

Molecular Basis of Diseases II

Introduction

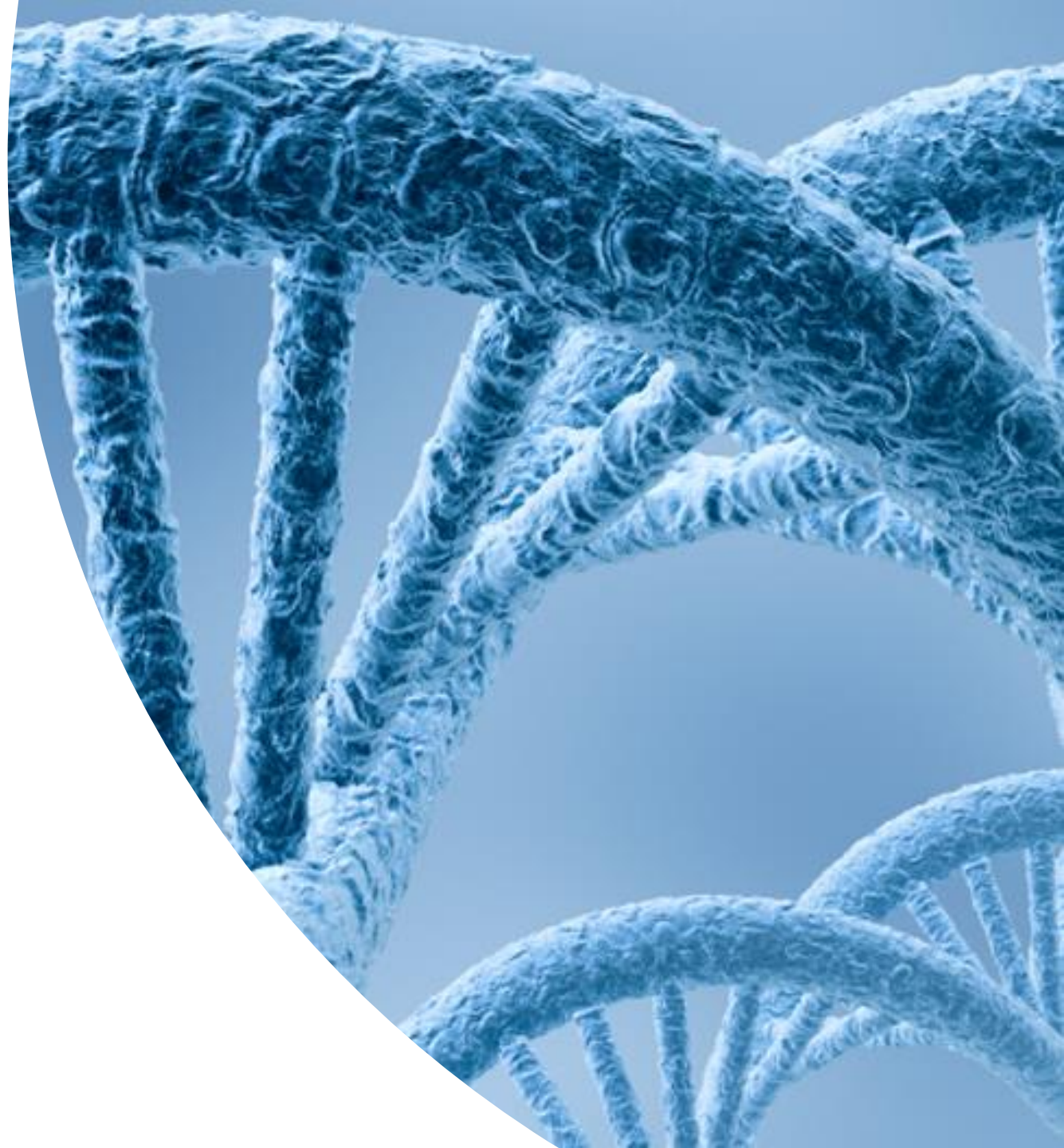
By

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Lesson Outcomes

- Describe the molecular basis of diseases
 - Receptor structure and function
 - Use of molecular biology approach



Targets for Drug Action



- Receptors
- Ion channels
- Enzymes
- Transporters (carrier molecules)

Match the therapeutic class of the following drugs from options at the bottom.

