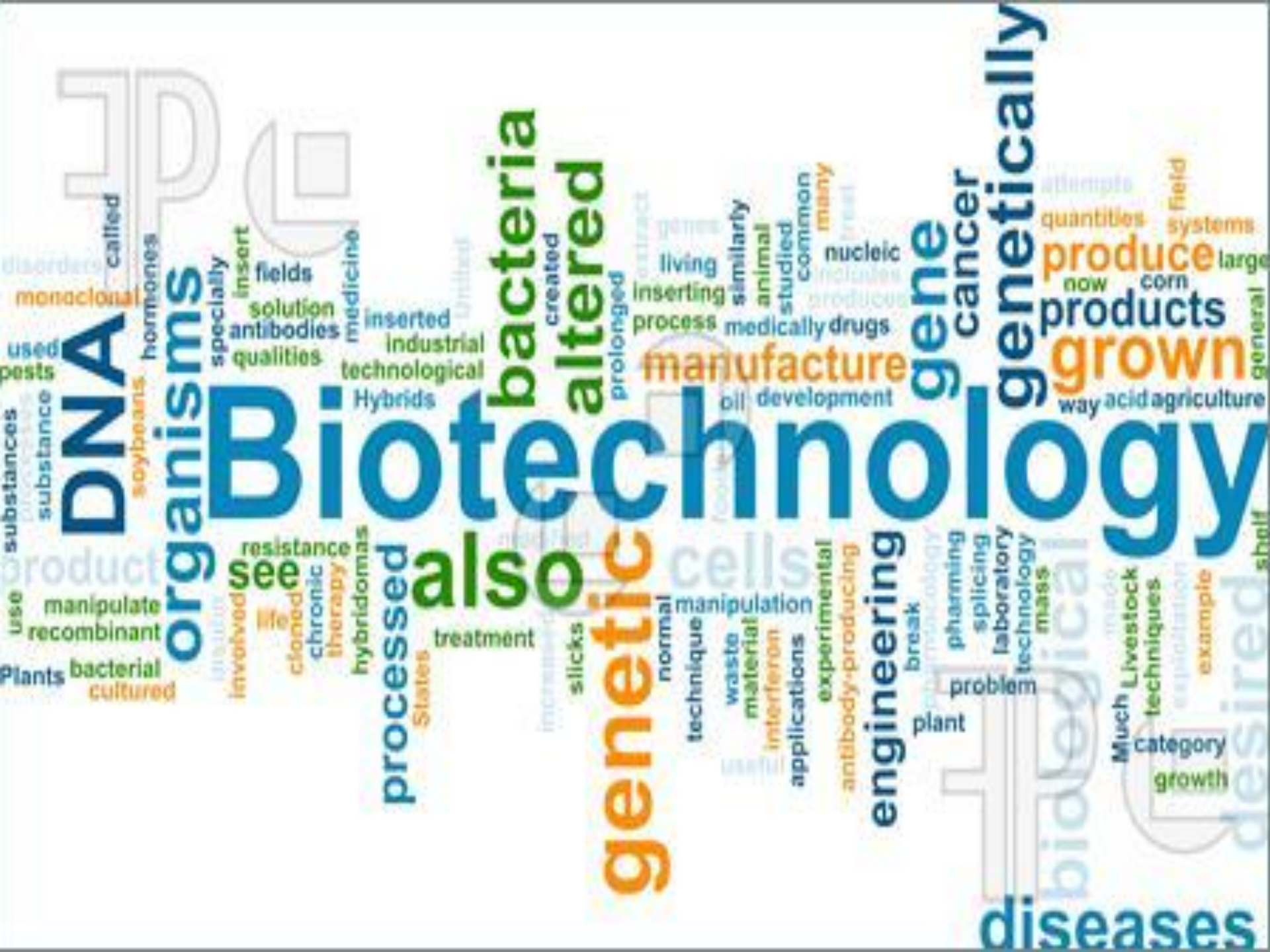
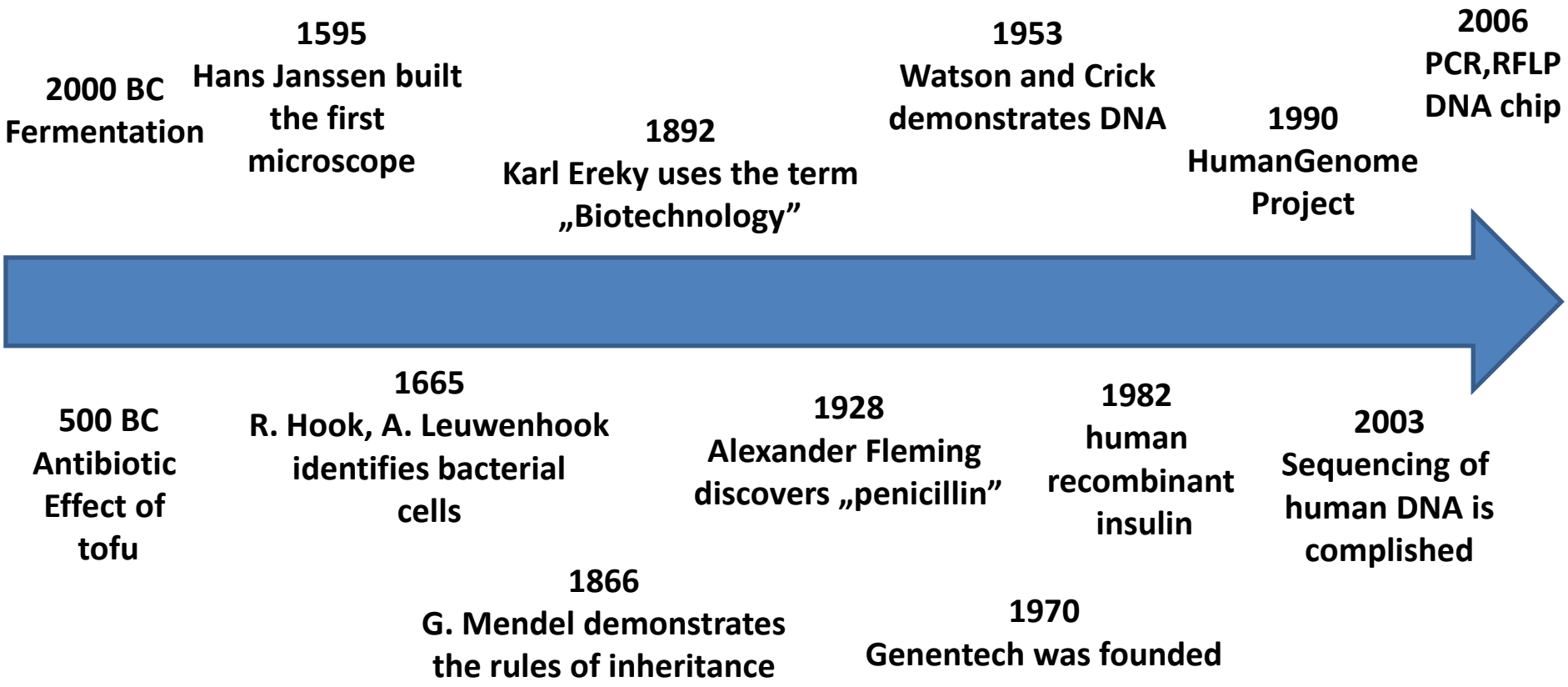
Biopharmaceuticals, Vasoactive peptides

