Biopharmacy and Pharmacokinetics

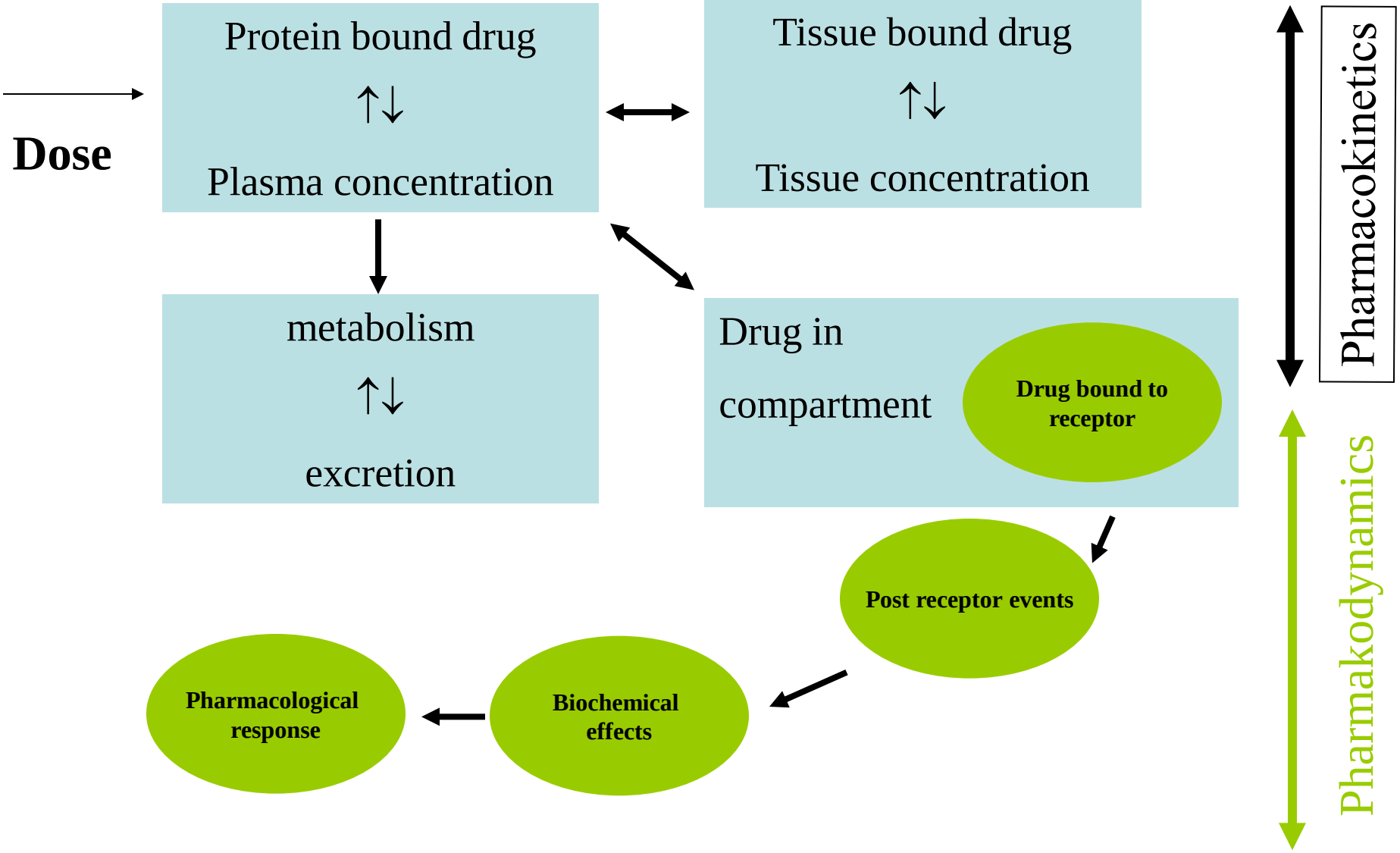
Oliver Kayser

Technische Biochemie

What should you learn?