Amlodipine (Norvasc®)

Losartan (Cozaar®)

Sildenafil (Viagra®)

Fluoxetine (Prozac®)

Phosphodiesterase 5 inhibitor

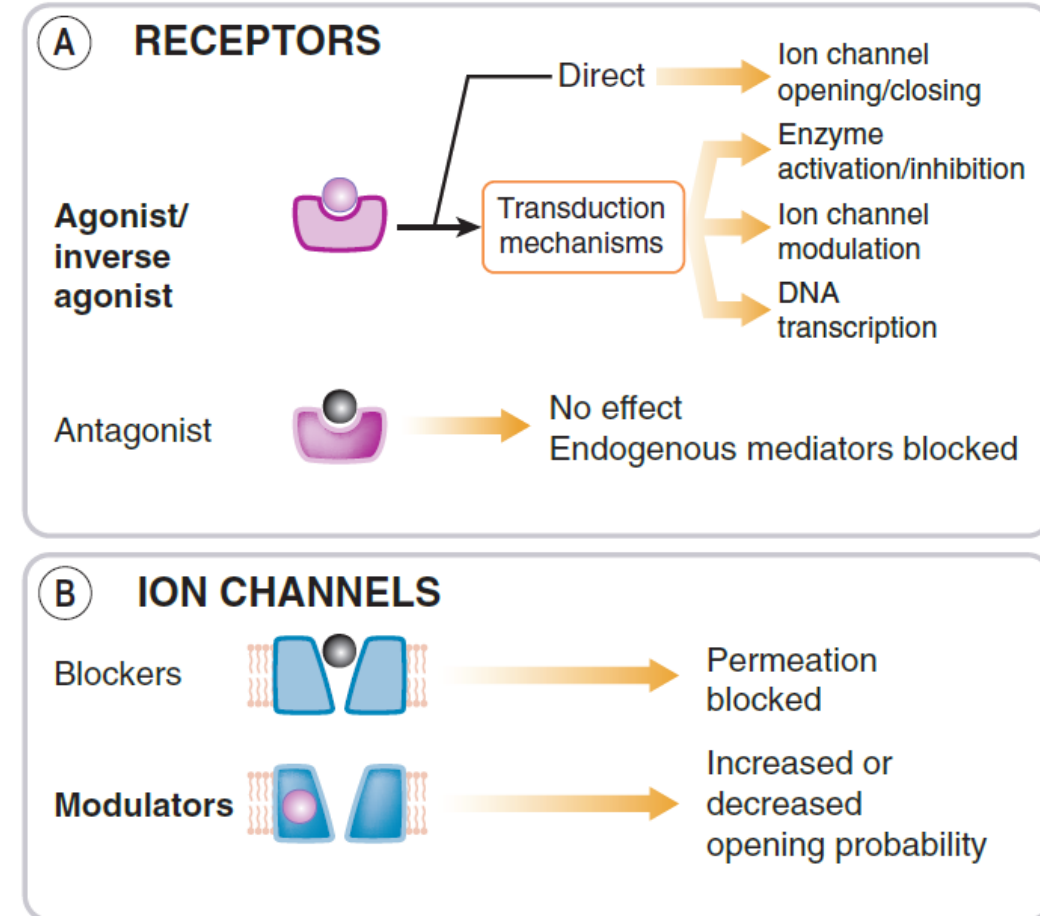
Angiotension receptor blocker

Calcium channel blocker

Selective serotonin reuptake inhibitor

Drug Targets

- Receptors
 - Sensing elements in the system of chemical communications
 - Coordinate function of all the different cells in the body
 - Ligands - hormones, transmitters and other mediators
- Ion channels
 - Gateways in cell membranes
 - Selectively allow the passage of particular ions
 - Open or close by a variety of mechanisms
 - Two important types - ligand-gated channels and voltage-gated channels