László Drimba MD
University of Debrecen
Health-, Education- and Science Center


Biotechnology
DNA
organisms
bacteria
altered
genetically
gene
cancer
produce
products
grown
manufacture
also
genetic
processed
engineering
diseases
Hybrids
inserted
industrial
technological
medicine
antibodies
solution
qualities
specially
insert
fields
called
monoclonal
hormones
used
pests
substances
soybeans
resistance
see
manipulate
recombinant
bacterial
cultured
Plants
hybridomas
chronic
therapy
cloned
life
involved
treatment
States
slicks
normal
technique
manipulation
waste
material
interferon
applications
experimental
antibody-producing
break
pharming
splicing
laboratory
technology
mass
problem
plant
Much
Livestock
techniques
example
category
growth
shelf
living
inserting
process
similarity
animal
studied
common
many
nucleic
medically
drugs
prolonged
created
development
bill
quantities
systems
Field
large
now
corn
general
way
acid
agriculture

Biopharmaceuticals

Evolution of „biotechnology”



Biotechnology

World's largest biotech companies by sales (million USD)

1	Amgen (USA)	8360
2	Genentech (USA)	3300
3	Serono (Switzerland)	2000
4	Biogen Idec (USA)	1850[1]
5	Chiron (USA)	1750
6	Genzyme (USA)	1570
7	MedImmune (USA)	1050
8	Invitrogen (USA)	780
9	Cephalon (USA)	710
10	Millenium (USA)	430

World's largest healthcare biotech companies by sales (million USD)

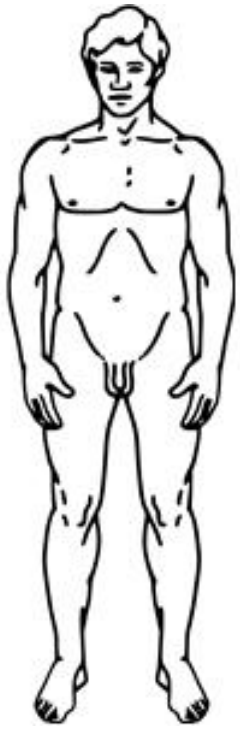
1	Amgen	7866
2	Roche Group including Genentech and Chugai	6191
3	Johnson & Johnson	6100
4	Novo Nordisk	3561
5	Eli Lilly	3043
6	Aventis	2075
7	Wyeth	1870
8	Schering-Plough	1751
9	Serono	1623
10	Baxter International	1125
11	Biogen	1057
12	Schering AG	1035
13	Genzyme	879
14	MedImmune	780
15	GlaxoSmithKline	729
16	Bayer AG	563
17	Pfizer	481
18	Abbott Laboratories	397
19	Akzo Nobel	375
20	Kirin	355

Source: Evaluate Service

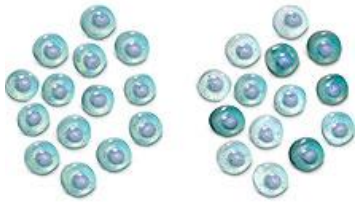
Drug development

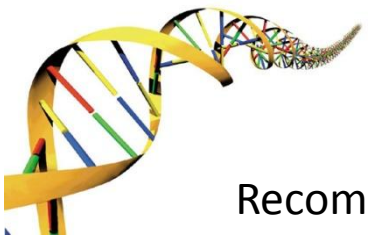
Bio vs. traditional: advantages and disadvantages of biopharmaceuticals

