Biochemistry of human organs and tissues I

EVROPSKÁ UNIE
Evropské strukturální a investiční fondy
Operační program Výzkum, vývoj a vzdělávání

MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY

Organs and tissues

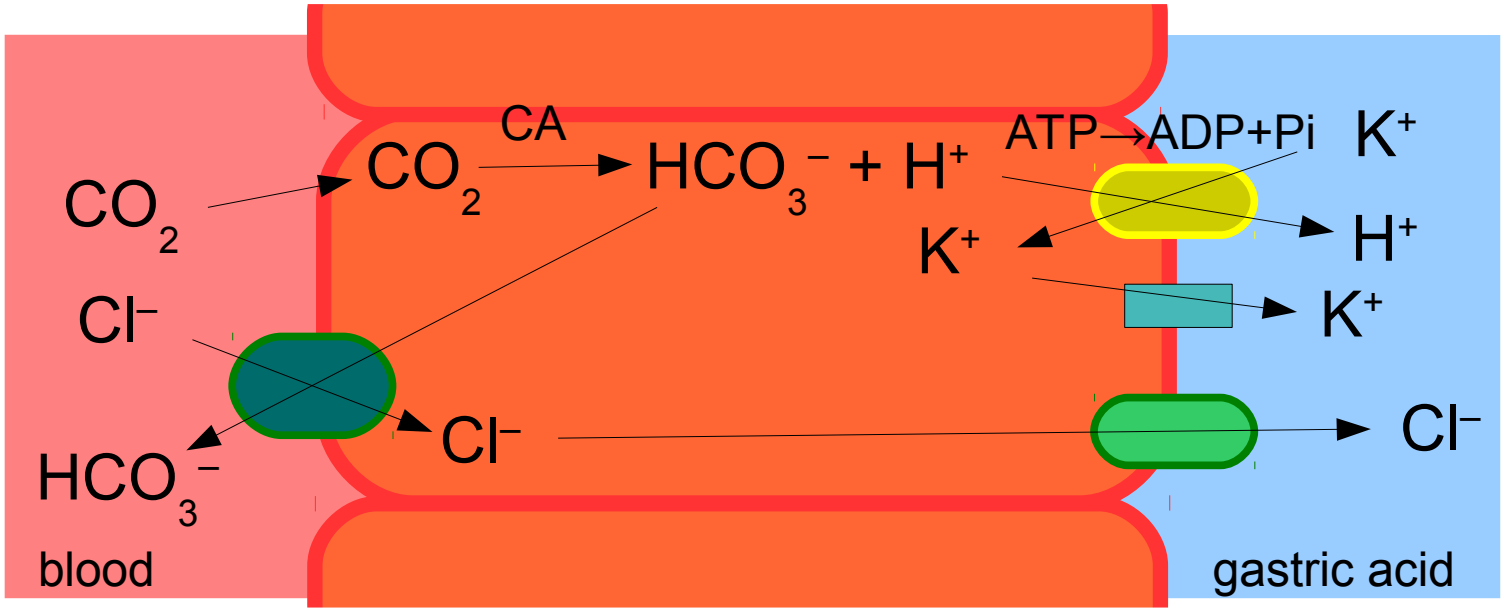
In this pair of lectures we will show biochemistry typical for human organs and tissues. We will start in the digestive tract and we will follow nutrients to blood circulation. Next we show other features of blood such as immunity or coagulation. Then we will mention biochemistry of liver, adipose tissue, kidney and muscles. At the end we will look at nervous system and hormonal signaling.

- digestive tract
- blood and immune system
- liver
- adipose
- kidney
- muscles
- connective tissues
- nervous system, senses

Digestive tract

Saliva - digestive function (α-amylase)
- protective function (antibodies, lysozyme)
- other functions (mucin – rheological properties)

Gastric acid - digestive function (HCl, pepsin, chymosin, lipase)
- absorption of some nutrients
- other functions (mucin)