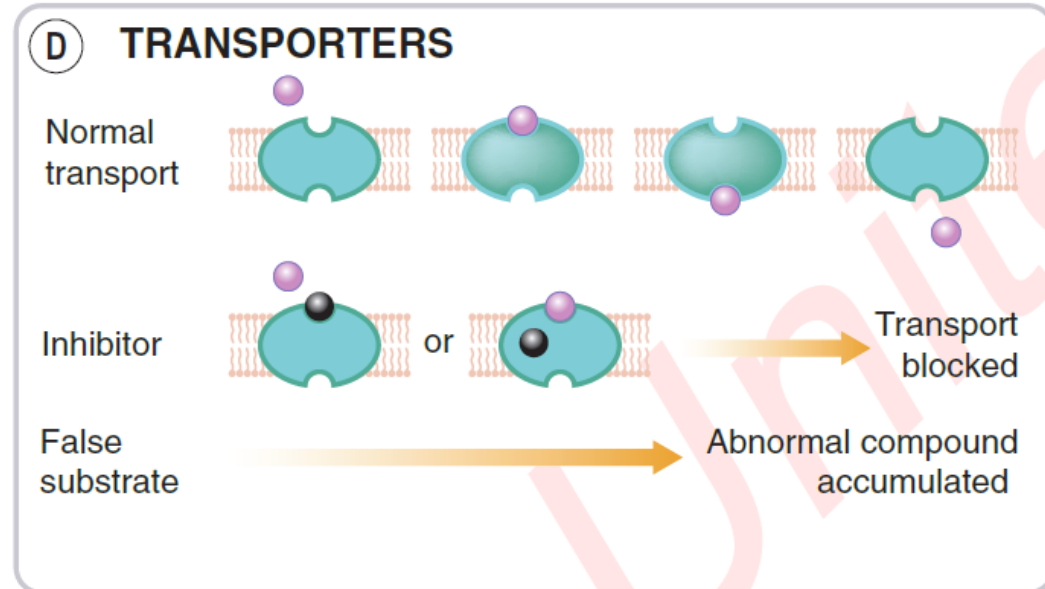
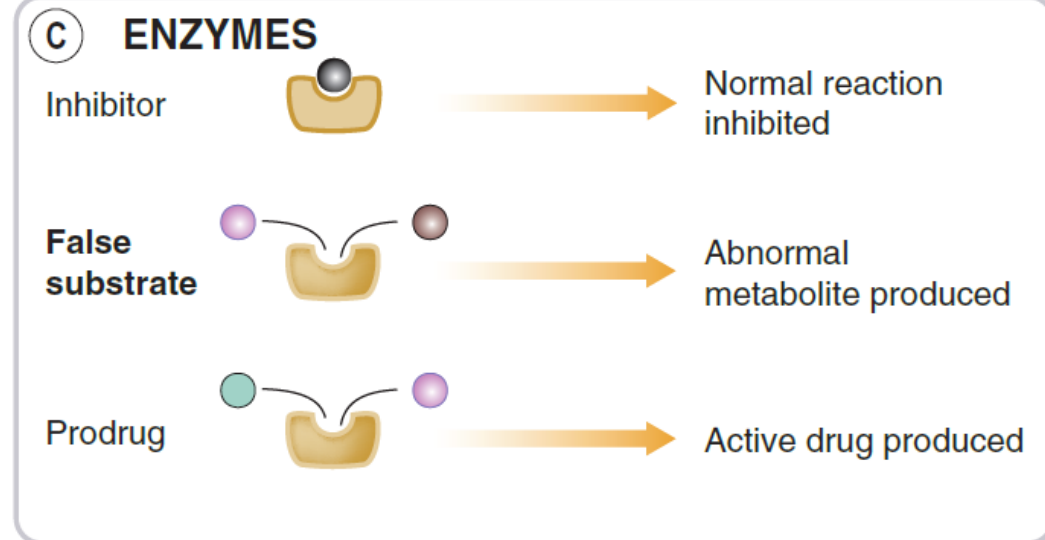
Drug Targets

- Enzymes

- Catalysts mediating various biochemical reactions
- Many drugs serve as enzyme inhibitors
- Prodrugs require enzyme activation