Traditional drugs	Biopharmaceuticals
Unspecific binding	Specific binding
Interactions with other drugs	Interactions rare
Carcinogenic substances possible	Not carcinogenic
Pharmacokinetics difficult	Breakdown is predictable for the most part
Immune reactions rare	Immunogenic effects possible
Theoretically, any target molecule can be reached	Target molecules limited, only outside the cell
6% success rate in phases I–III	25% success rate in phases I–III
Development costs high, production costs low	Development costs low, production costs high



Immunisation





Recombination

BIOPHARMACEUTICALS

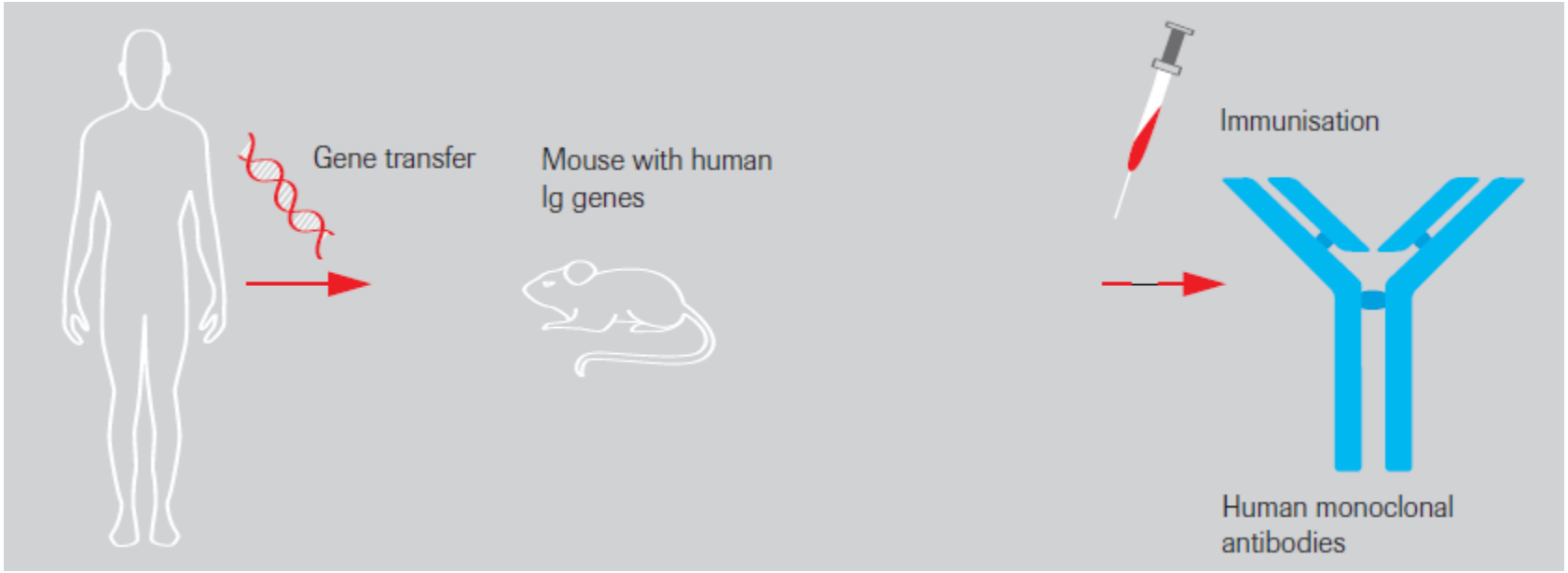
Biopharmaceuticals as therapeutics…

- Blood factors (VII., VIII.)
- Thrombolytic agents (tPA, rtPA)
- Haemopoetic growth factors (EPO, CSF)
- Hormones (insulin, glucagon, GH)
- Interferones (IFN α, -β, -γ)
- Vaccines (Hepatitis, HPV)
- Interleukines (IL-2)
- Monoclonal antibodies

Biopharmaceuticals as diagnostics…

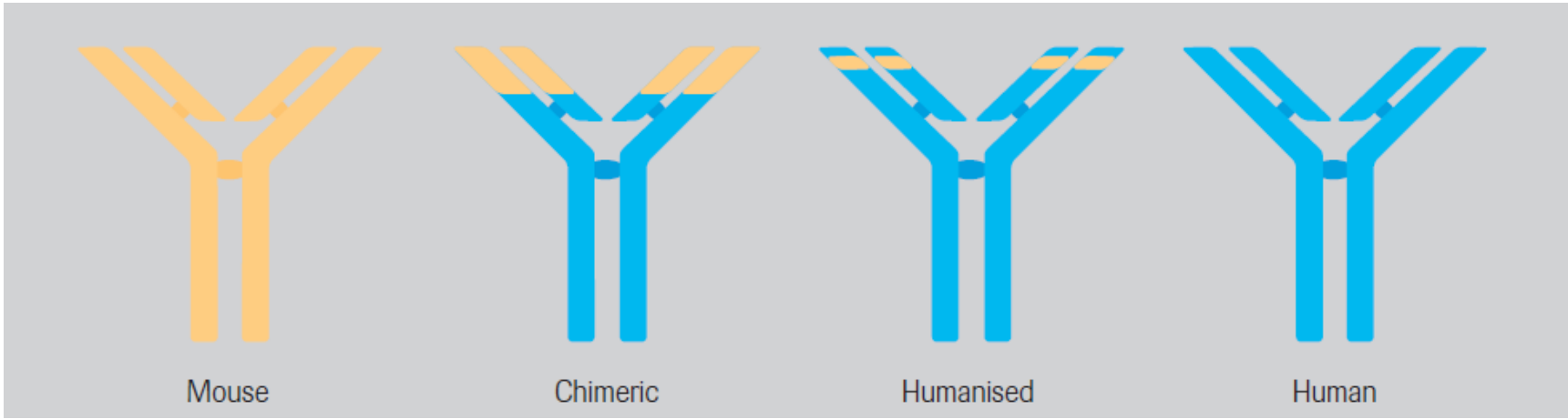
- Proteins (biomarkers)
  - AB (ELISA, IRMA, RIA)
- DNA sequences (SNP)
  - Genetic testing
    - PCR, RFLP
    - DNA chip, DNA fingerprinting