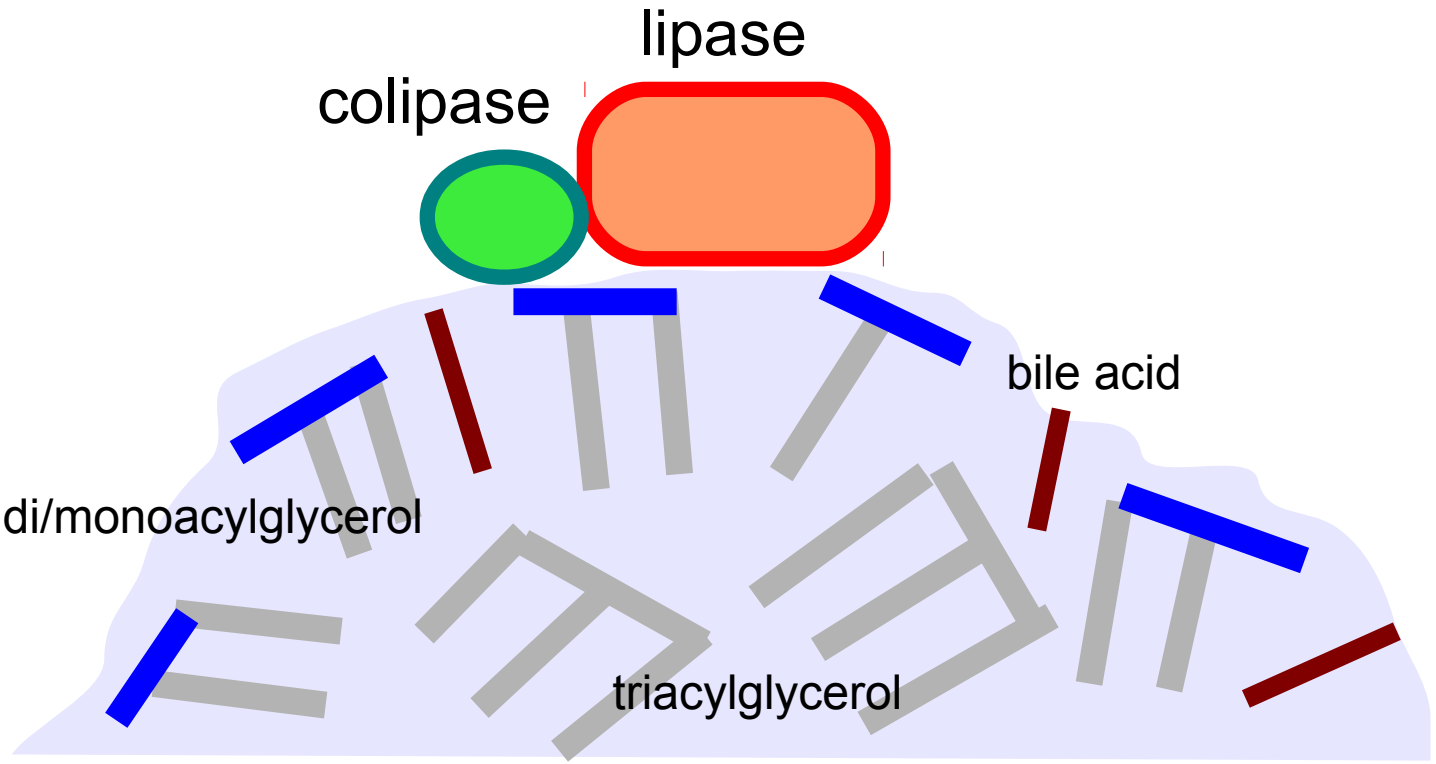


Digestive tract contains many hydrolytic enzymes. Important part of stomach is gastric acid containing HCl. HCl is produced by active transport of protons into the stomach. Other proteins such as potassium and chloride channel or carbonic anhydrase (CA) participate in this process.

Digestive tract

Pancreatic juice

- neutralization of gastric acid (HCO_3^-)
- digestive function (trypsin, chymosin, elastase, carboxypeptidase, α-amylase, lipase, colipase, phospholipase, nucleases, …)

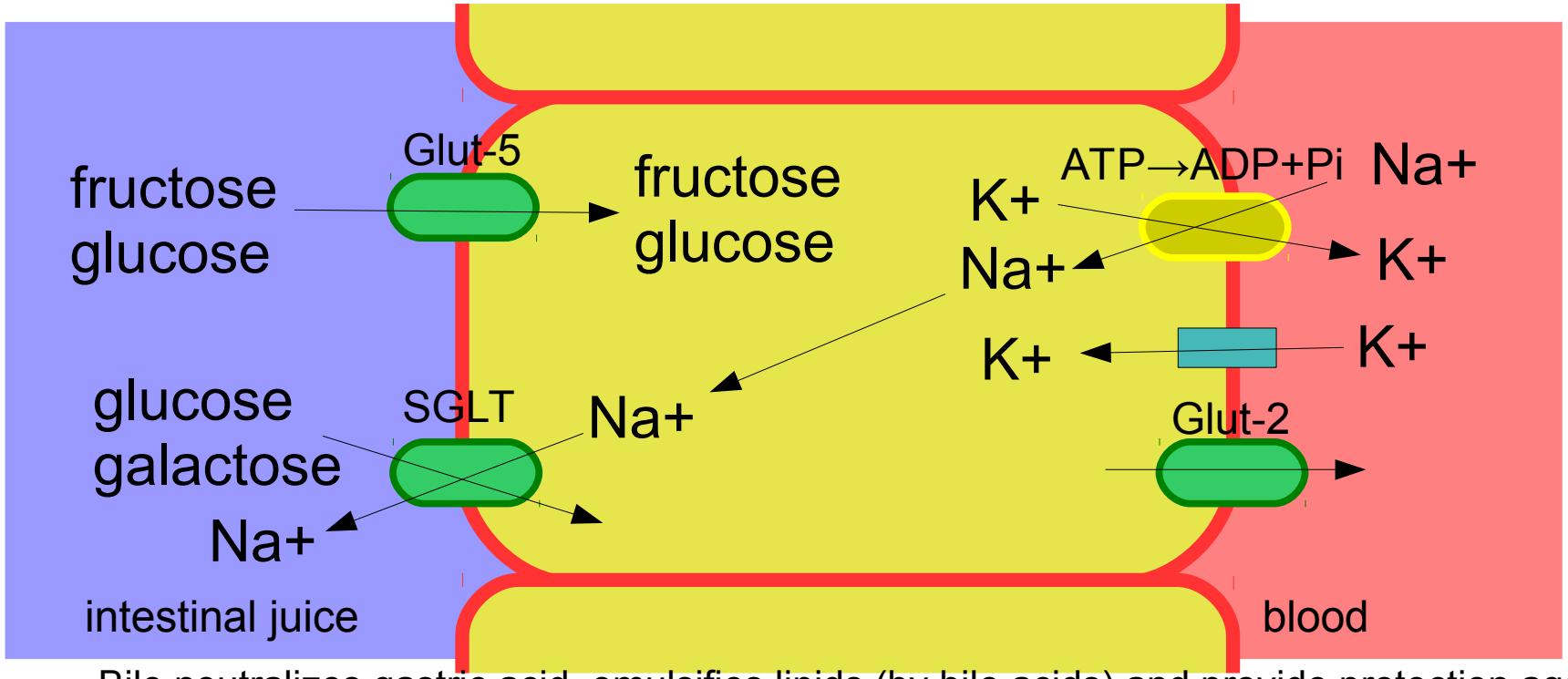


Pancreatic juice hydrolyses many nutrients. Lipase (with its helper colipase) is an interesting enzyme because it works at the phase interface.