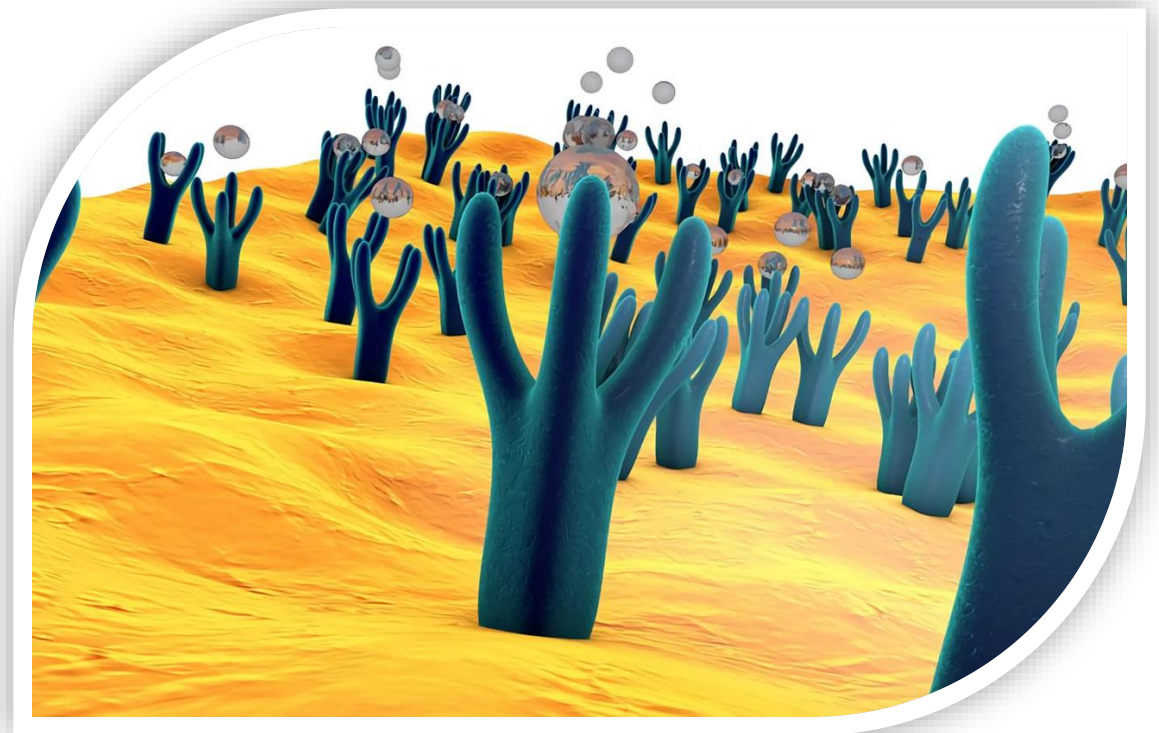
- Transporters

- Movement of ions and small molecules across cell membranes
- Renal tubule, intestinal epithelium, blood–brain barrier, nerve terminals



Receptors

- A protein molecule usually found inside or on the surface of a cell, that receives chemical signals from outside the cell.
- Four major classes of proteins
 - Ligand-gated ion channels
 - G-protein coupled receptors
 - Kinase-linked and related receptors
 - Nuclear receptors