- What is bioengineering?
- Aspects of system biotechnology

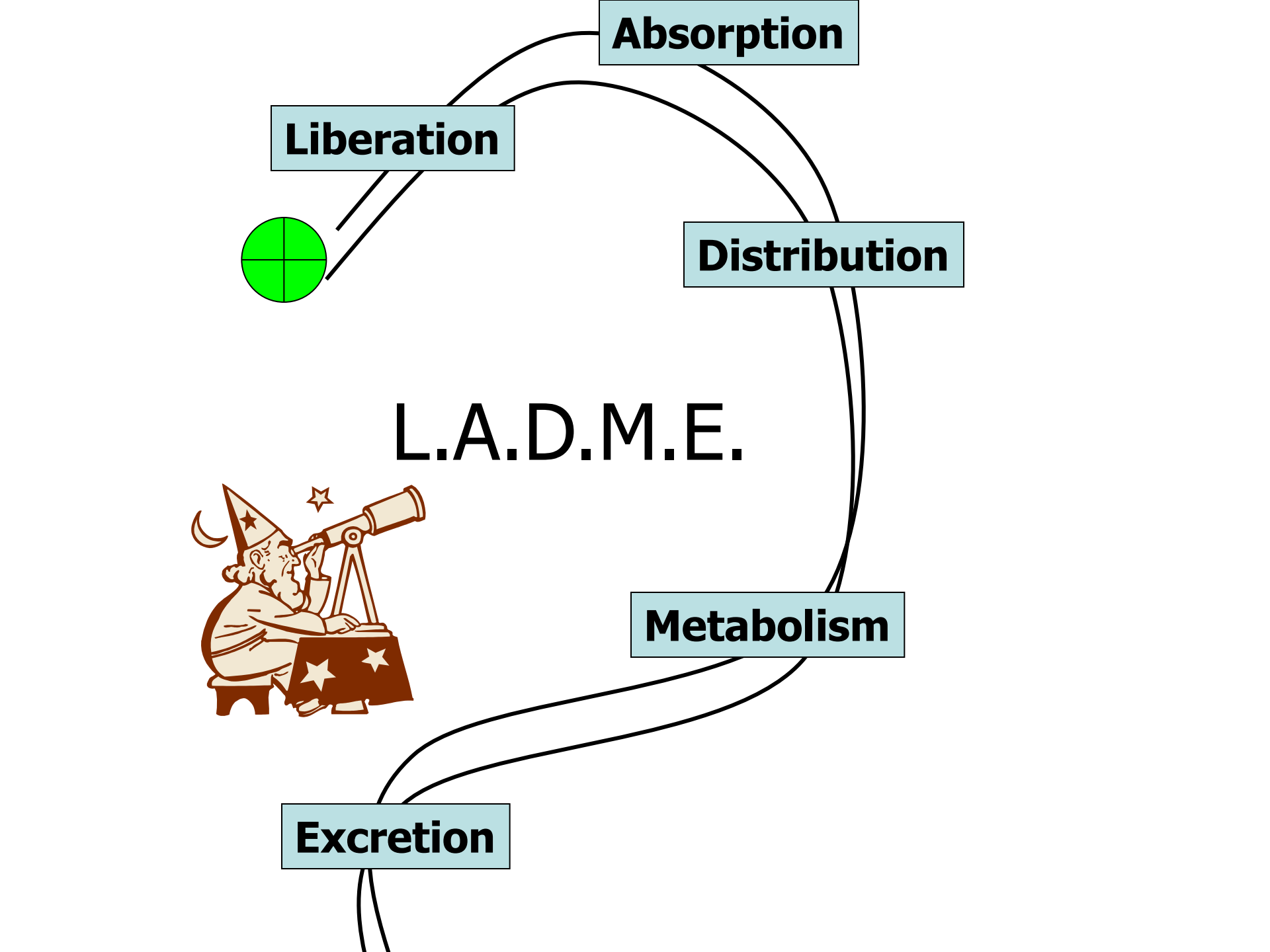
Pharmacokinetics vs. Pharmacodynamics



Comparison biopharmaceutical vs. classic drug

important:
Same conditions for biopharmaceuticals as you find for conventional drugs

1. **Biopharmaceuticals are endogenous compounds**
2. **Basic level varies from time and physiological conditions**
3. **Use of immunoassays, radioassays, bioassays, LC-MS because of low blood concentrations**
4. **Pharmacokinetics defined by biological function:**
   high potency – short half life time
   low potency – increased half life time (e.g. albumin)
5. **no oral application**
6. **Low body distribution (3-8 L)**


Absorption
Liberation
Distribution
L.A.D.M.E.
Metabolism
Excretion

Pharmacokinetics - absorption

after oral application low bioavailability (< 5%) because of

- **proteases, peptidases in GIT**
- **GIT as physical barrier**
- **High first pass effect because of cytochrome P450**

Solution to these problems:

- **parenteral application:** **nasal (e.g. Insulin, Oxytocin)**
  bukal
  perkutan
  pulmonal (Insulin)
  (Insulin: Dry Powder Inhaler)
  (rhDNAse, Pulmozyme®)

Bioavailability of proteins given orally, nasal or pulmonary

	Proteins	Peptides
Oral	0-1 %	0-1%
Nasal	1-10%	3-30%
Pulmonal	20-80%	

Pharmacokinetics – Protein binding

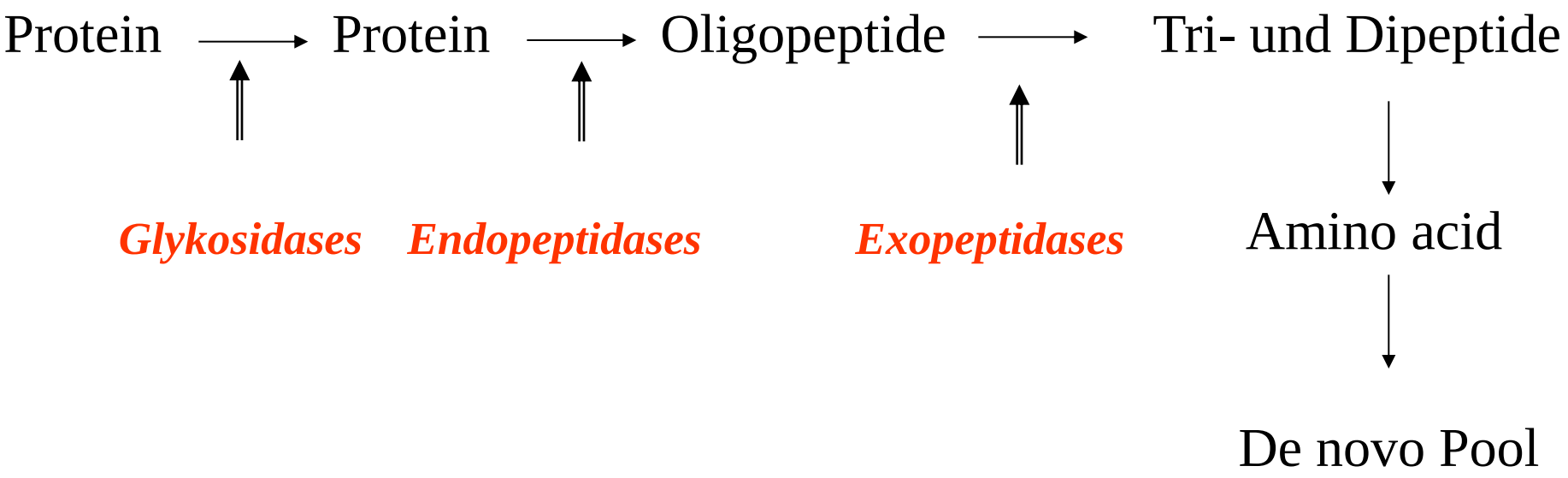
As known for small drug molecules
Only the free drug is active and can pass through membranes for distribution, metabolisation and excretion

