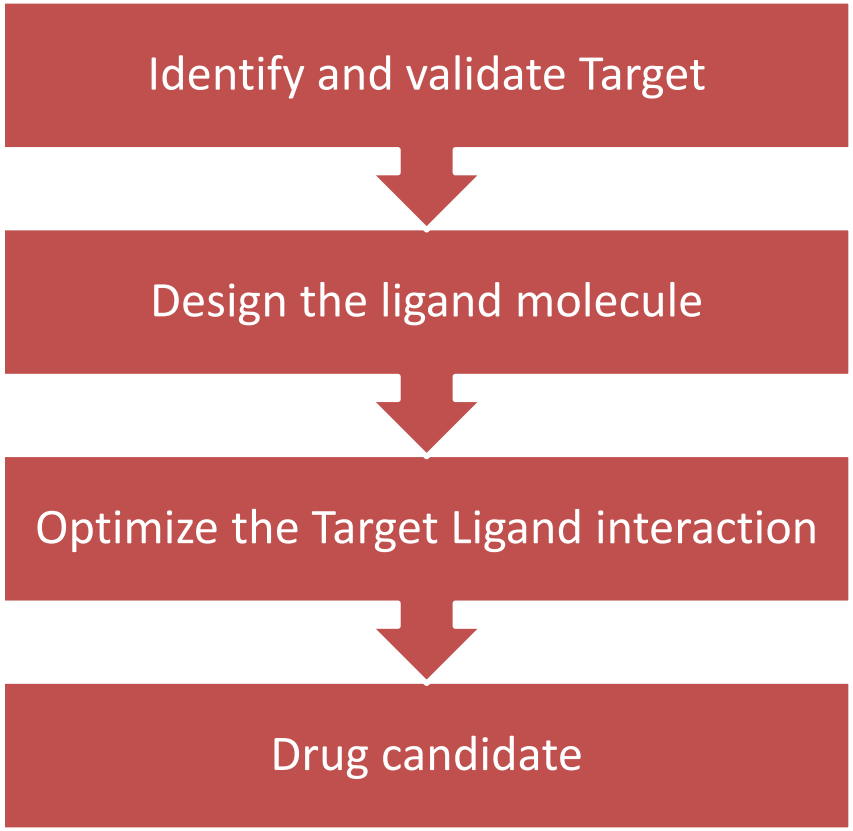
Vincent Zoete et al; *J.Chem.Educ. 335-344, 94, 2017*