Digestive tract

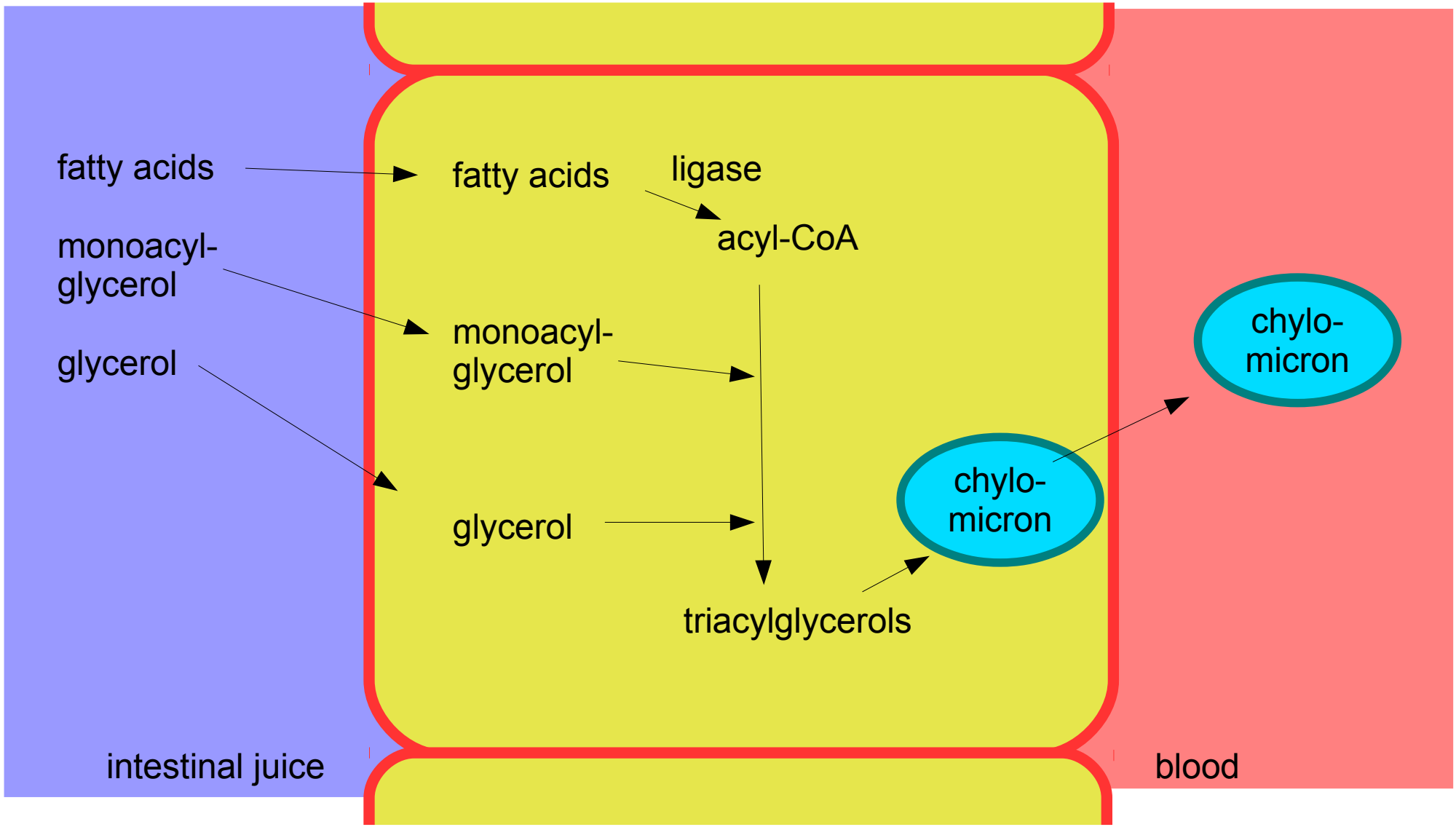
Bile - emulgation (bile acids)
- neutralization of gastric acid (HCO_3^-)

Intestinal juice
- digestive function (peptidases, glycosidases, lipases, phospholipases, nucleases etc.)



Bile neutralizes gastric acid, emulsifies lipids (by bile acids) and provide protection against many microorganisms. Transport of saccharides may be active (sodium-glucose linked transporter, SGLT) or passive (Glut).

Lipid resorption, resynthesis, lipoproteins



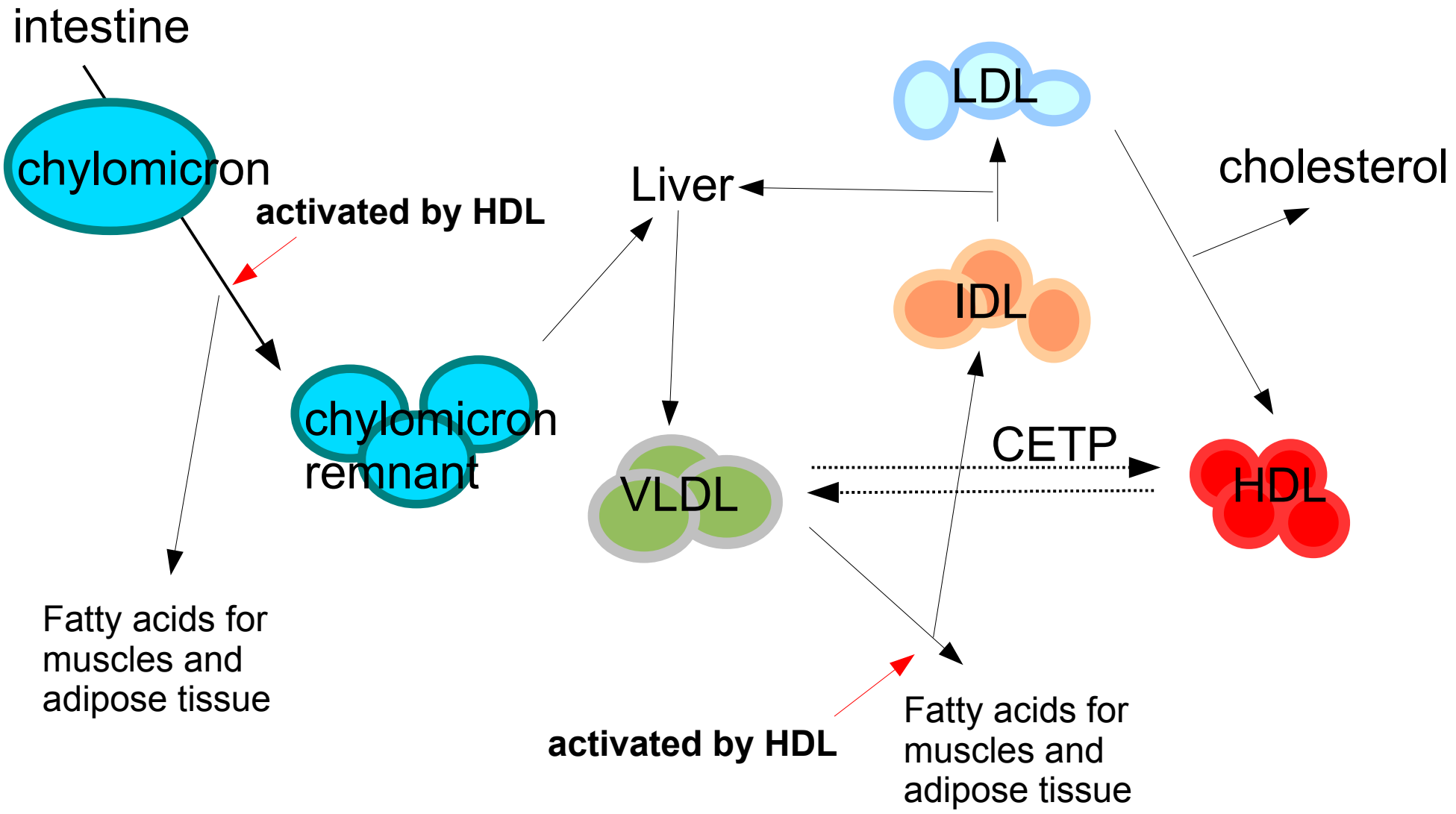
Lipids are insoluble in water. Thus they cannot be simply transported by the blood stream. Instead they are transported in the form of lipid-protein complexes – lipoproteins. In order to control lipoprotein formation, composition, release etc. intestinal cells hydrolyse tryacylglycerols and then resynthesize them. Largest lipoprotein particles, which are produced by digestive tract, are called chylomicrons.