Endogenous proteins show specific interaction with other proteins: IGF-1, IL-2, Somatropin

e.g.: 95 % IGF-1 bound to proteins
92 % Nartogastrim
49 % met-Enkephalin bound to albumin
65 % Octreotid bound to LDL)

Pharmacokinetics – elimination principles

elimination and proteolysis through identical catabolic pathways as known for endogenous proteins



Metabolisation by	**Liver** **Kidney** **others**

Pharmacokinetics – hepatic elimination

Uptake from blood to hepatocytes
(e.g.: cyclosporin by diffusion)

Problem: **Carrier-mechanism for large proteins**
Receptor mediated: Insulin, Glycoproteins
LDL-Receptor: t-PA, Urokinase

Pharmacokinetic – receptor mediated elimination

Metabolisation also in target cells
e.g. Insulin, t-PA, EGF, ANP, IL-10

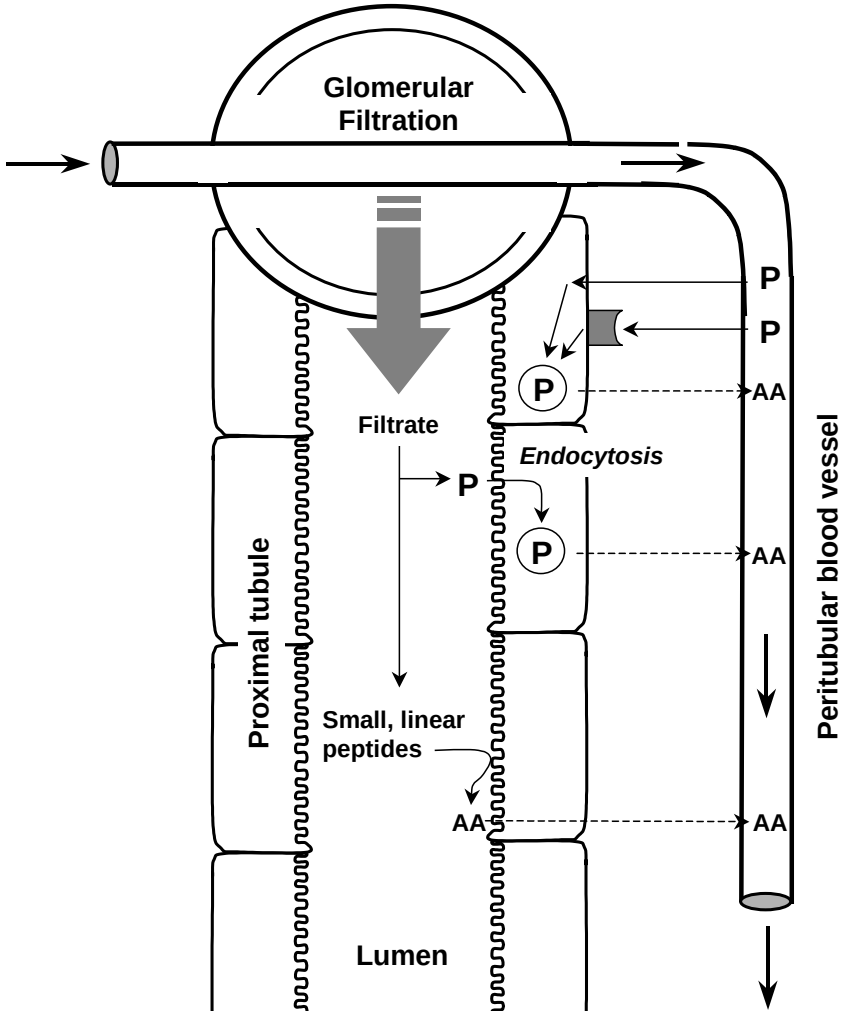
Pharmacokinetics – Renal Elimination

Kidney important for biopharmaceuticals below 60 kDa
e.g.: IFN, IL-2, M-CSF

Key process: Metabolisation in proximal tubulus

Elimination correlates with kidney function

Pharmacokinetics – renal elimination



P	Protein
AA	Amino acid

Peritubular extraction (Receptor- and non-receptor-mediated)