Comparison

Traditional Drug Discovery



Rational Drug Design

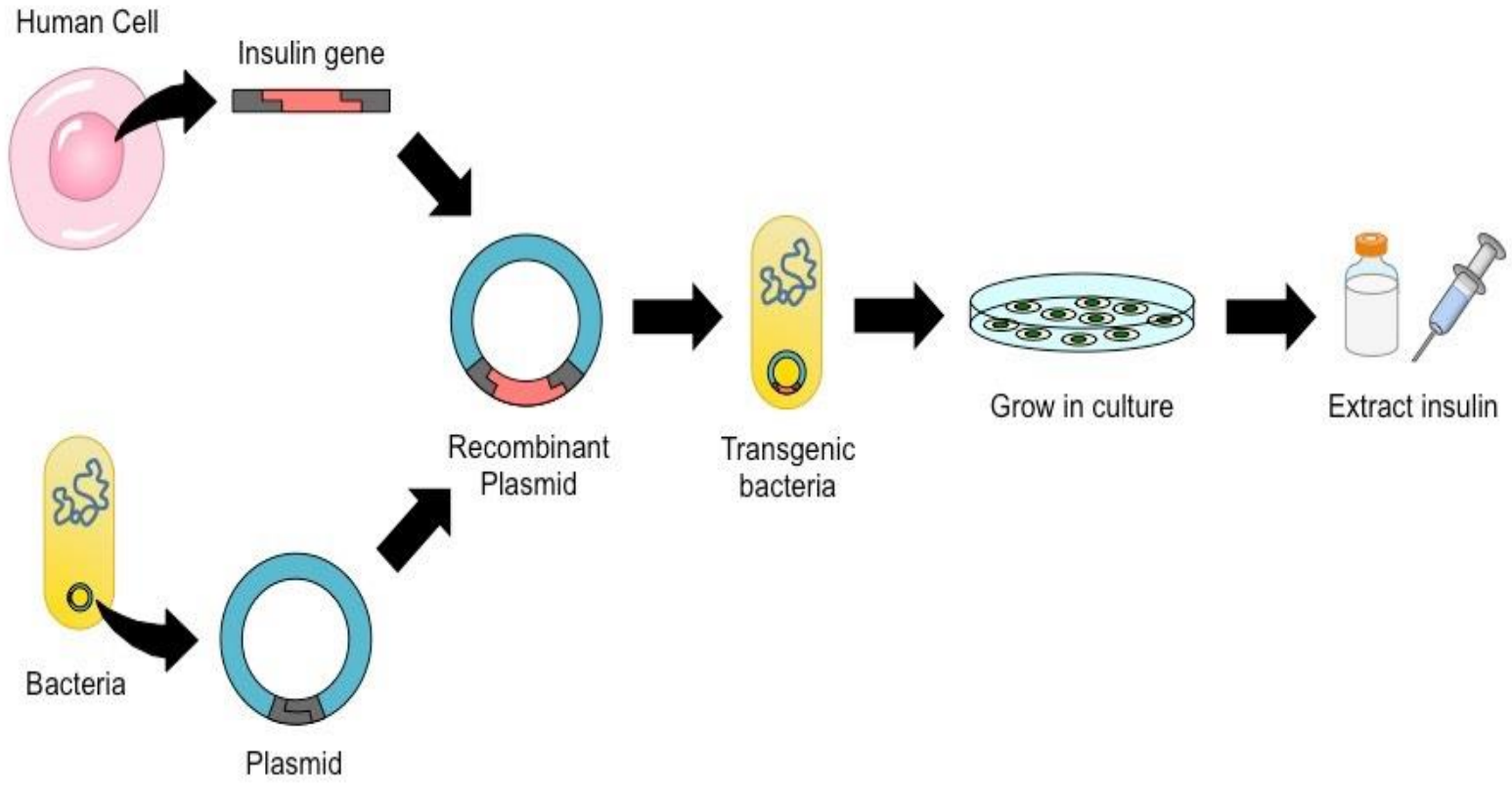


Biologics (Biopharmaceuticals)

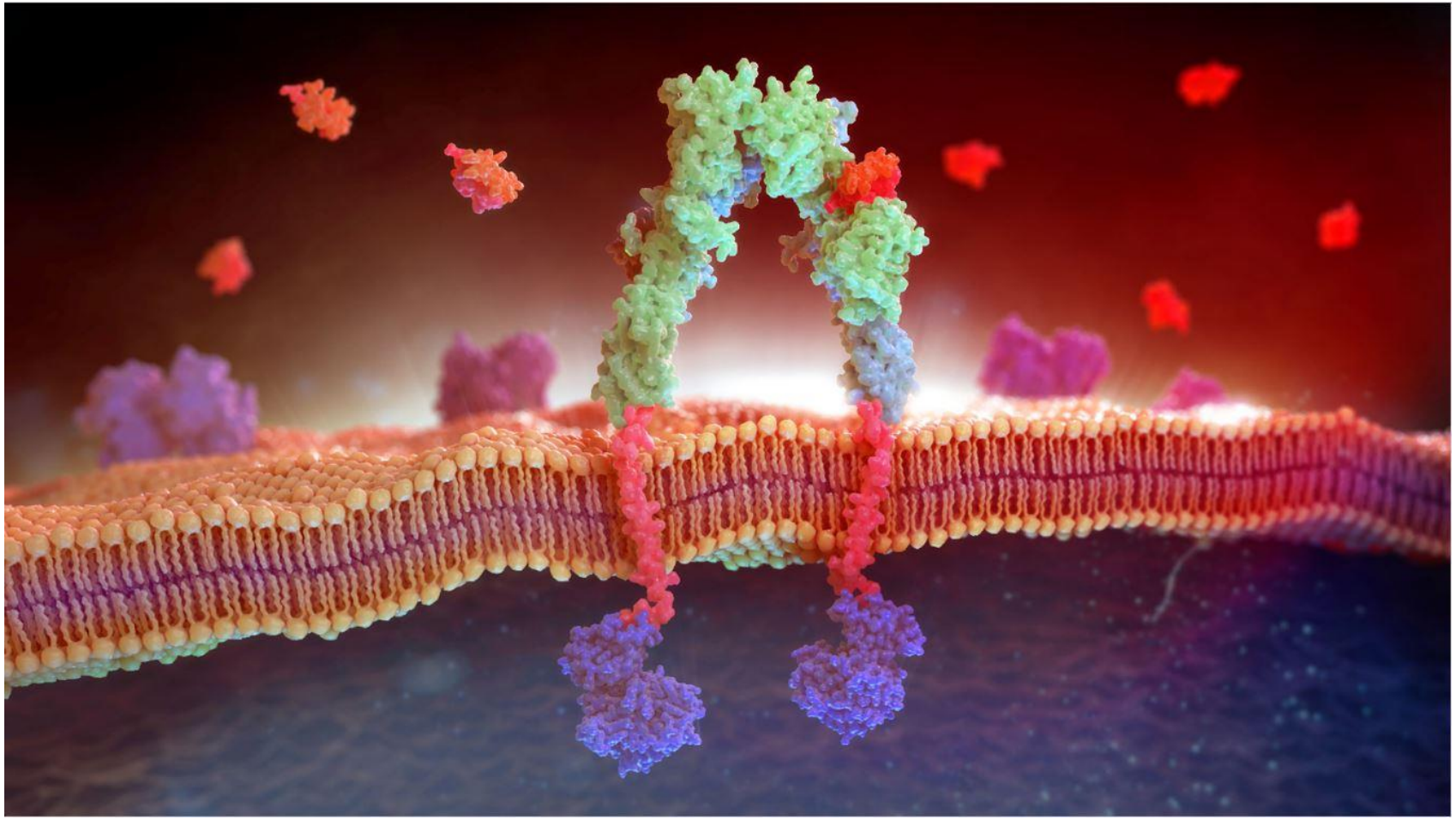
- Example: **Insulin**
  - Discovered in early twenties by Canadian scientists. Banting , Best & Macleod.
  - Developed for commercial use in the States by Eli Lilly.
  - Insulin was obtained from Animal Pancreas.
    - Bovine Insulin and Porcine Insulin
    - Side effects : Allergic reaction