Monoclonal antibodies



-ximAB = chimeric antibody

-umAB = humanised/human antibodies



Monoclonal antibodies

- unarmed AB
  - affecting target antigene
  - activation of CDC, ADCC
- armed AB
  - linked to toxins
- radioimmunoconjugates

Monoclonal antibodies

- unarmed AB
  - affecting target antigene
  - activation of CDC, ADCC
- armed AB
  - linked to toxins
- radioimmunoconjugates

Rituximab (MAbThera®/Rituxan®)

- chimeric monoclonal AB

- Pharmacodynamics:
  - targets/activates CD20 (B-cell antigen)
  - activation of Ser/Tyr kinase
  - induction of *c-myc*
  - modulation of Ca^{2+} conductance - apoptosis

- Pharmacokinetics:
  - i.v. infusion
  - $t_{1/2}$: 22 days
  - combination with chemotherapeutics (MTX)

- Adverse effects:
  - hypersensitivity reactions
  - tumor-lysis syndrome (hyperkalemia)

- Therapeutic application:
  - B-cell lymphomes (CLL)
  - AD (RA, TTP, AHA) – if no response to anti-TNF-alfa therapy

Trastuzumab (Herceptin®)

- humanized monoclonal AB

- Pharmacodynamics:
  - inhibits HER2/neu
  - prevents activation of receptor kinase
  - blockade of angiogenetic effect, and tumor growth

- Pharmacokinetics:
  - i.v. infusion
  - $t_{1/2}$: 5.8 days
  - combination with chemotherapeutics (paclitaxel)

- Adverse effects:
  - cardiac failure!, LVF (20% of patients)
  - cardiomyopathy

- Therapeutic application:
  - metastatic breast cancer (overexpresses HER2/neu)

Cetuximab (Erbitux®)