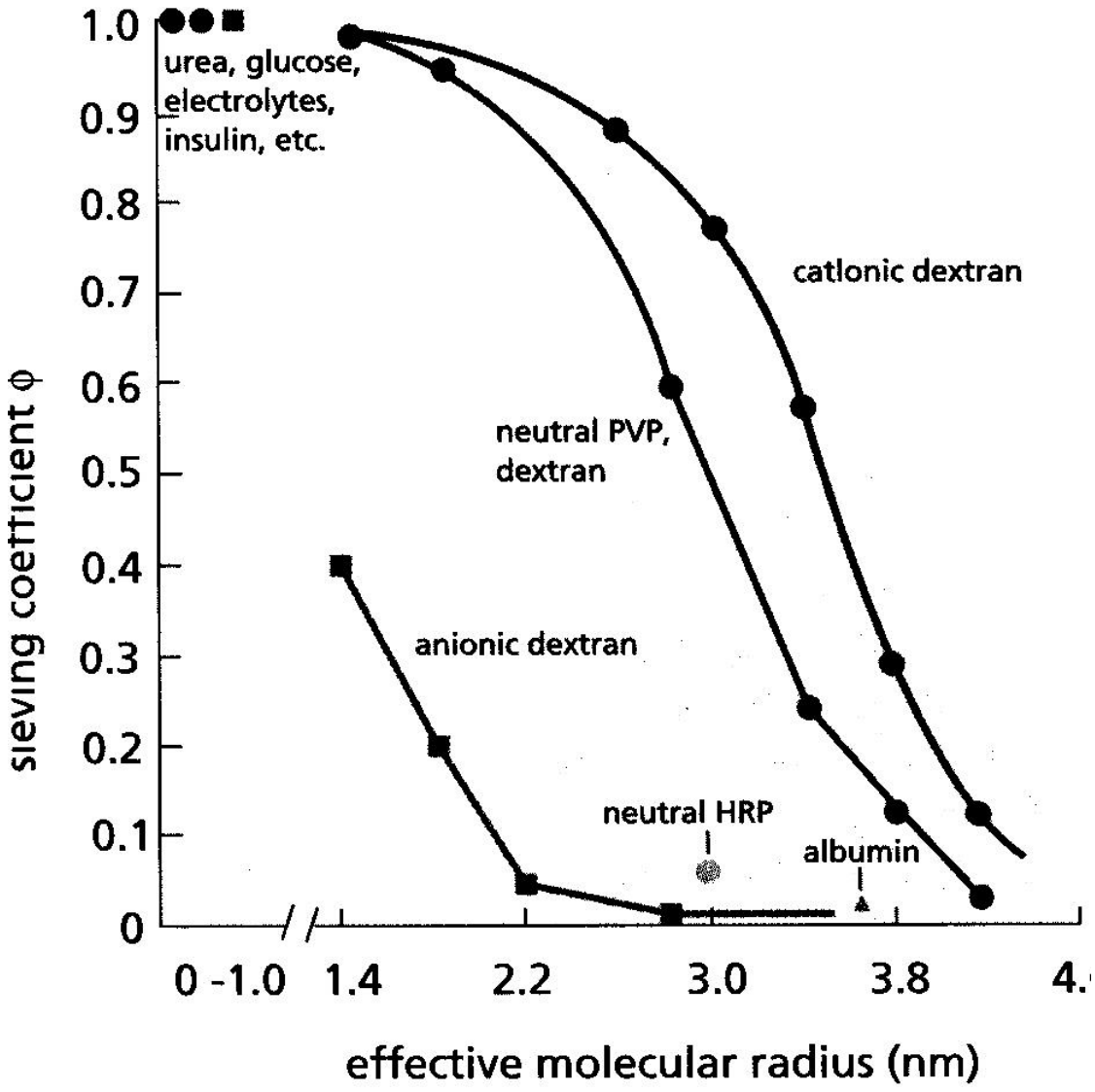
Calcitonin
Vasopressin
Angiotension II

Lysosomal degradation

Intraluminal metabolism

Angiotensin
Bradykinin

Glomular sieving curves of different macromolecules



Chemical and technological modifications of biopharmaceuticals

1. Modification depends on biosynthesis

e.g.: glycosylation (G), no G. in *E. coli* as producer

different G. in different mammilian cells

t-PA unsatisfied in *E. coli* biosynthetised, why changing to CHO-System

2. Gene technology

amino acid substitution; Insulin lispro and Insulin glargin

cyclisation: Cyclosporines

deglycolisation

3. PEGylation, e.g.: IL-2

Drug delivery - Problems

„If you had the choice between one, two or three injections per day, or one, two or three drinks per day, which would you take?“

L. Bender, Emisphere Technologies Inc.

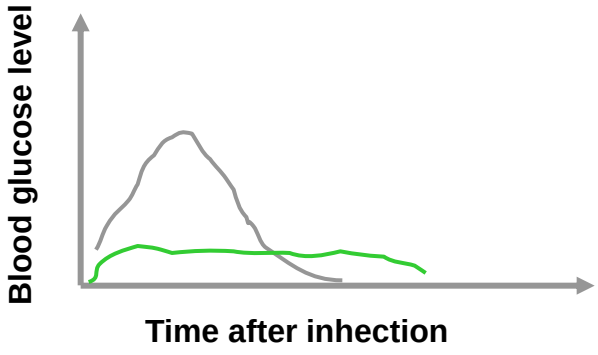
- **low oral bioavailability (max 1%)**
- **Parenteral application**
  - **high cost in production**
  - **high safety levels**
  - **pulmonal, transdermal nasal, bucal**
    - **application not well understood by now**
- **Application by medical professionals**
- **Immunogenicity**
- **Chemical and physical stability**