Human Insulin Production

- Recombinant DNA synthesis of Human Insulin
  - Marketed in 1982



Insulin

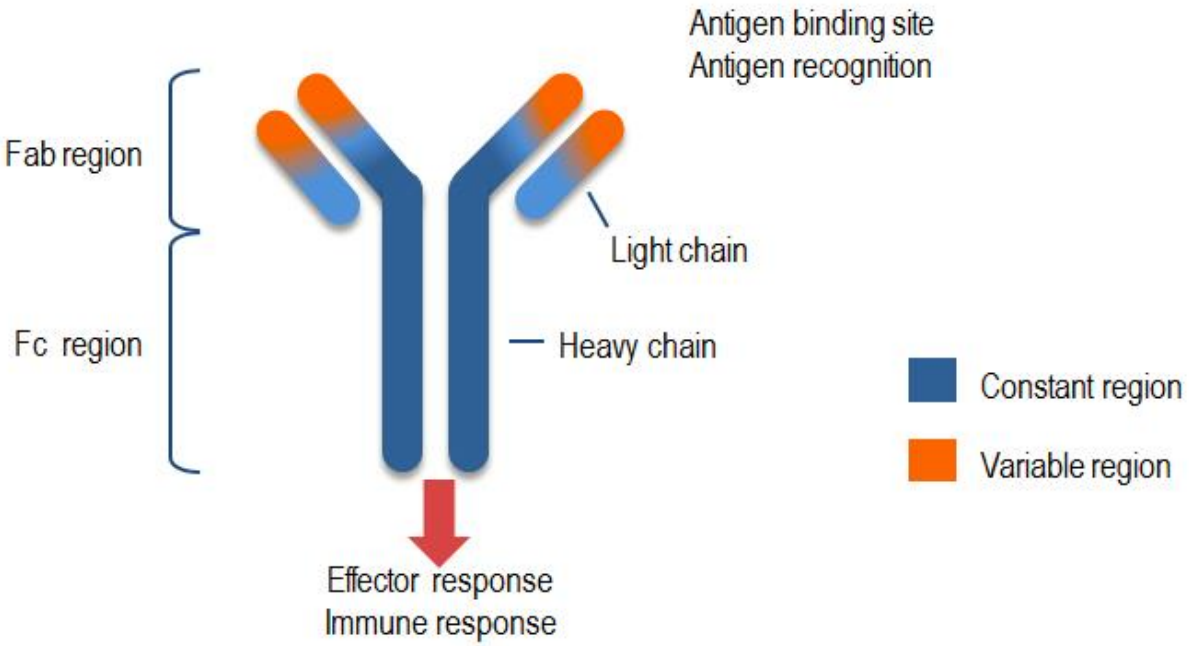


Biologics (Biopharmaceuticals)

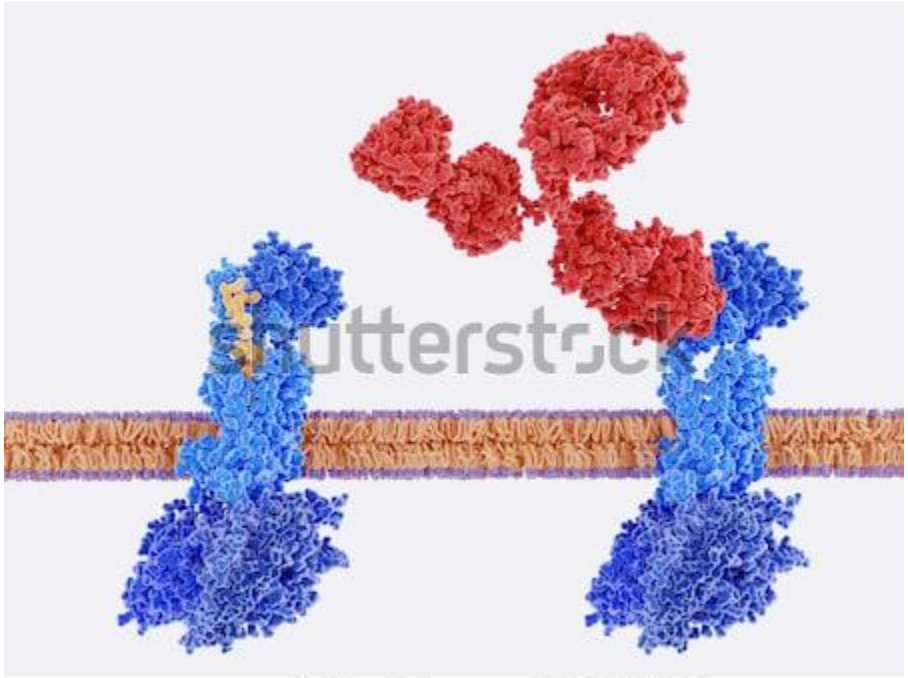
- Protein and macromolecules as Ligands
- Development of drugs based on the immune system.
  - Specificity: Antigen - Antibody interaction
  - Antibodies produced by immunizing animals
    - Side effects and allergic reactions
    - Research in Biotechnology and 2 Nobel Prizes in the field led to the Monoclonal Antibodies (mAb).