Lipid resorption, resynthesis, lipoproteins

Lipoproteins are microscopic (5-1000 nm) particles composed of triacylglycerols, phospholipids, cholesterol, acylated cholesterol (cholesterol esters) and proteins (known as apolipoproteins). Largest chylomicrons deliver triacylglycerols from digestive tract to muscles, adipose tissue and to liver. In this process they lose lipid content and become chylomicron remnants. These are uptaken by liver. Liver synthesizes very low density lipoproteins (VLDL). These deliver triacylglycerols to muscles and adipose tissue. In this process they lose triacylglycerols and change to intermediate (IDL) and low density lipoproteins (LDL). These particles can be reuptaken by liver. Another lipoprotein particles are high density lipoproteins (HDL). They act as scavengers of cholesterol from the body. Then they are reuptaken by liver and cholesterol is degraded. While LDL are associated with atherosclerosis (“bad” cholesterol), HDL is protective (“good” cholesterol). Hypercholesterolemia is treated by cholesterol lowering drugs called statins. They inhibit hydroxymethylglytaryl-CoA dehydrogenase in the cholesterol biosynthesis pathway. However, they lower good as well as bed cholesterol. Therefore cholesteryl ester transfer protein (CETP) was proposed as a new drug target. This protein facilitates exchange of triglycerides from VLDL or LDL for cholesterol esters from HDL, and vice versa. Several compounds inhibiting the function of this protein have been developed, but their medicinal application was disappointing.

Lipid resorption, resynthesis, lipoproteins

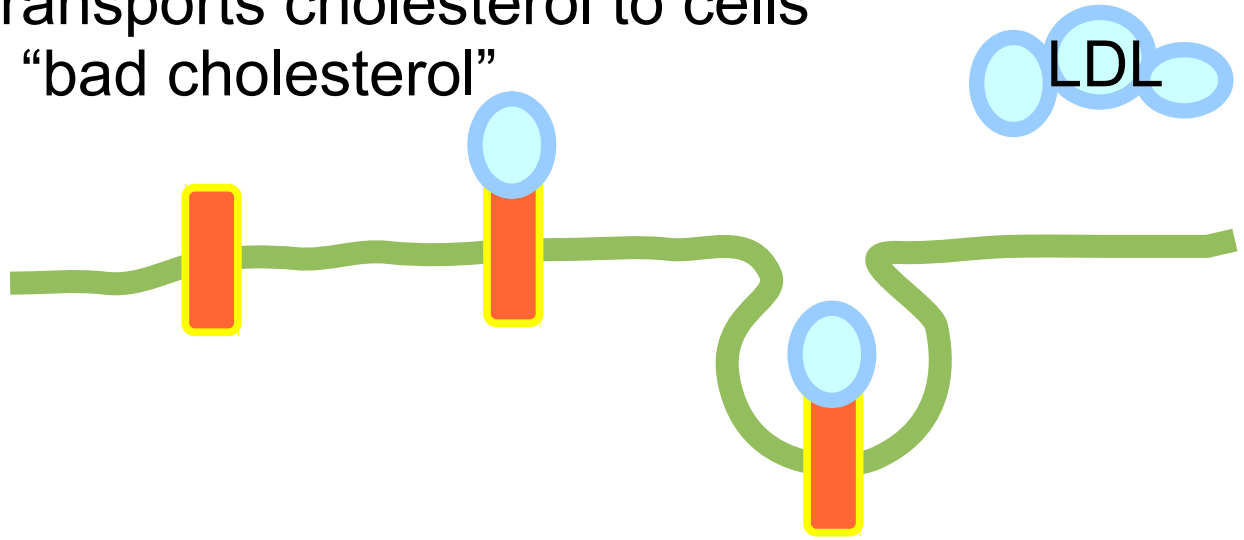
Composition: triacylglycerols, cholesterol, phospholipids, proteins (1-50 %, apoproteins)



Lipid resorption, resynthesis, lipoproteins

HDL: transports cholesterol to liver for degradation
"good cholesterol"

LDL: transports cholesterol to cells
"bad cholesterol"



CETP – cholesterol ester transfer protein

Torcetrapib:

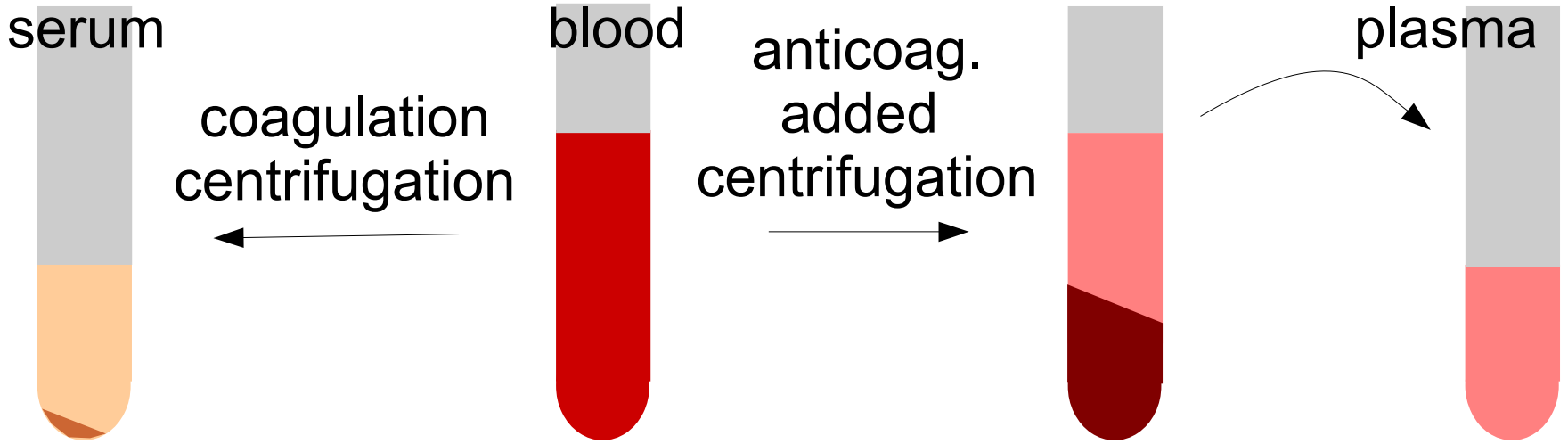
November 30, 2010 – "*This will be one of the most important compounds of our generation*" Jeff Kindler, Pfizer's chief executive