Pharmacokinetics

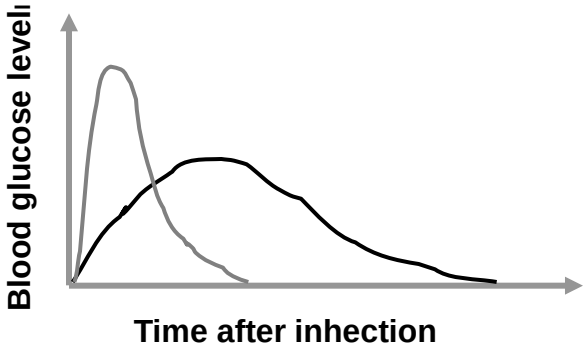
Insulin

Biotech-Process

Insulin-muteine



- Zn-Insulin
- Lantus®
- Physiological insulin
- Humalog®

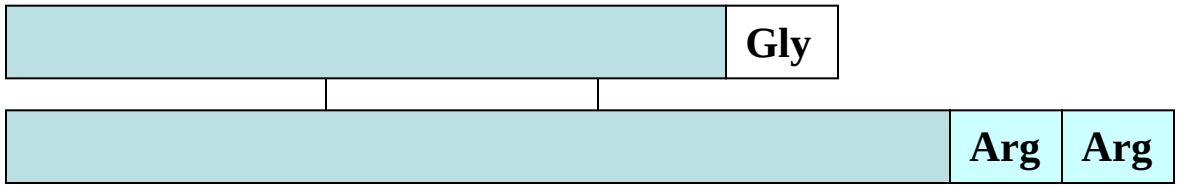


Long acting insulin

Fast acting insulin

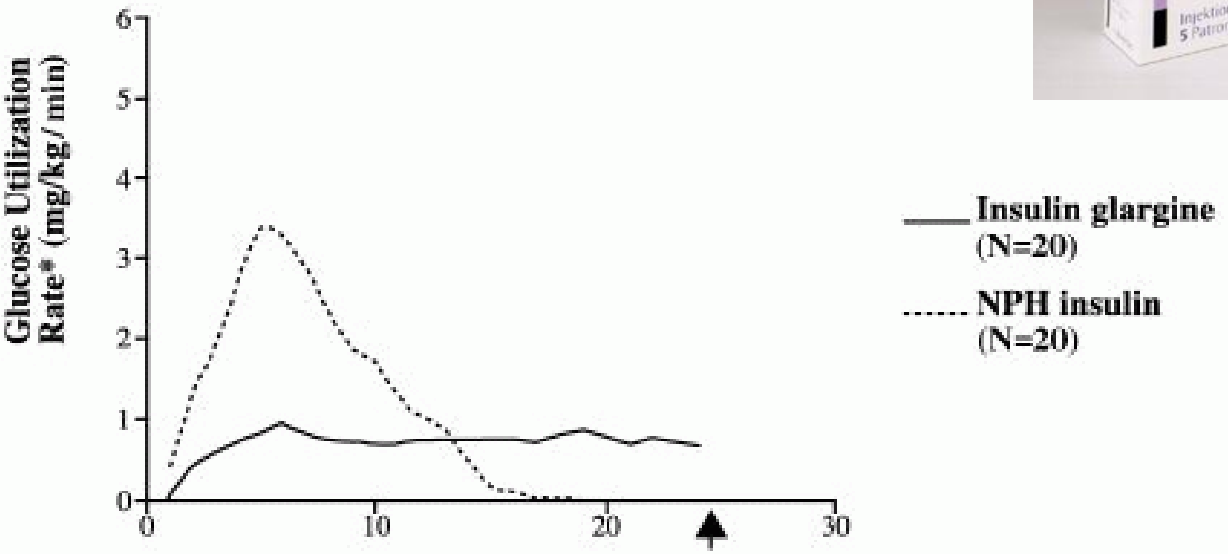
Lantus vs. Insulin

Insulin

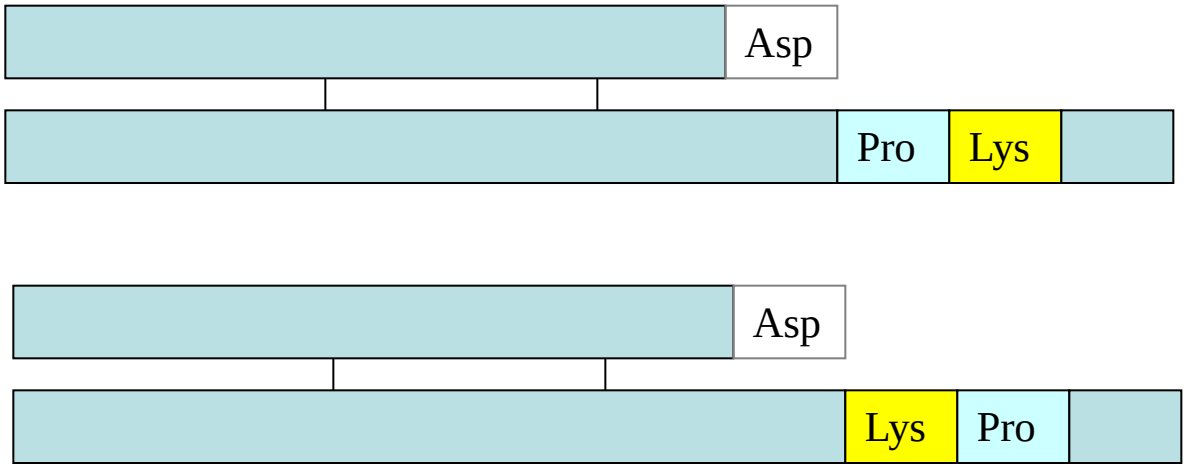