Monoclonal Antibodies

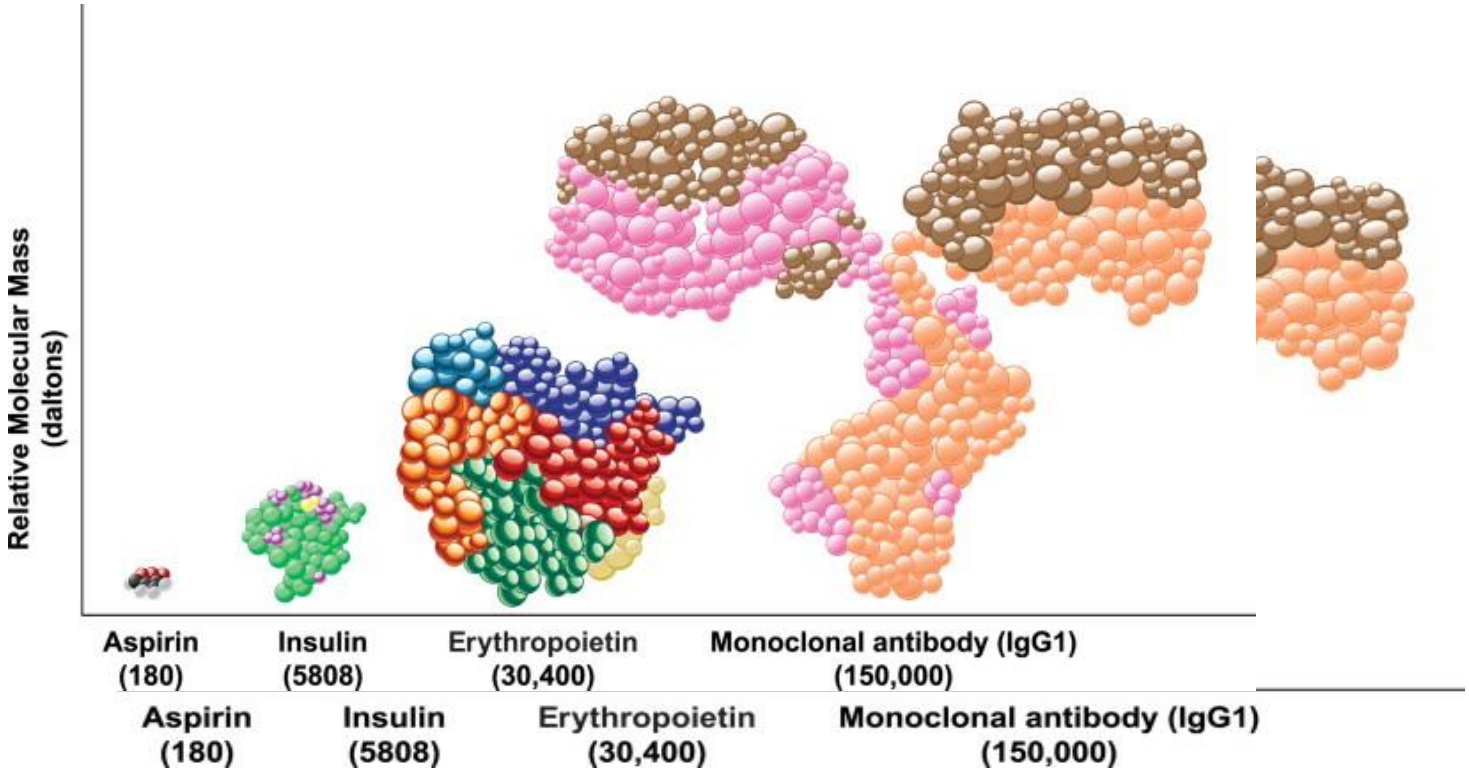
- Immunoglobulin molecules (antibodies) produced form a single B-Cells Clone