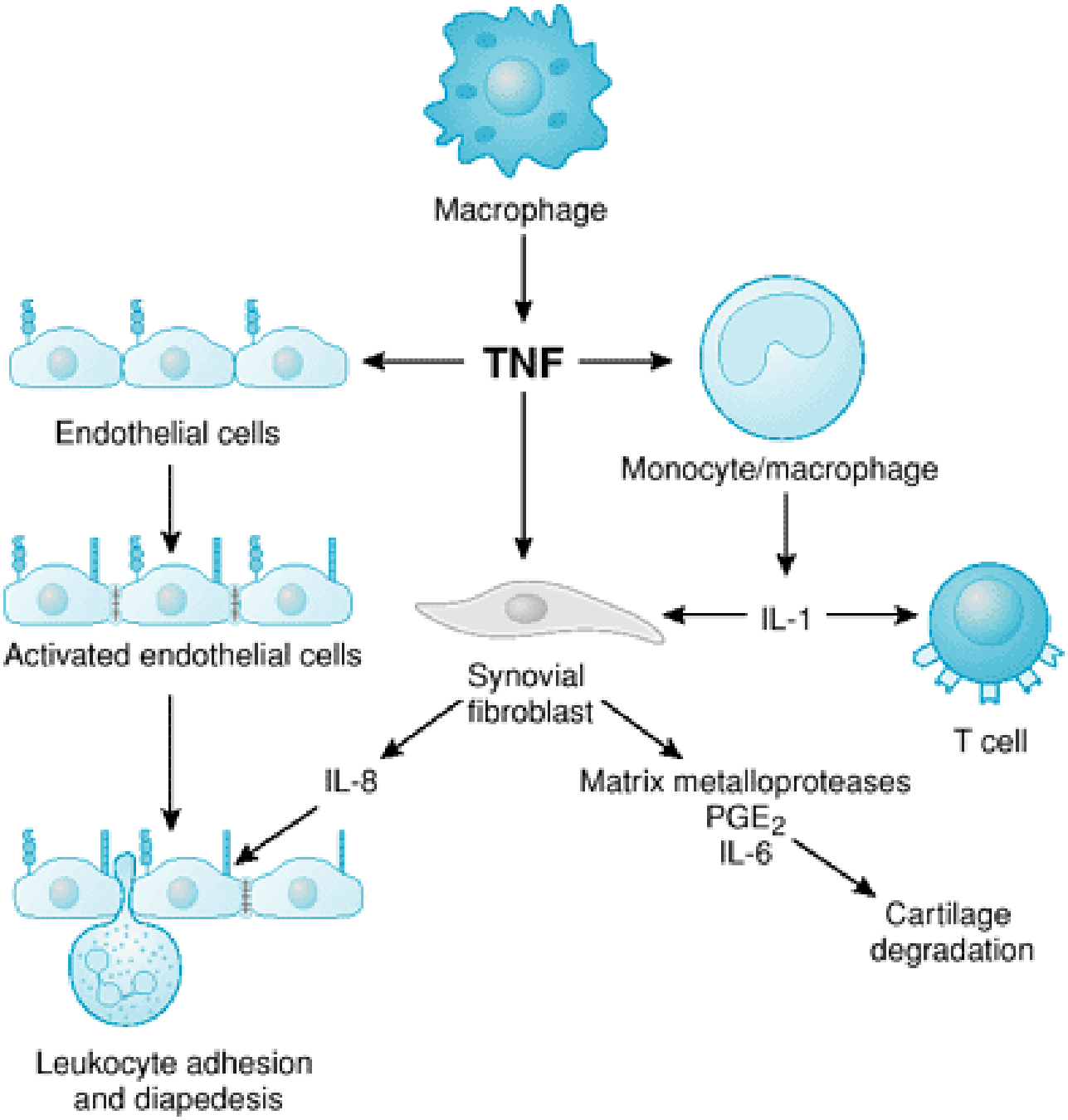
- chimerized monoclonal AB

- Pharmacodynamics:
  - inhibits EGFR
  - prevents activation of receptor kinase, dimerization
  - blockade of cell growth

- Pharmacokinetics:
  - i.v. infusion
  - combination with chemotherapeutics (5-FU)

- Adverse effects:
  - hypersensitive reactions

- Therapeutic application:
  - squamous cell carcinoma of head and neck (HNSCC)
  - metastatic colon cancer (EGFR+)


Macrophage
TNF
Endothelial cells
Monocyte/macrophage
Activated endothelial cells
IL-1
Synovial fibroblast
T cell
IL-8
Matrix metalloproteases
PGE2
IL-6
Cartilage degradation
Leukocyte adhesion and diapedesis

Infliximab (Remicad®)

- chimerized monoclonal AB

- Pharmacodynamics:
  - binds and neutralizes TNF-α (inhibits TNF- α binding to R)
  - binds to membrane-bound TNF-α (induces CDC)

- Pharmacokinetics:
  - i.v. infusion (5mg/kg)
  - combination with AZT

- Adverse effects:
  - hypersensitivity reactions
  - immunsuppression (resp. inf.)

- Therapeutic application:
  - Crohn's disease (IBD)

Adalimumab (Humira®)

- humanized monoclonal AB

- Pharmacodynamics:
  - binds and neutralizes TNF-α (inhibits TNF- α binding to R)
  - binds to membrane-bound TNF-α (induces CDC)

- Pharmacokinetics:
  - sc. application
  - $t_{1/2}$: 10-20 days

- Adverse effects:
  - hypersensitivity reactions

- Therapeutic application:
  - Crohn's disease (IBD)
  - RA, psoriasis

Etanercept (Enbrel®)

- fusion protein (TNF α-R + IgG)
- soluble TNF-α receptor

- Pharmacodynamics:
  - binds and neutralizes TNF-α
  - induces ADCC

- Pharmacokinetics:
  - s.c. administration
  - combination with MTX

- Adverse effects:
  - immunesuppression

- Therapeutic application:
  - RA, Ankylosing spondylitis

Monoclonal antibodies

- unarmed AB
  - affecting target antigene
  - modifying genetic response
  - activation of CDC, ADCC
- armed AB
  - linked to toxins
- radioimmunoconjugates

Gemtuzumab + Ozogamicin

- humanized monoclonal AB + antitumor antibiotics

- Pharmacodynamics:
  - targets CD33 antigene (AML)
  - endocytosis, cleavage, toxin release
  - induces DNA breaks and cell death

- Pharmacokinetics:
  - i.v. infusion
  - $t_{1/2}$: 5 days

- Adverse effects:
  - myelosupression
  - hepatocellular damage
  - tumor lysis syndrome (hyperkalemia, hyperuricemia)