Lantus®

Lantus pharmacokinetic profile

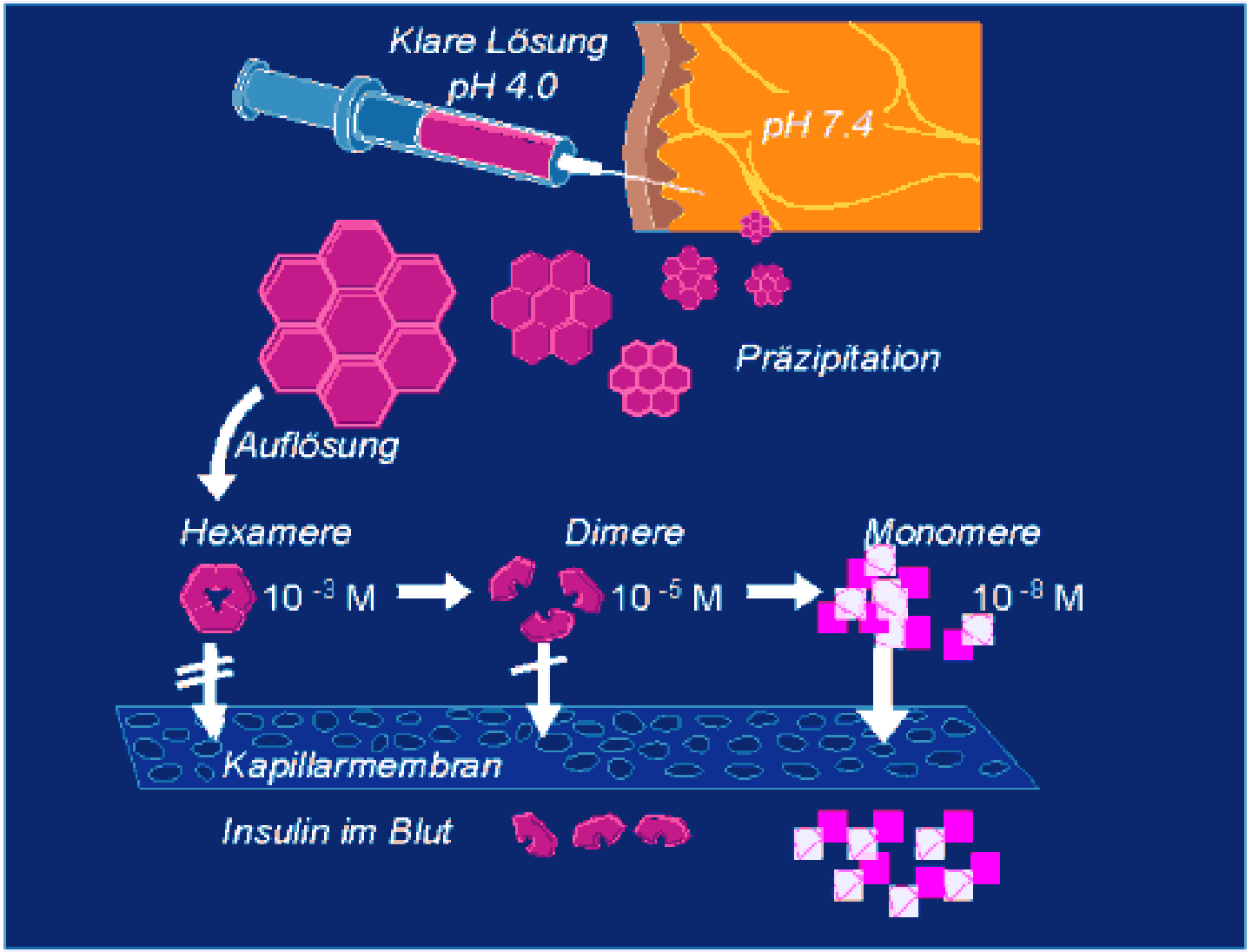


Humalog®



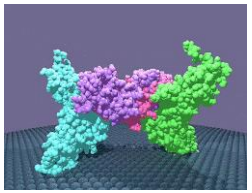
Humalog®
Insulin-Lispro

Insulin Glargin – Sustained release principle



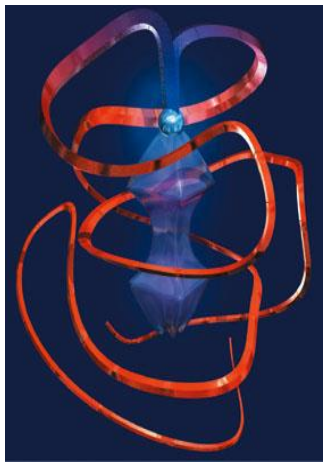
Pharmacokinetic II

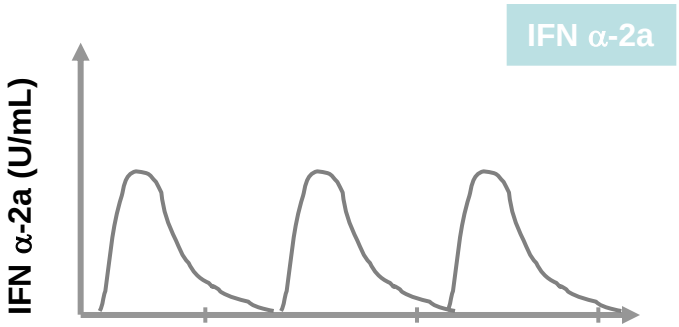
- **Pegylation of IFN-alpha (Pegasys®)**