Monoclonal Antibodies

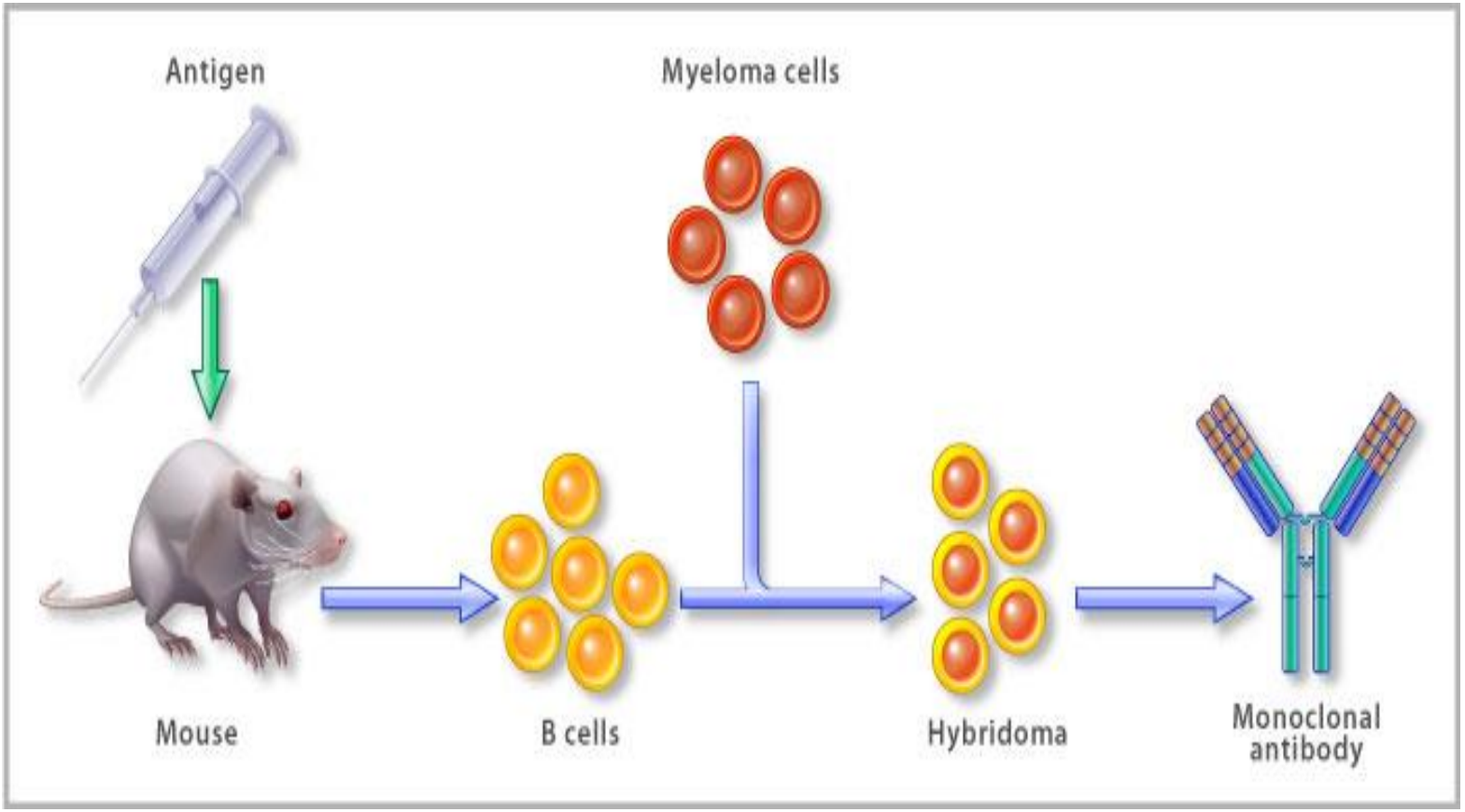


Monoclonal Antibodies



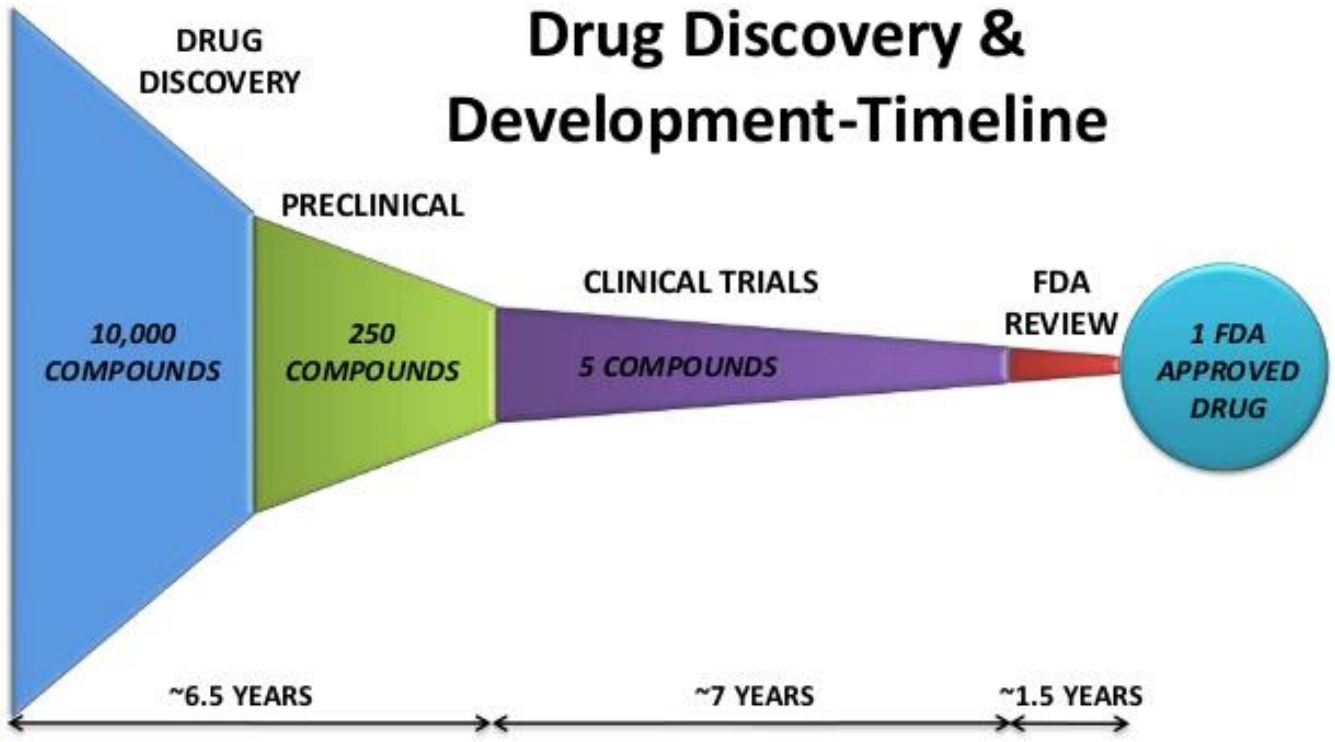
Sciencedirect.com

Monoclonal Antibodies



Monoclonal Antibodies

- Therapeutic Applications
  - Immunosuppression
  - Autoimmune diseases
  - Malignancies (Cancer)
  - Antiplatelet therapy
  - Infectious diseases
  - Asthma (allergic diseases)
  - Osteoporosis
  - Drug reversal


Drug Discovery & Development-Timeline
DRUG DISCOVERY
PRECLINICAL
CLINICAL TRIALS
FDA REVIEW
10,000 COMPOUNDS
250 COMPOUNDS
5 COMPOUNDS
1 FDA APPROVED DRUG
~6.5 YEARS
~7 YEARS
~1.5 YEARS

Lead Identification

- Most Important scientific and Business Decision
- A “Hit” Chemical or biological is identified as possible Drug. Usually 5-10 Candidates
- Research on the characterization and analytical procedures.
- Preliminary Toxicology

Lead Optimization

- Enhance solubility and Stability- (Formulation)
- Improve Specificity.
- Decrease Toxicity
- Study possible mechanism of action
- Study the feasibility of commercial production

Preclinical Studies

- Testing and Screening:
  - ***In vitro* testing for chemical characteristics and Scale-up Manufacturing**
  - ***In Vivo :* Biological activity and <u>Safety</u>**
    - **Cell cultures**
      - **Stem Cells Organoids**
    - **Devices**
    - **Organs**
    - **Animals**

Preclinical studies

- Proposed:
  - Formulation and Route of administration.
  - Dosage and its frequency.
  - Anticipated side Effects.
- Prepare and Submit the:

  "**Investigational New Drug Application**"

  IND reviewed by the FDA and the Institutional Review Boards prior to clinical trials

Clinical Trials

- Phase I : emphasis on Safety. 20- 80 healthy volunteers.
- Phase II : emphasis on Effectiveness and Safety. 100-200 patients. Special groups
- Controlled Studies vs. Placebo.
- First formal meeting