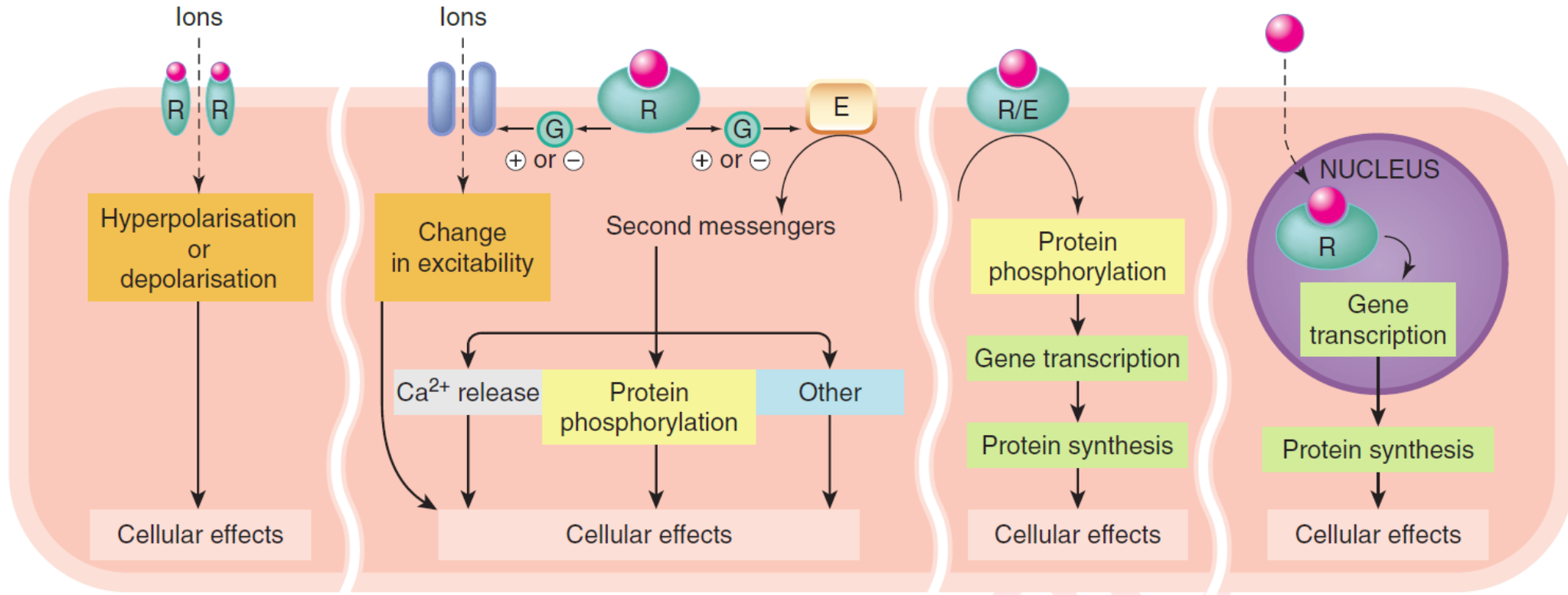


**1.Ligand-gated ion channels
(ionotropic receptors)**

**2.G protein-coupled receptors
(metabotropic)**

3.Kinase-linked receptors

4.Nuclear receptors



Time scale

Milliseconds

Examples

Nicotinic
ACh receptor

Seconds

Muscarinic
ACh receptor

Hours

Cytokine receptors

Hours

Oestrogen
receptor

Receptors – mechanisms of transduction

- **Ligand-gated ion channels**

- Targets for fast neurotransmitters

- **G-protein coupled receptors**

- Also called metabotropic receptors or 7-transmembrane (7-TM or heptahelical) receptors.
- Coupled to intracellular effector systems primarily via a G proteins
- Receptors for many hormones and slow transmitters

- **Kinase-linked and related receptors**

- Extracellular ligand-binding domain linked to an intracellular domain by a single transmembrane helix
- Receptors for protein mediators

- **Nuclear receptors**

- Regulator of gene transcription

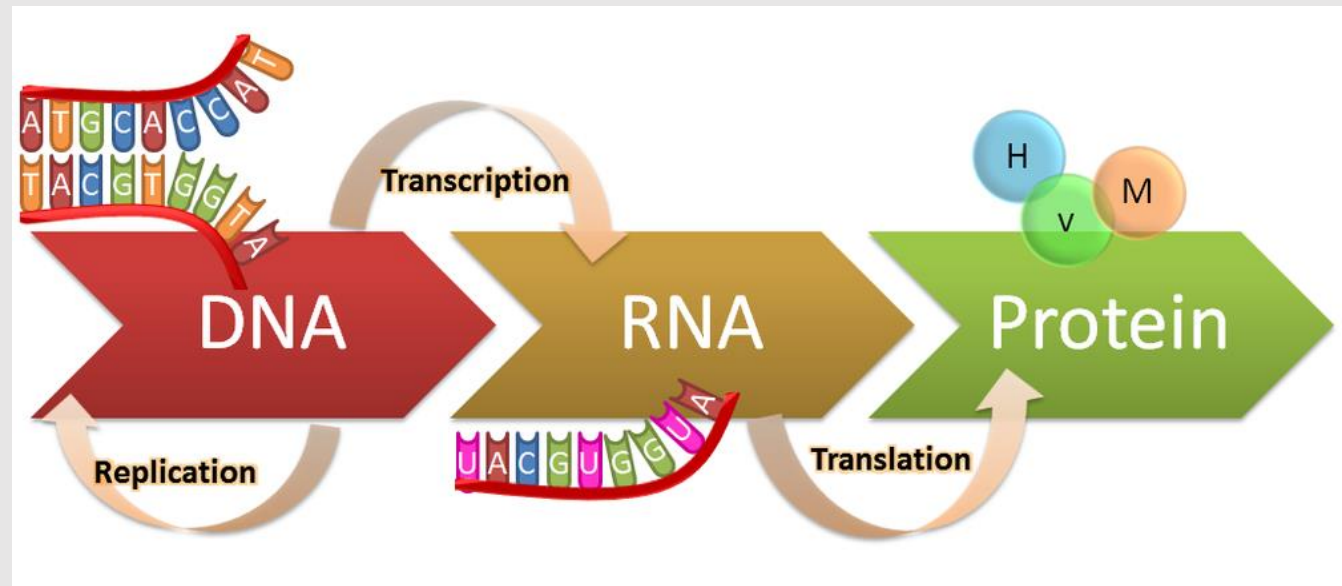
Receptors – structures and functions

- Study of structure-function relationship
 - Important basis for understanding their roles in diseases
- Various ways / approaches to investigate
 - *In vitro* and *in vivo* models
 - Molecular biology methods
 - Examples
 - *In vitro* - gene cloning and recombinant protein expression
 - *In vivo* - Gene knock-out mice, various disease animal models