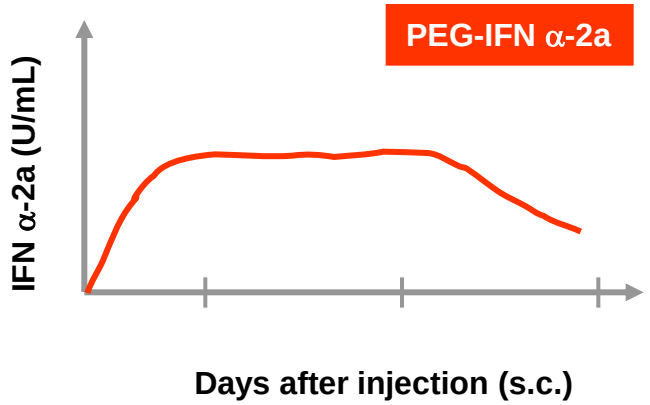


IFN α-2a

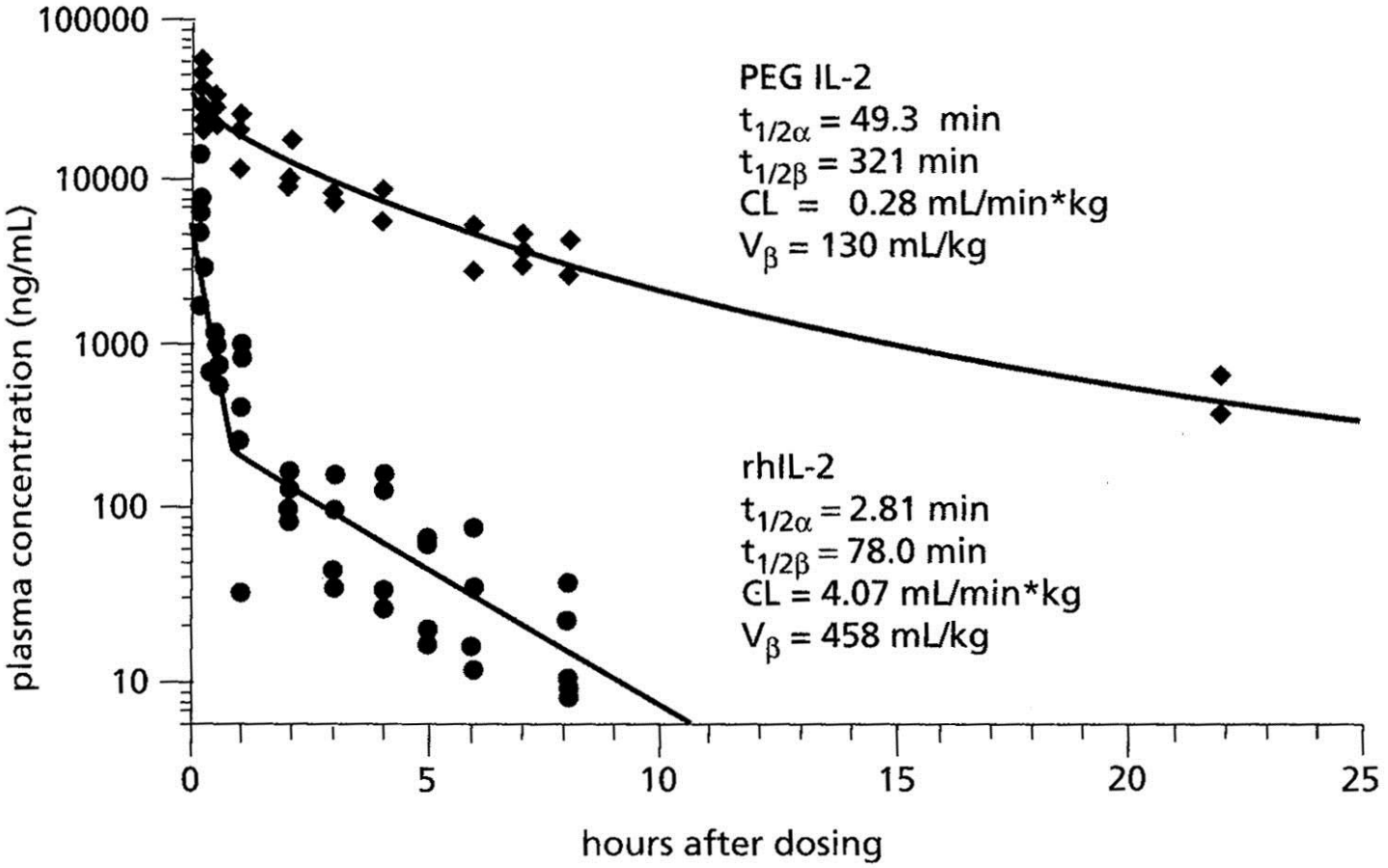
PEG



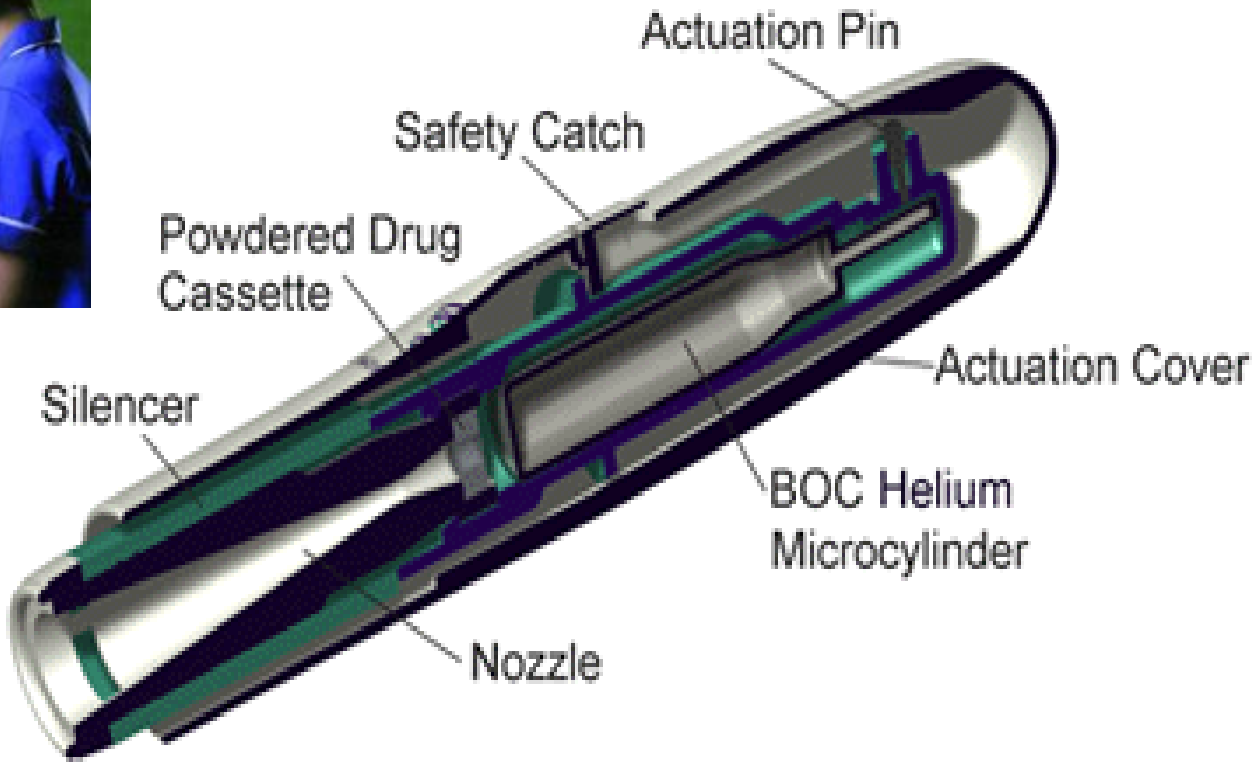




Half life time increased


100000
10000
1000
100
10
plasma concentration (ng/mL)
0
5
10
15
20
25
hours after dosing
PEG IL-2
$t_{1/2\alpha}$ = 49.3 min
$t_{1/2\beta}$ = 321 min
CL = 0.28 mL/min*kg
V_β = 130 mL/kg
rhIL-2
$t_{1/2\alpha}$ = 2.81 min
$t_{1/2\beta}$ = 78.0 min
CL = 4.07 mL/min*kg
V_β = 458 mL/kg