Clinical Trials

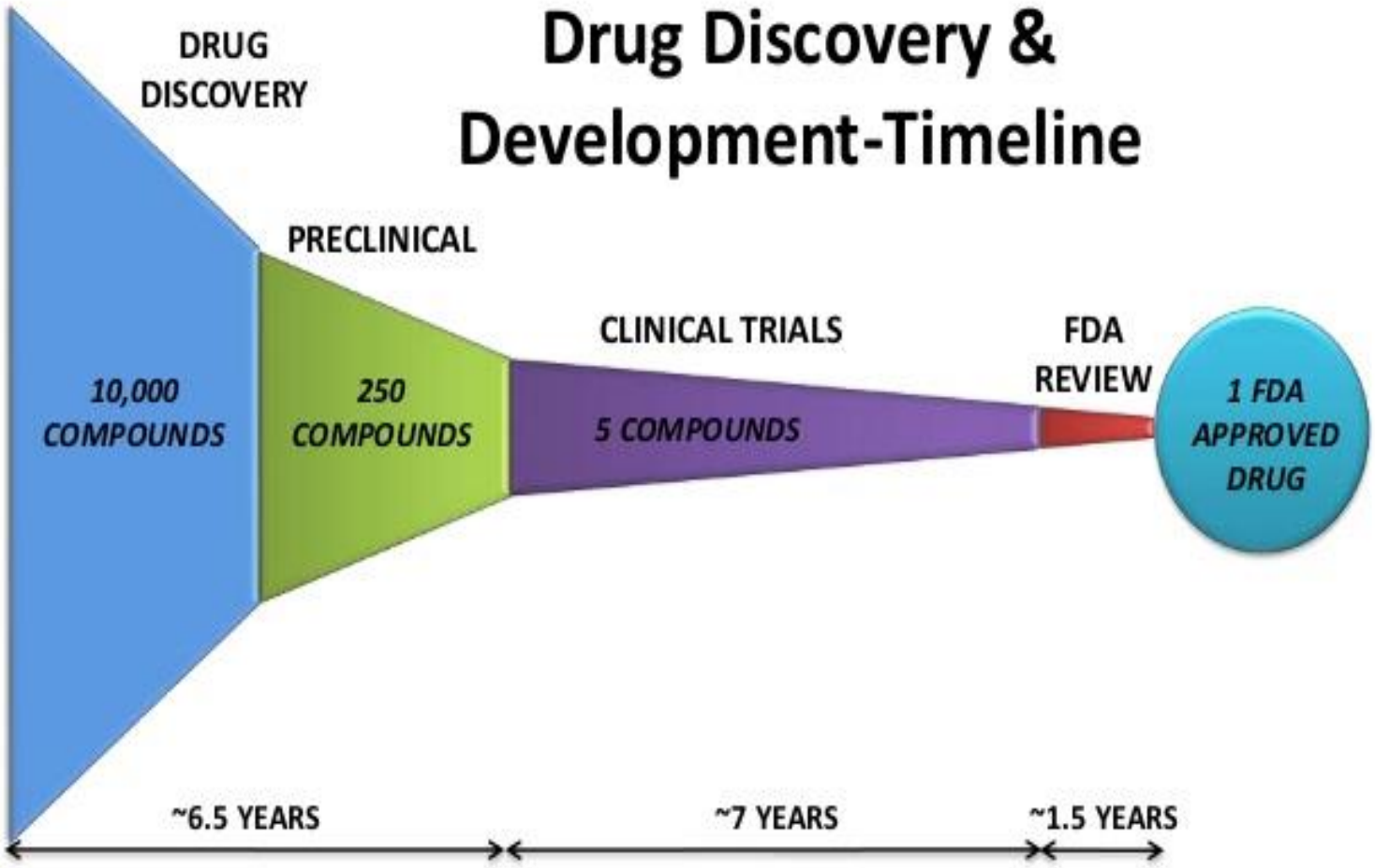
- Phase III : Large scale studies, Thousands of patients studied, different populations, different doses or combination.

- Second Meeting between FDA and Sponsors.

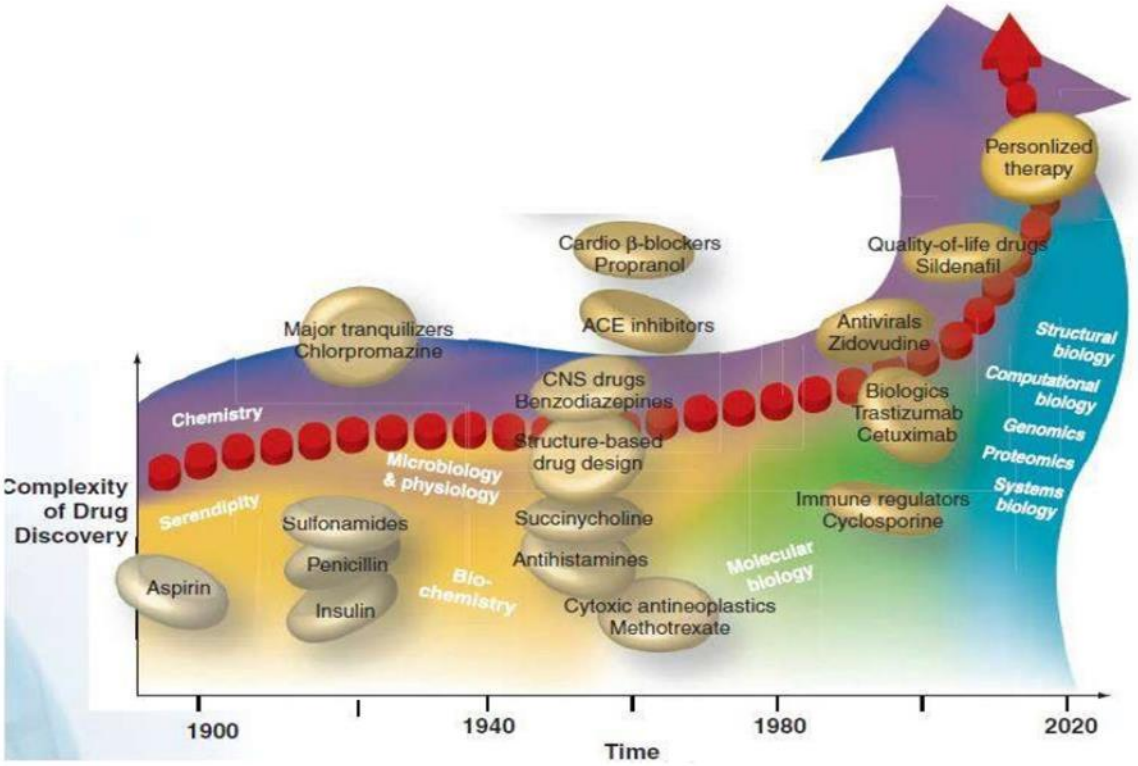
"**New Drug Application**"