December 2, 2010 – Pfizer announces halt of phase III clinical trials of Torcetrapib

Blood

Roles: - transport of oxygen, carbon dioxide, nutrients
- water distribution
- acidobasic homeostasis
- thermoregulation
- immunity
- self-protection (blood coagulation)

Composition: ~45% of cellular elements



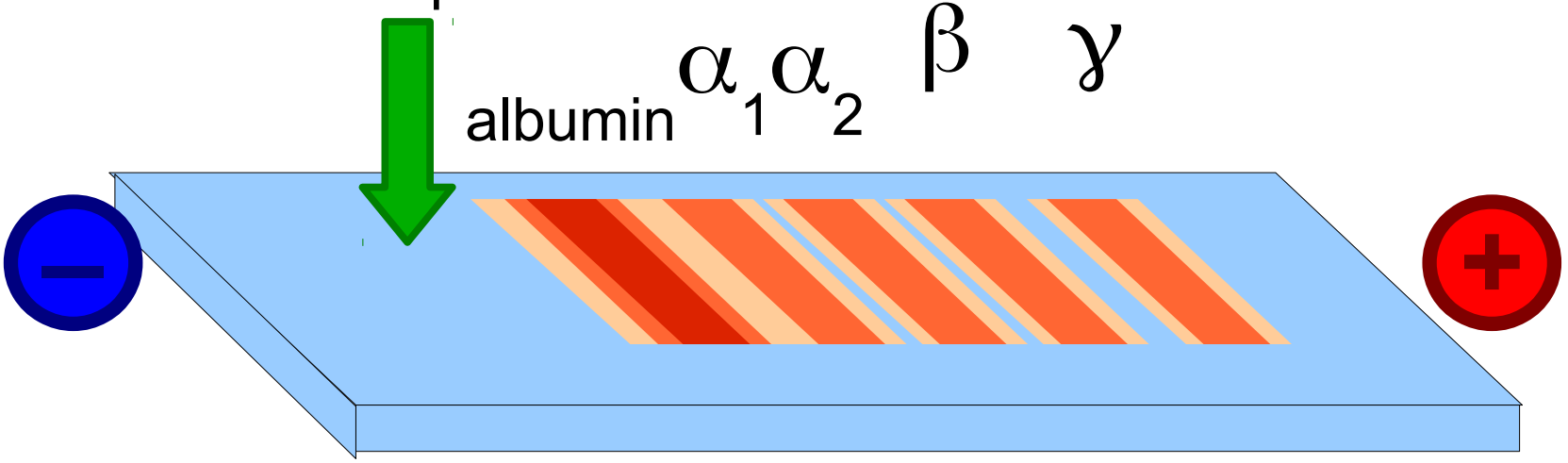
Hematopoiesis: bone marrow, fetal spleen and liver

Blood after removal of blood elements (erythrocytes, white cells, platelets) is called plasma. Blood naturally coagulates and after removal of a coagulum we can get blood serum. It is possible to avoid coagulation by addition of metal chelating agents such as EDTA.

Blood

Composition of plasma:

- salts (mostly Na^+, Cl^-, 0.15M NaCl, 0.9% NaCl)
- glucose, lactate, urea, amino acids, triacylglycerols, cholesterol
- proteins 6-8 %

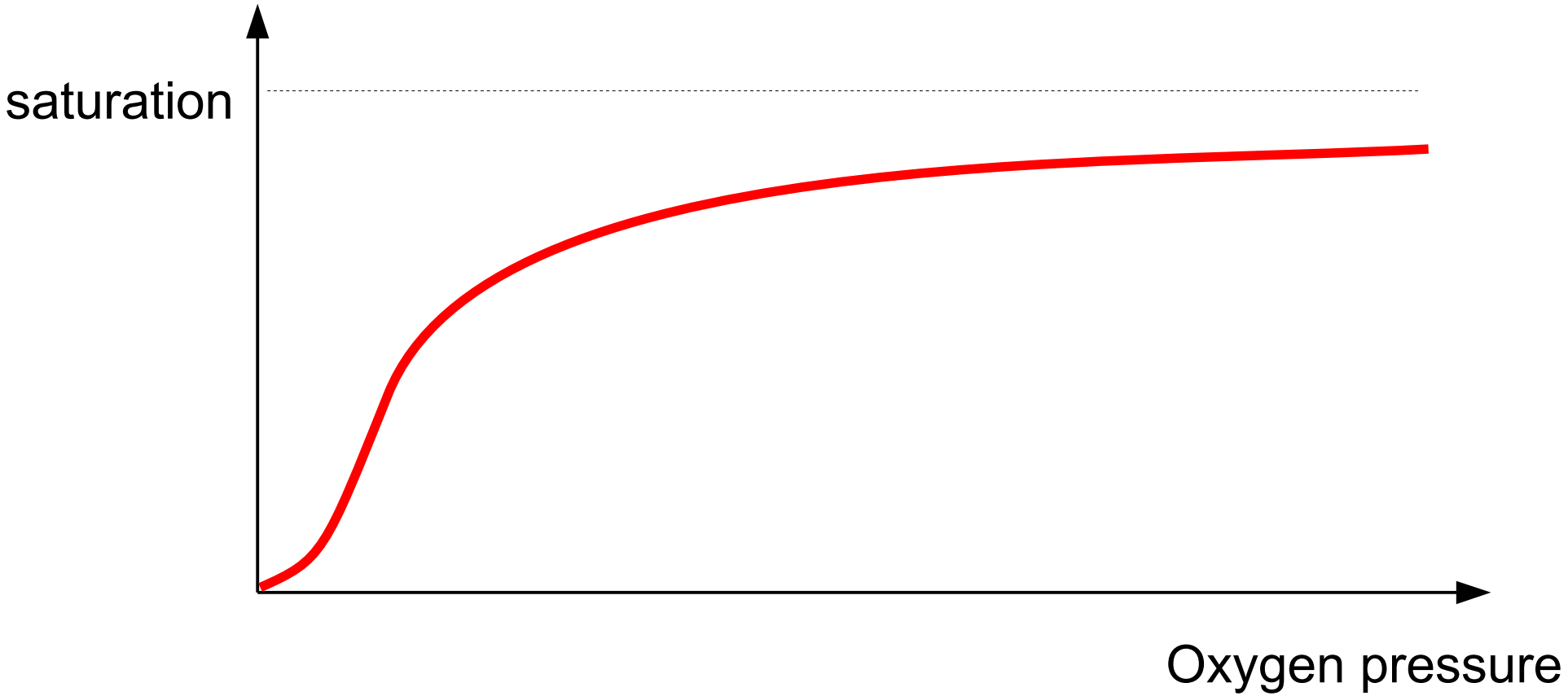


albumin – colloidal, transport and osmotic function

Serum proteins can be separated by a traditional electrophoresis procedure in agarose gel. Agarose (purified algal polysaccharide) is mixed with buffer and heated. While cooling down it forms a gel. It is possible to make a well in the gel, load it with sample and apply electric field. After separation it is possible to visualize separated proteins by stain them by a dye or by precipitation with antibodies.