- Therapeutic application:
  - AML

Monoclonal antibodies

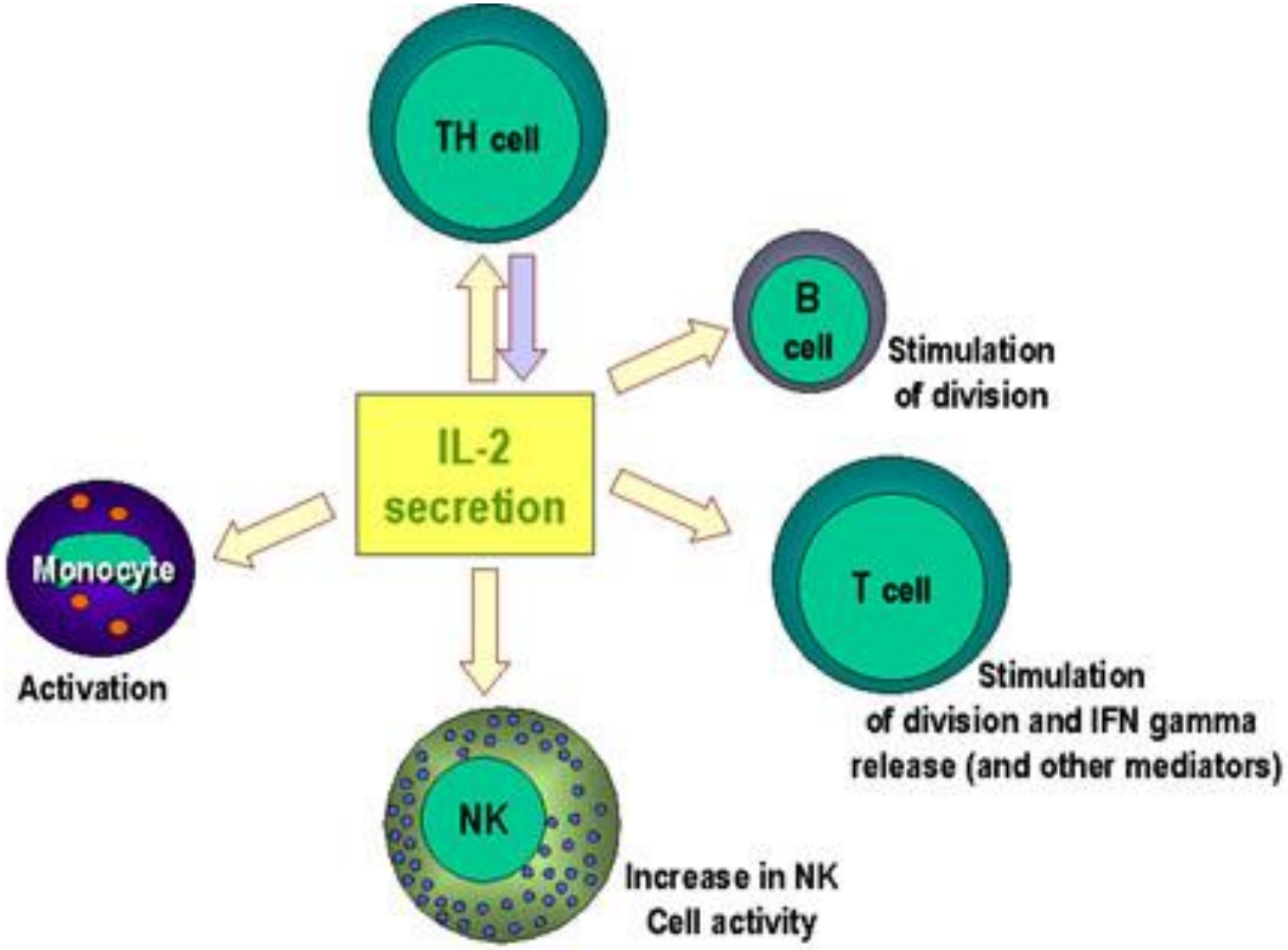
- unarmed AB
  - affecting target antigene
  - modifying genetic response
  - activation of CDC, ADCC
- armed AB
  - linked to toxins
- radioimmunoconjugates

Radioimmunoconjugates

– monoclonal antibody + radionuclid (^{131}I, ^{90}Y)

– diagnostic, therapeutic application

Interleukin-2



Aldesleukin (Proleukin)

- glycoprotein

- Pharmacodynamics:
  - targets IL receptor of T-cells and NK cells
  - induces cytokin release (IFNs)
  - enhances cytotoxicity

- Pharmacokinetics:
  - i.v. infusion

- Adverse effects:
  - enhanced immun response, hypersensitivity
  - irritation (at adm. site)

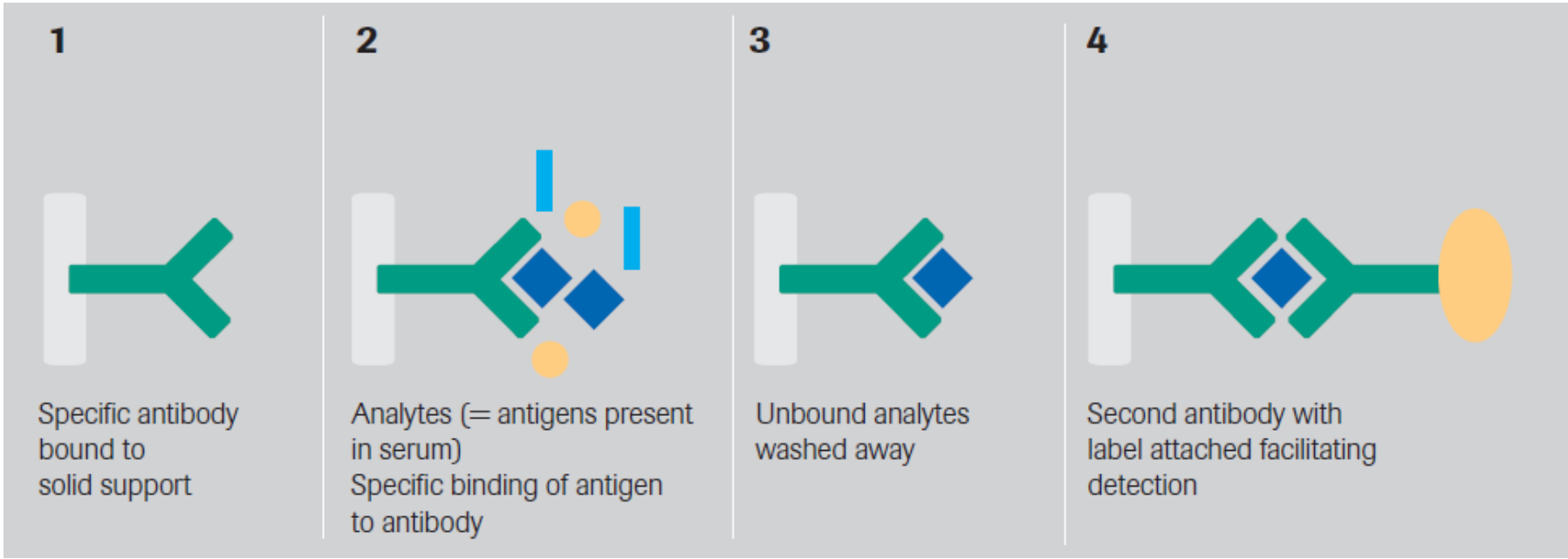
- Therapeutic application:
  - melanoma malignum
  - renal cell carcinoma