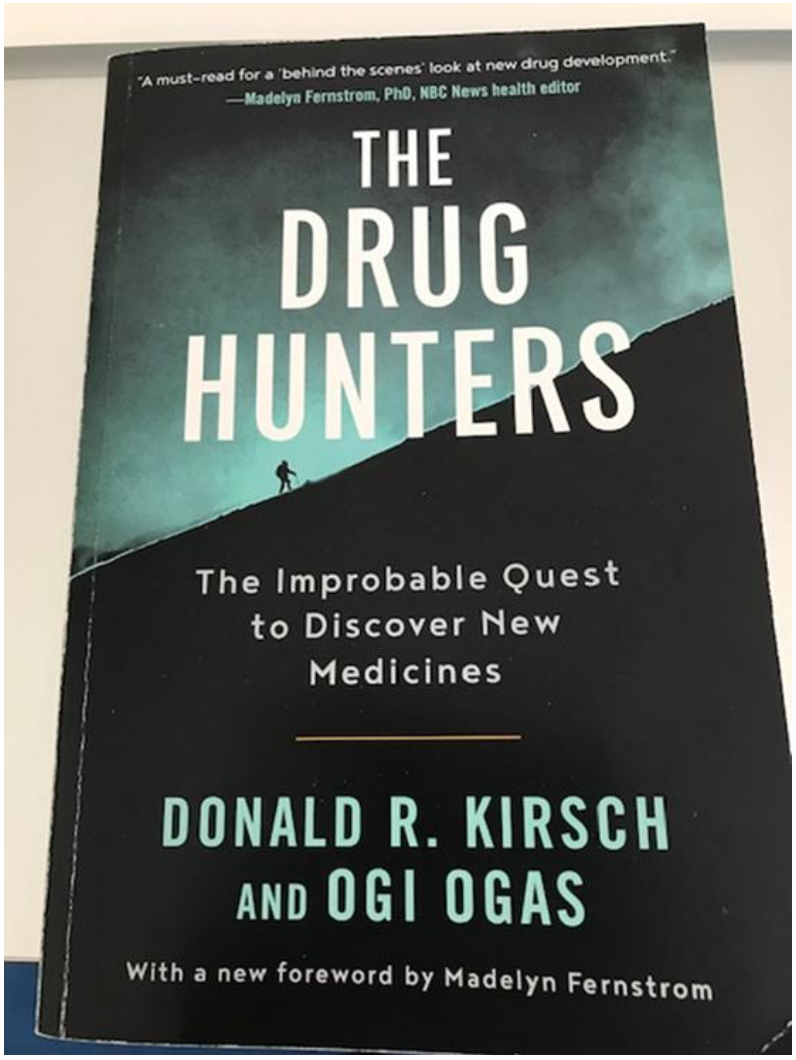
FDA Approval

- FDA Review and Approval may take up to 10 months.
- Different Tracks
- Phase IV : Post Marketing phase to gather more information about Safety, efficacy, side effects and adverse effects.


Drug Discovery & Development-Timeline
DRUG DISCOVERY
PRECLINICAL
CLINICAL TRIALS
FDA REVIEW
10,000 COMPOUNDS
250 COMPOUNDS
5 COMPOUNDS
1 FDA APPROVED DRUG
~6.5 YEARS
~7 YEARS
~1.5 YEARS

Future Prospects




"A must-read for a 'behind the scenes' look at new drug development."
—Madelyn Fernstrom, PhD, NBC News health editor
THE DRUG HUNTERS
The Improbable Quest to Discover New Medicines
DONALD R. KIRSCH AND OGI OGAS
With a new foreword by Madelyn Fernstrom