Blood

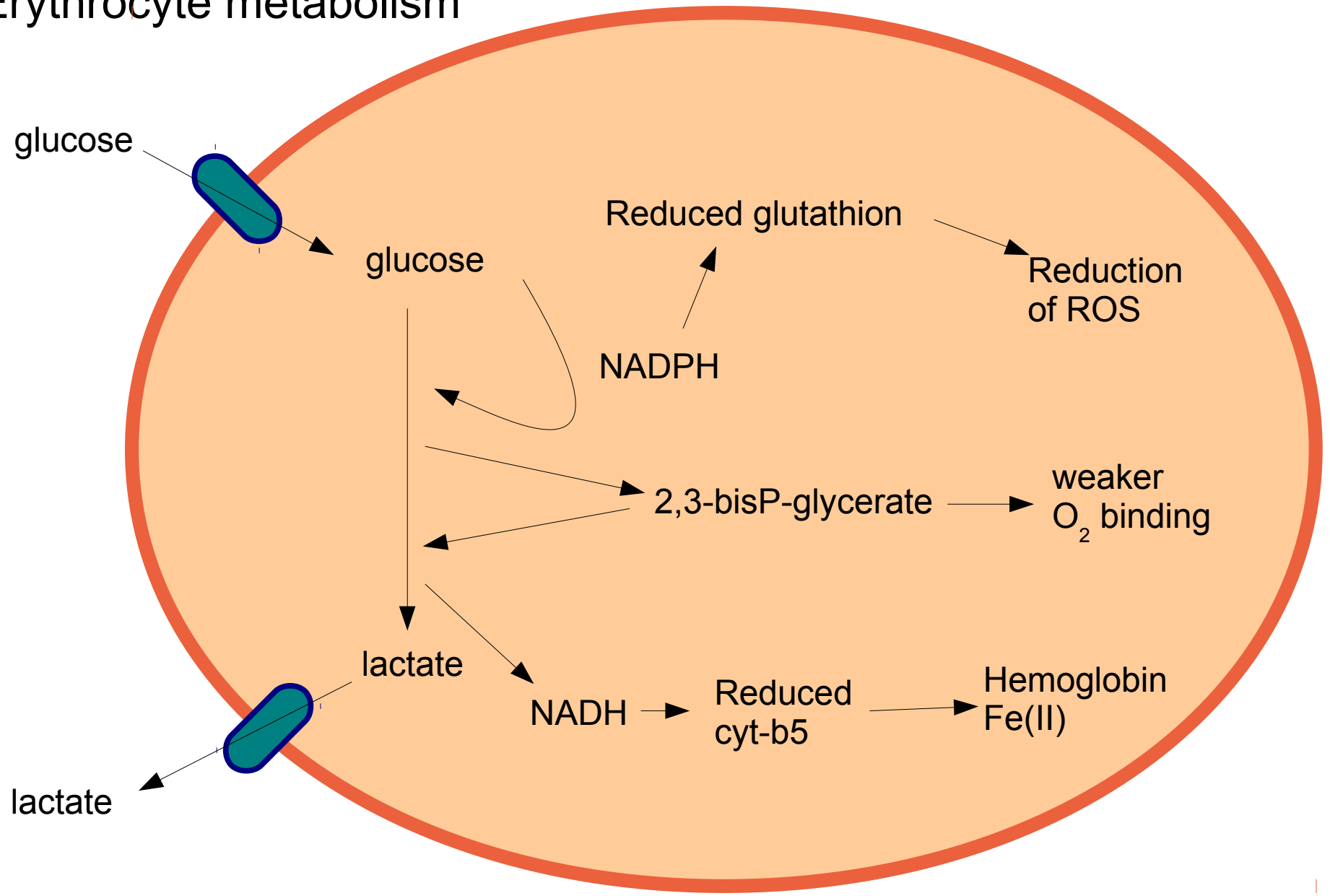
Oxygen transport
hemoglobin – allosteric effect



Blood transport oxygen. Saturation curve of hemoglobin-oxygen complex is not hyperbolic (as for usual binding proteins). Instead it is sigmoid. This makes it possible to almost fully load hemoglobin in lungs and release almost all oxygen in tissues. The reason behind this was explained in the lecture dedicated to regulation of enzymatic activities.