Biopharmaceuticals as diagnostics

- Proteins (biomarkers)
  - AB (ELISA, IRMA, RIA)

- DNA sequences (SNP)
  - Genetic testing – Pharmacogenetics
    - PCR, RFLP
    - DNA chip, DNA fingerprinting

Proteins, as biomarkers



Biopharmaceuticals as diagnostics

- Proteins (biomarkers)
  - AB (ELISA)

- DNA sequences (SNP)
  - Genetic testing - Pharmacogenetics
    - PCR, RFLP
    - DNA chip, DNA fingerprinting

PERSONALIZED/INDIVIDUALIZED MEDICINE

Genetic testing

The first pharmacogenomic product:
AmpliChip CYP450

Vazoactive peptides

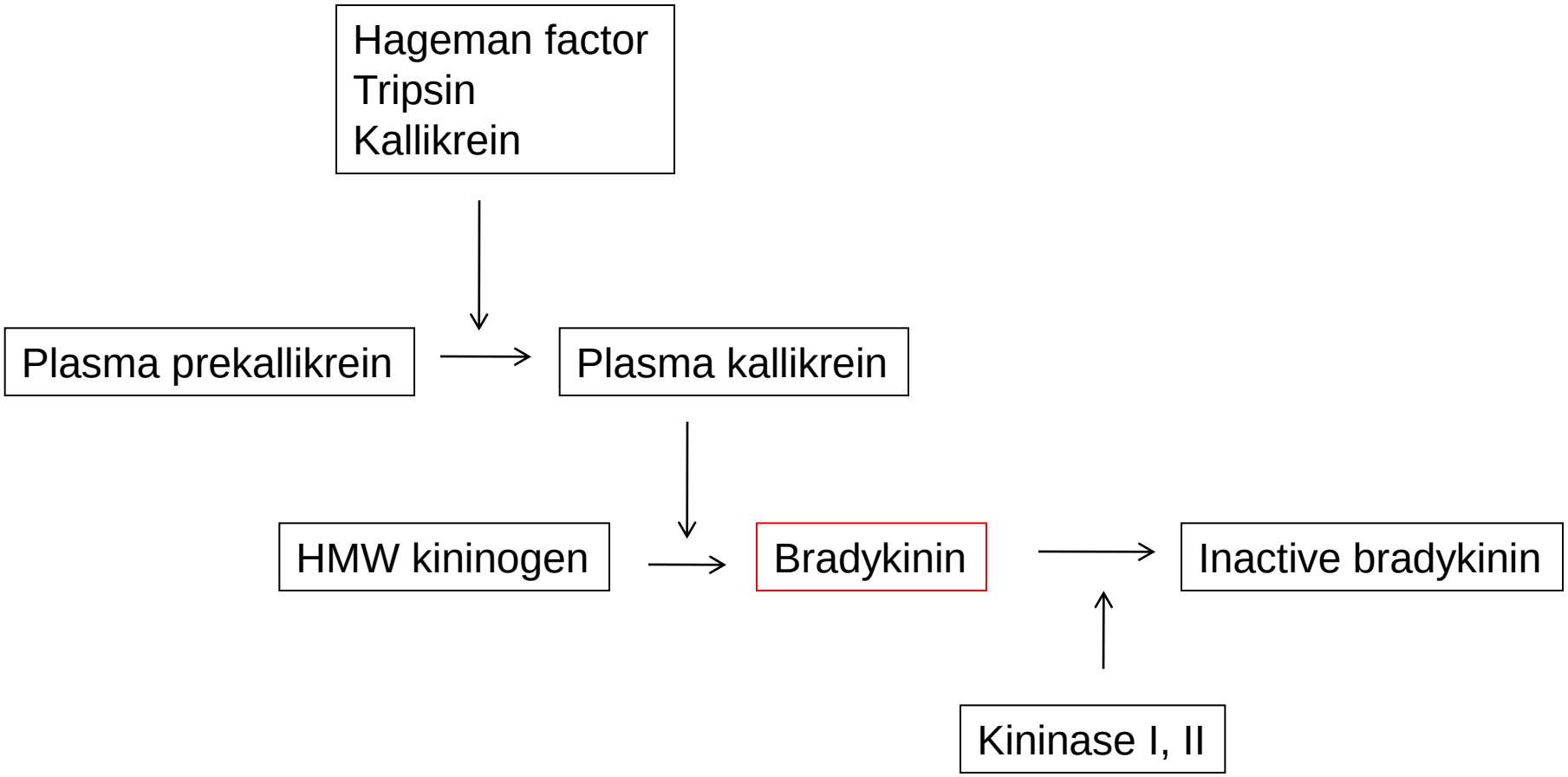
Vazodilators

- bradykinin
- natriuretic peptides
- VIP
- Substance-P
- CGRP

Vasoconstrictors

- angiotenzin II
- vasopressin
- endothelin
- neuropeptide Y

Bradykinin synthesis



Vasoactive peptides

  - bradykinin
  - lysil-bradikinin (kallidin)
  - methionyl-lysyl bradykinin

- Receptors:
  - B_1, B_2
- Effects:
  - VD (RR↓)
    - directly
    - PGE_2, PGI_2 release↑ (endothel)
  - capillar permeability↑
  - pain (nociceptive stimulus)
  - Σ: inflammation!
- Drugs:
  - icatibant
    - pain relief
    - anti-inflammatory

Natriuretic peptides

- ANP /BNP/CNP

- Loc.: atrial , ventricular myocardial cells/ CNS
  - ↑: „stretch”, Na^+↑, RR↑, hyperhidr.