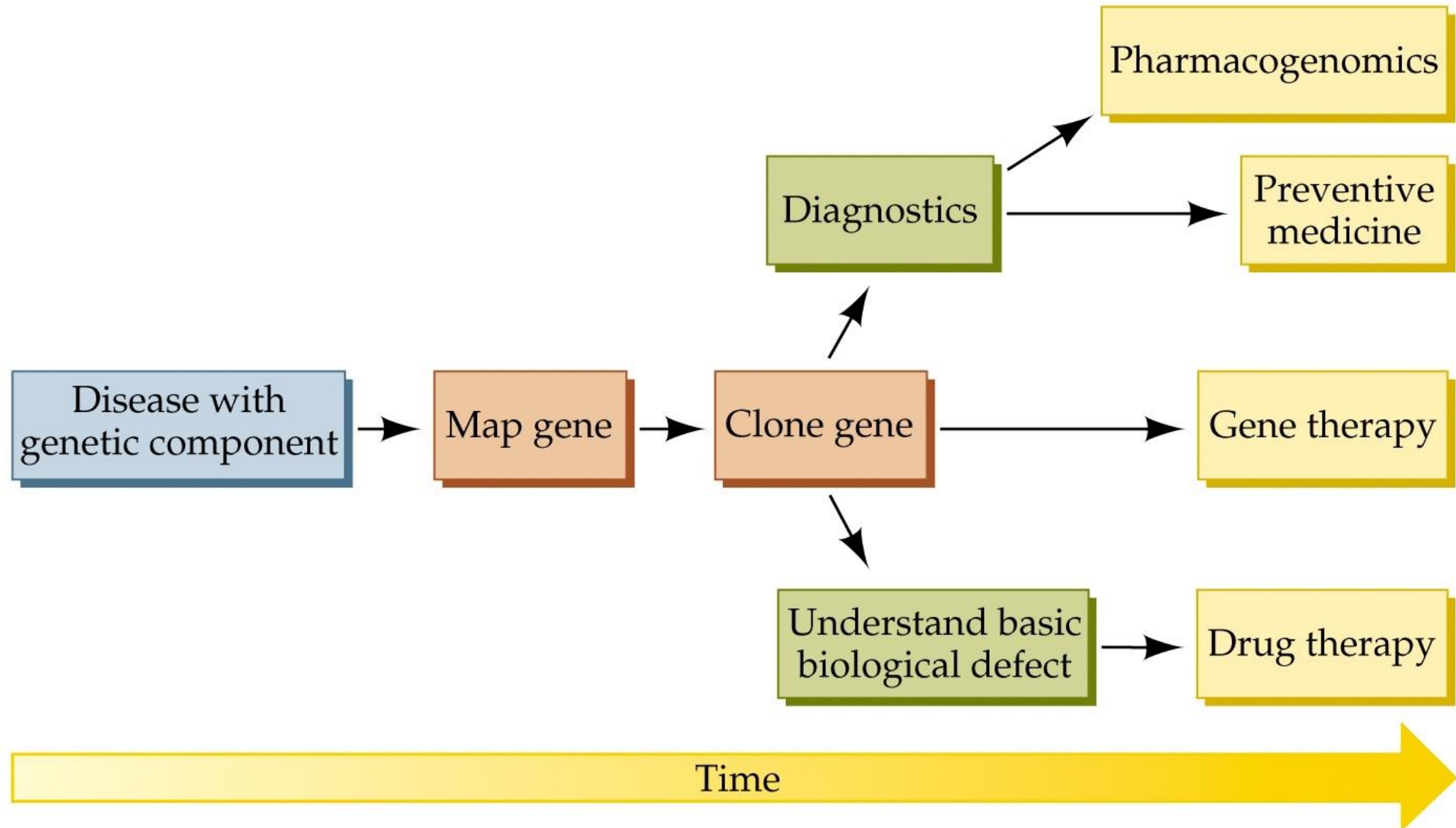
Molecular biology and Medicine



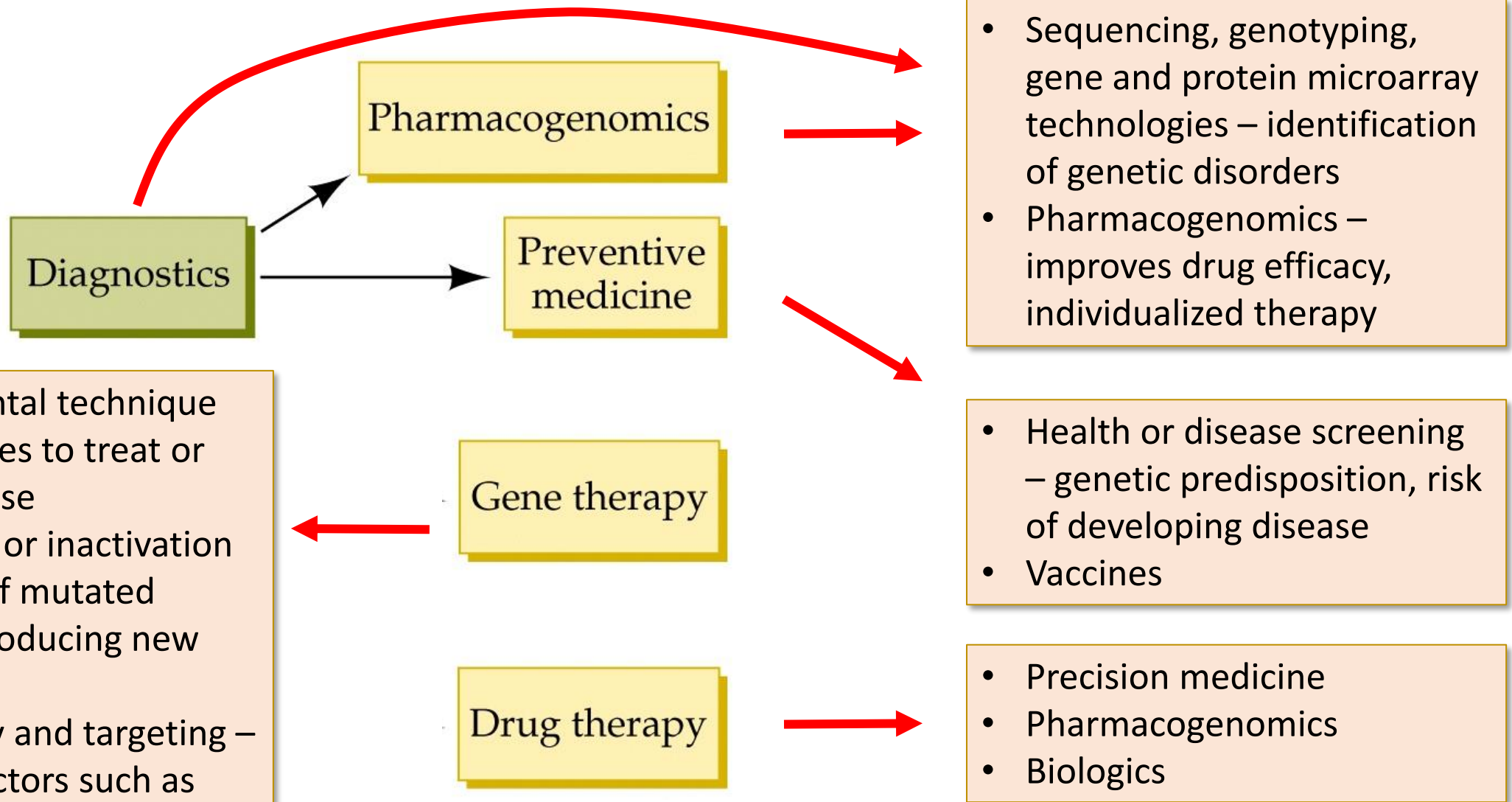
Central dogma of molecular biology



Application of molecular Biology in Medicine



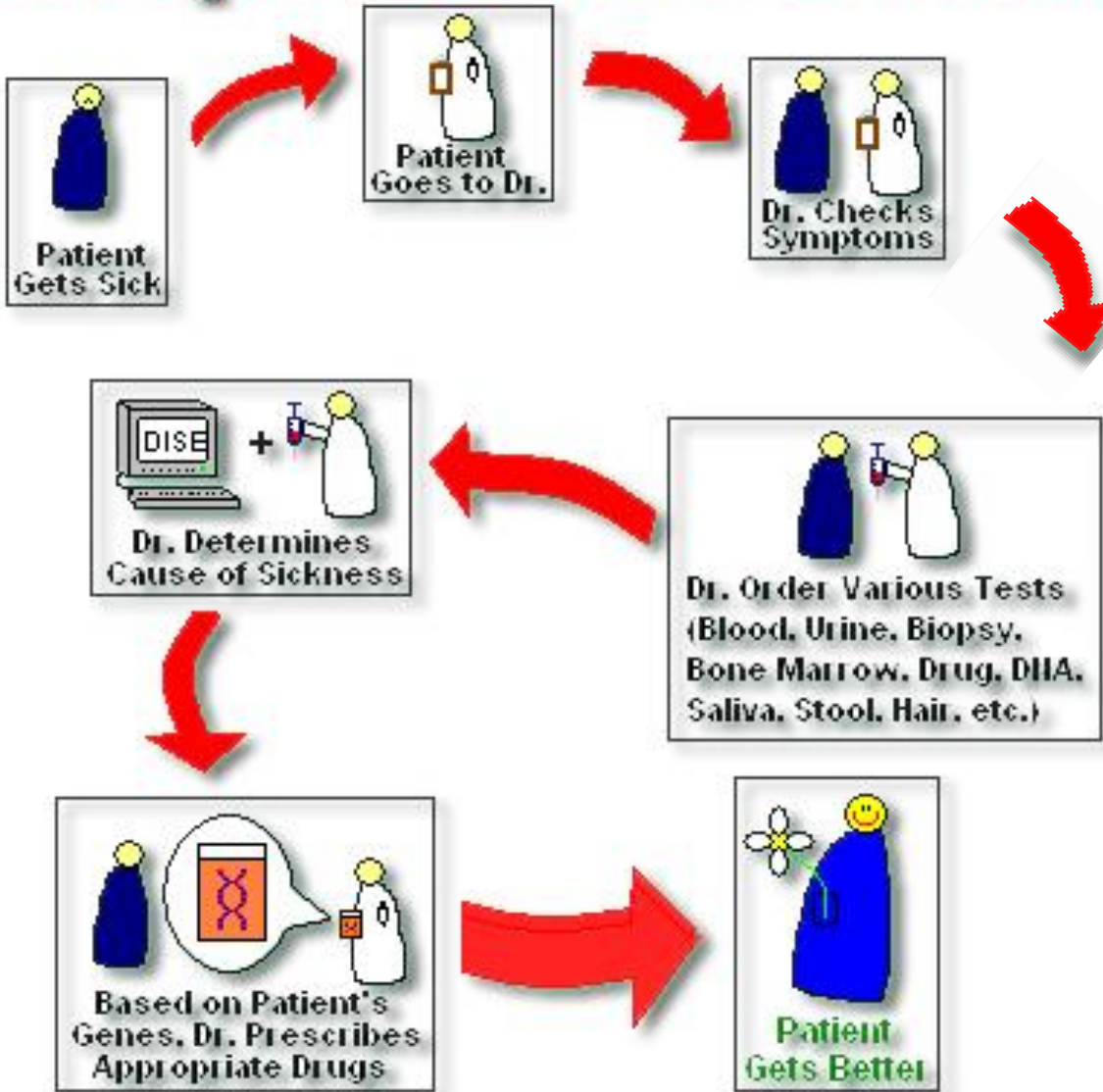
Application of molecular Biology in Medicine



- An experimental technique that uses genes to treat or prevent disease
- Replacement or inactivation (knock-out) of mutated genes, or introducing new gene
- Gene delivery and targeting – using viral vectors such as adenovirus
- CRISPR gene editing

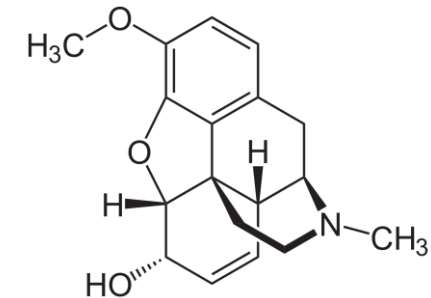
CRISPR - clustered regularly interspaced short palindromic repeats

Hope for the Future



Codeine dosing guidelines

CYP2D6 extensive metaboliser
CYP2D6 poor metaboliser
CYP2D6 intermediate metaboliser
CYP2D6 ultra-rapid metaboliser



Use normal dose
Use normal dose but monitor response
Avoid codeine

Summary

- Describe the molecular basis of diseases
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