Blood

Erythrocyte metabolism



Blood

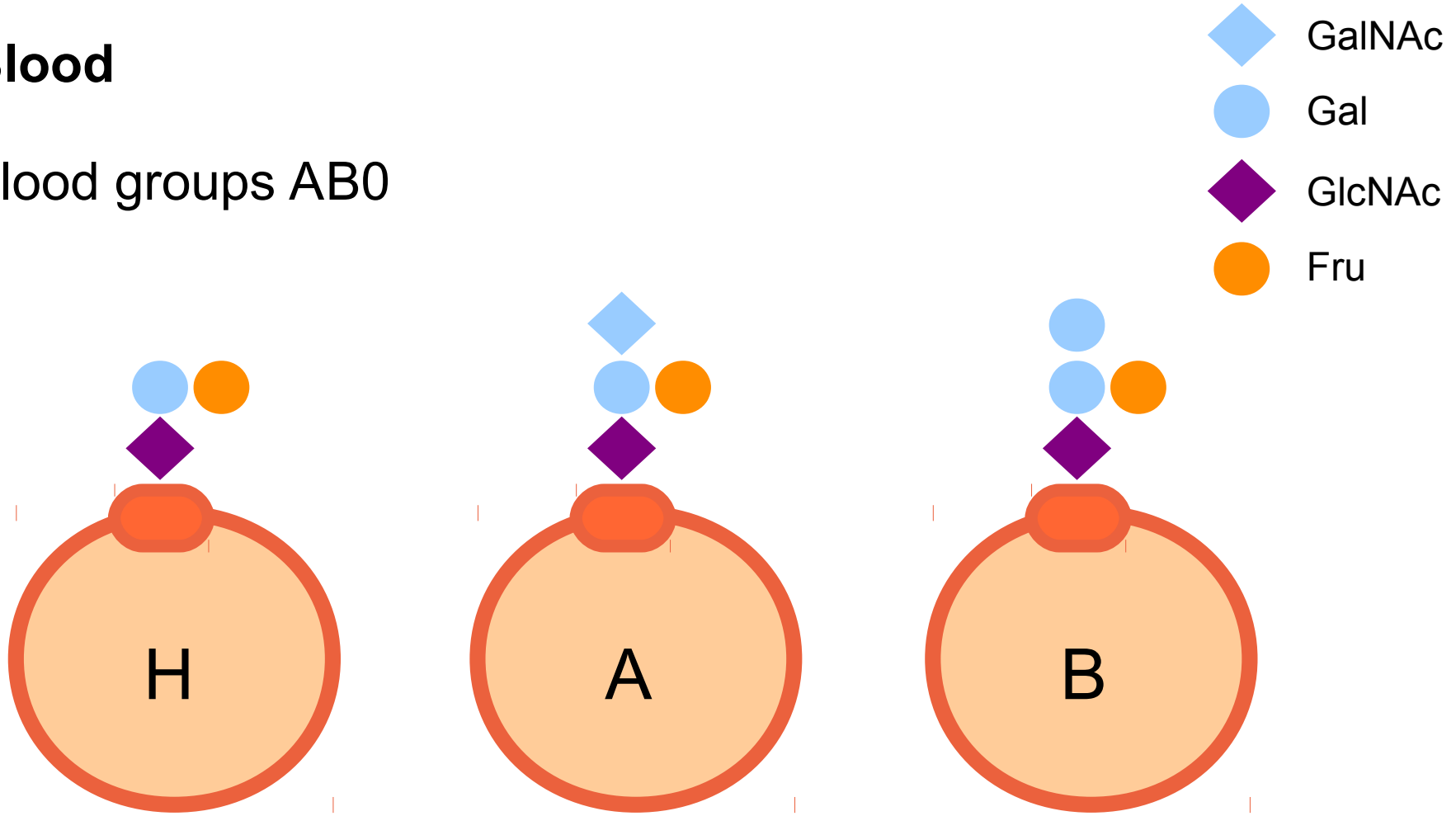
Erythrocyte metabolism

Erythrocytes are strange “cells”. “Cells” (but not cells) because they lose nucleus (in mammals) and mitochondria in the process of hematopoiesis. Therefore they cannot divide, respire, degrade fatty acids etc. Erythrocytes metabolize glucose to lactate. Produced ATP is used to fuel ion pump, which maintain concentration gradients on the cytoplasmatic membrane. Erythrocytes can synthesize 2,3-bisphosphoglycerate in glycolysis. This compound influences the function of hemoglobin. Some NADH produced can be used to reduce iron in hemoglobin to II form. Pentose phosphate pathway is also very intensive in erythrocytes. It produces NADPH, which reduces glutathione. Glutathione reduces oxidative species, which are widespread in erythrocytes.

Erythrocytes carry blood group antigens. Depending on person’s genome, antigen H, A, B or both A and B can be present. People with just antigen H (blood group 0) may produce antibodies against A and B. Therefore they can receive blood transfusion only from blood group 0 donors. In contrast, people with antigens A and B (blood group AB) produce no antibodies and they can receive blood from any donor. Mixing of incompatible bloods causes precipitation (agglutination) of red blood cells. This is visible in a test tube and can be used in diagnostics.

Blood

Blood groups AB0



acceptor donor	A (anti-B)	B (anti-A)	AB (-)	0 (anti-A, anti-B)
A	-	A	-	A
B	A	-	-	A
AB	A	A	-	A
0	-	-	-	-

Immunity

Immune system targets all elements that are foreign to the body and simultaneously it does not target elements that are own to the body. This mechanism is highly specific (difference between own and foreign might be very small). Occasionally it may happen that the immune system targets own elements, which causes autoimmune diseases. Immunity can be classified as innate (non-adaptive) and adaptive. Adaptive immunity can “learn” to recognize new antigens. Human genome is in general the same for all somatic cells, but there are exceptions to this rule. The gene coding antibodies is an example of such exception. This gene undergoes hypermutation, which causes that certain part of the gene (the one coding variable region of antibodies) is variable. The resulting proteins are displayed on surface of these cells. When these cells get in the contact with antigen they are activated to grow and produce antibodies. Specificity for foreign and not own antigens is achieved by elimination of cells coding for antibodies against own antigens in the prenatal development. Only cells not coding for antibodies against own antigens can mature.

Immunity can be also classified as cellular or humoral. Humoral immunity uses antibodies as soluble proteins. These proteins – immunoglobulins – can be applied in many fields including diagnostics, analytical chemistry, affinity purifications and therapies.