- Receptors:
  - ANP_A, ANP_B, ANP_C

- Effects:
  - VD
  - natriuretic/diuretic
  - ↓ renin synthesis

- Drugs (synthetic analogues):
  - neseritid
  - ularitid

VIP

- Loc.:
  - peptidergic neurons (GIT, CNS)

- Receptors:
  - $VPAC_1$, $VPAC_2$

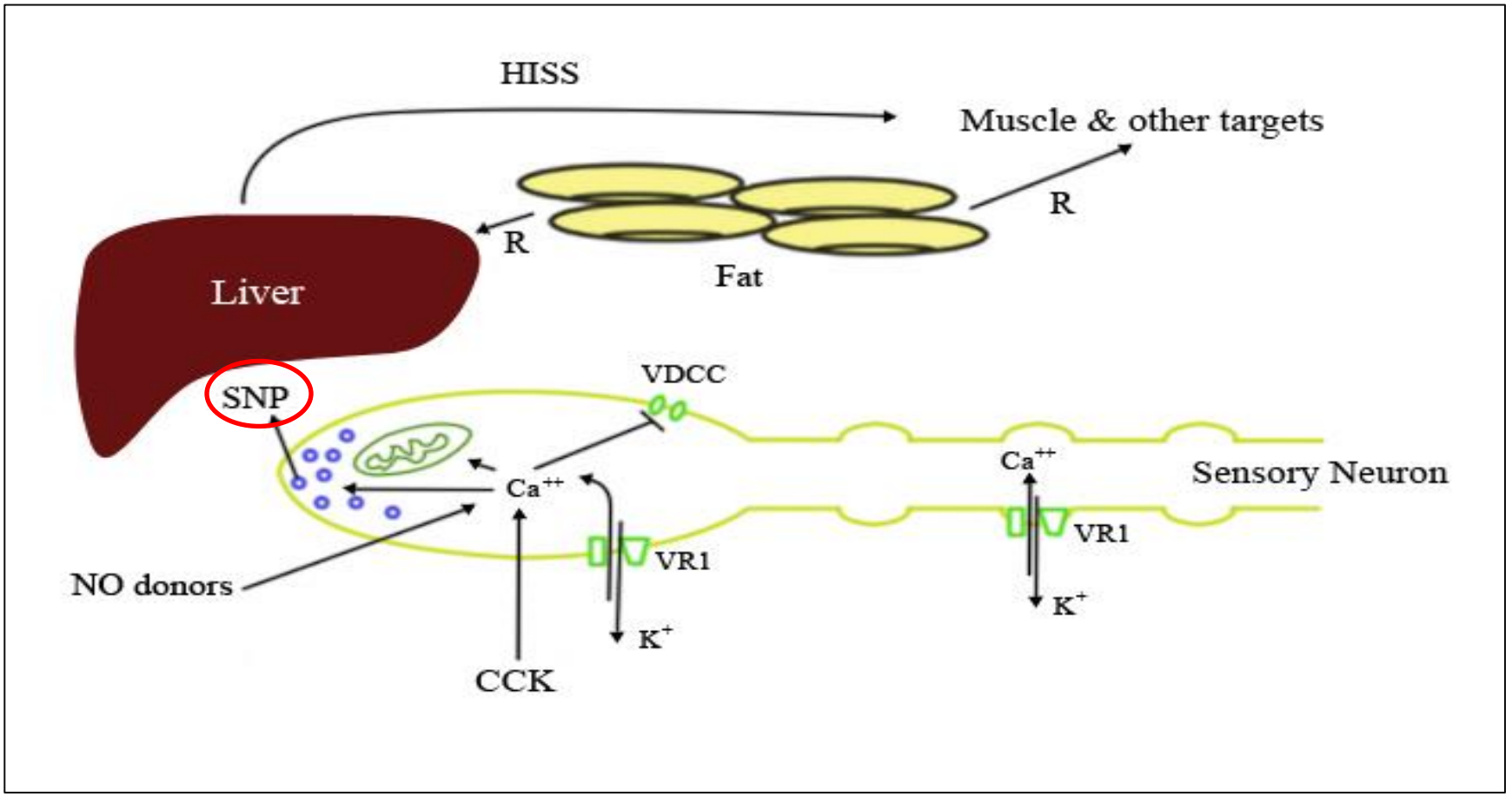
- Effects:
  - VD (flushing, hypotension)
  - (+) inotrop, kronotrop
  - prokinetic (diarrhea)
  - inflammation

- VIPoma (WDHA)

Substance-P

- Loc.:
  - CNS, GIT
- Receptors:
  - NK_1, NK_2, NK_3
- Effects:
  - VD
  - inzulin sensitivity ↑ (HISS mechanism)
  - anxiety, depression, nausea, vomiting
- Drugs:
  - aprepitant

HISS-mechanism



Endothelin

- ET_1
- ET_2
- ET_3

- Loc.:
  - endothel, CNS, kidney, urogenital tract

- Receptors:
  - ET_A, ET_B

- Effects:
  - VC (initial VD)

- Drugs:
  - bosentan
  - sitaxsentan
  - ambrisentan