Immunity

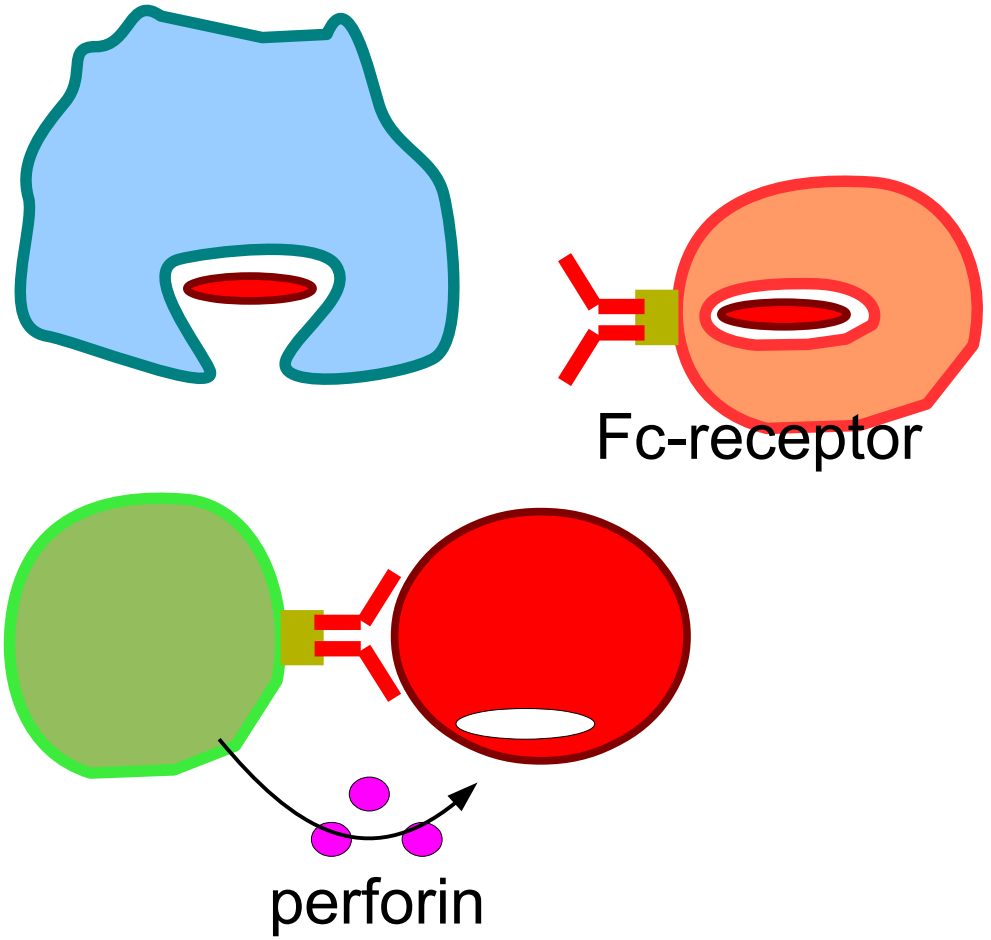
Innate immunity *vs.* adaptive immunity

cellular immunity *vs.* humoral immunity

Innate immunity:
macrophages

granulocytes

NK-cells

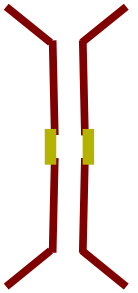


Blood

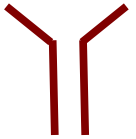
Immune system

Antibodies

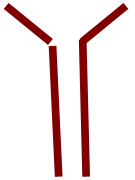
IgA – mostly in intestinal fluid and other secrets



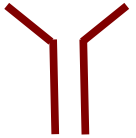
IgD – B-lymphocyte receptor



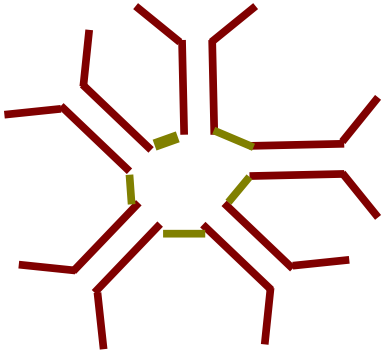
IgE – allergy-related



IgG – ~75 % of all Igs in blood

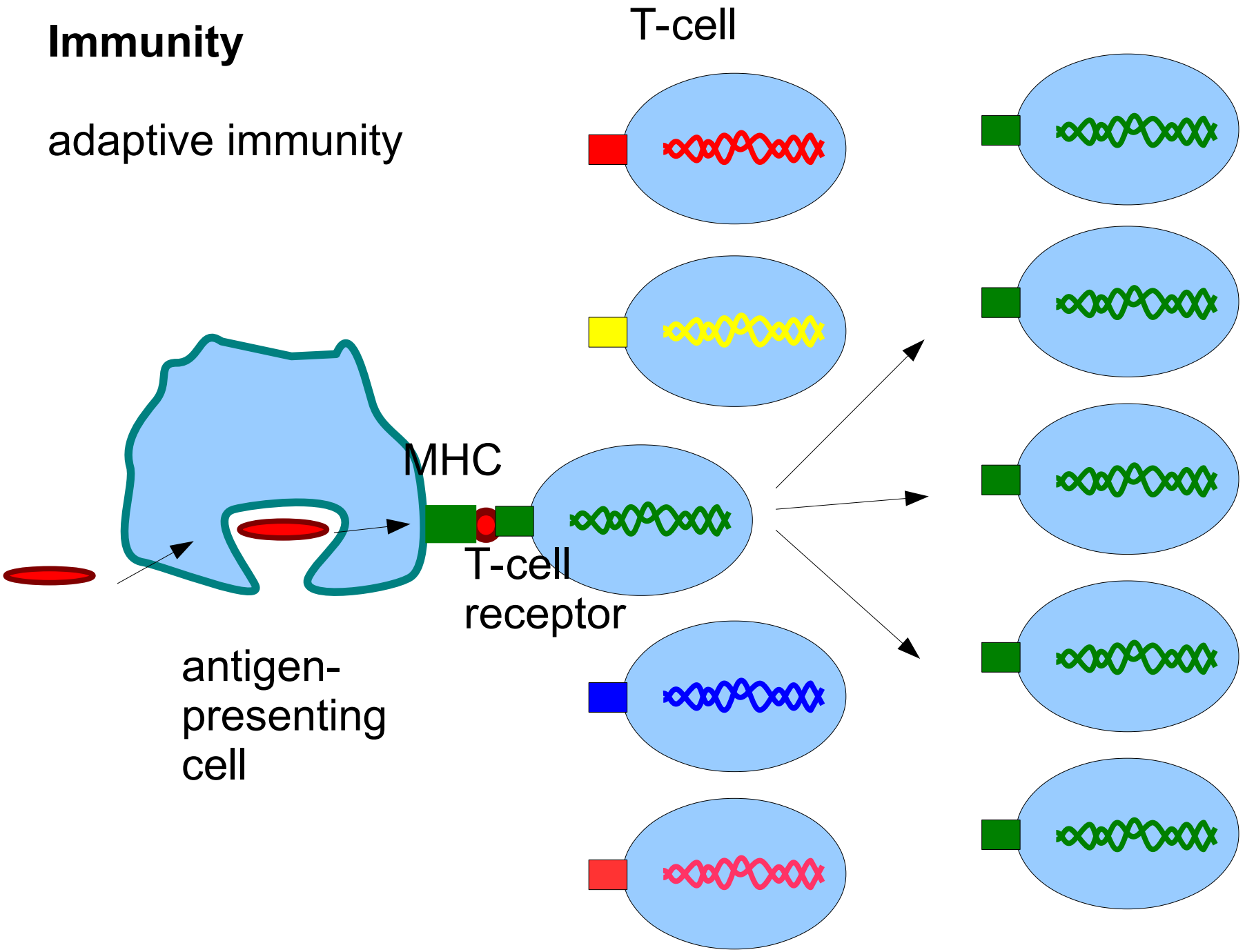


IgM



Immunity

adaptive immunity



Immunity

adaptive immunity

antigen-presenting cell	macrophage B-lymphocytes	almost all cells
MHC	MHC class II.	MHC class I.
T-lymphocyte	helper	cytotoxic
role	activation of antigen-presenting B-cells, production of soluble antibodies	attacking of viral-infected or cancer cell by perforin and granzyme, start of apoptosis