Drug Delivery - solutions



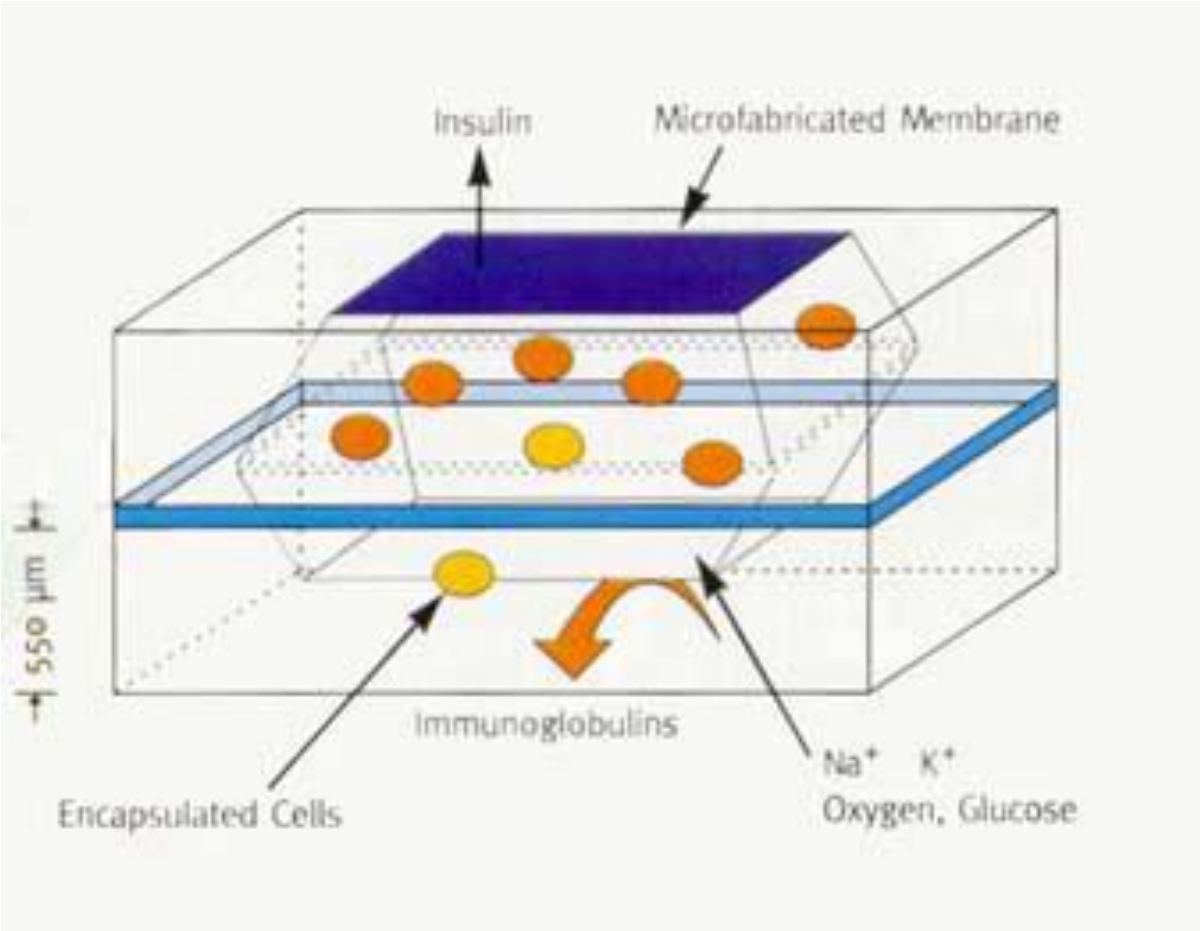
Powderject®

Controlled release systems

Idea

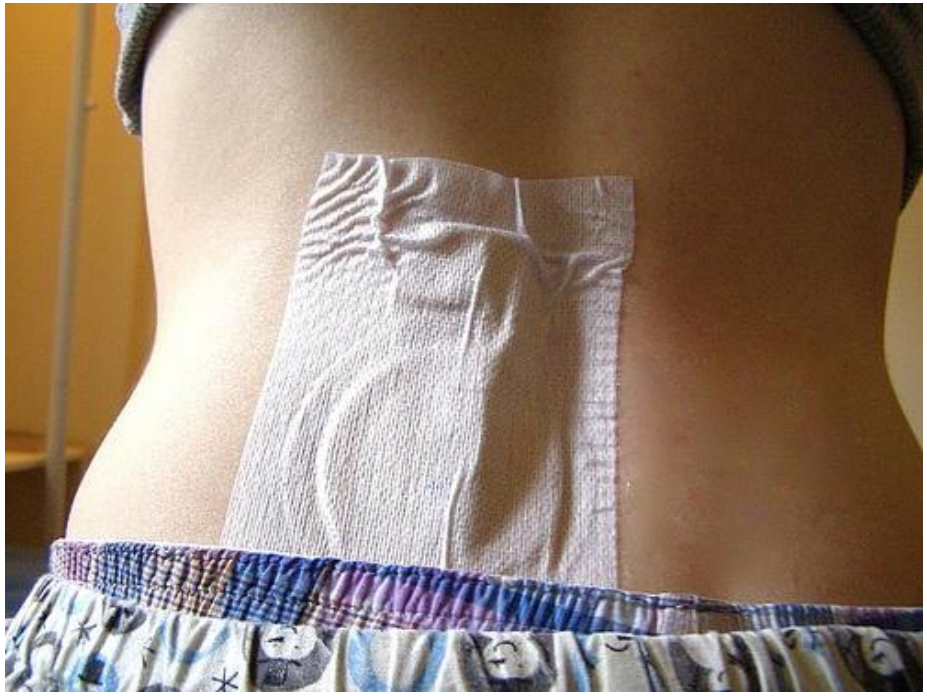
- Controlled release of the drug from depot system, controlled by time, concnetration, markers
- Dream: implanted insuline releasing cells under direct control of blood glucose (artificial pancreas)

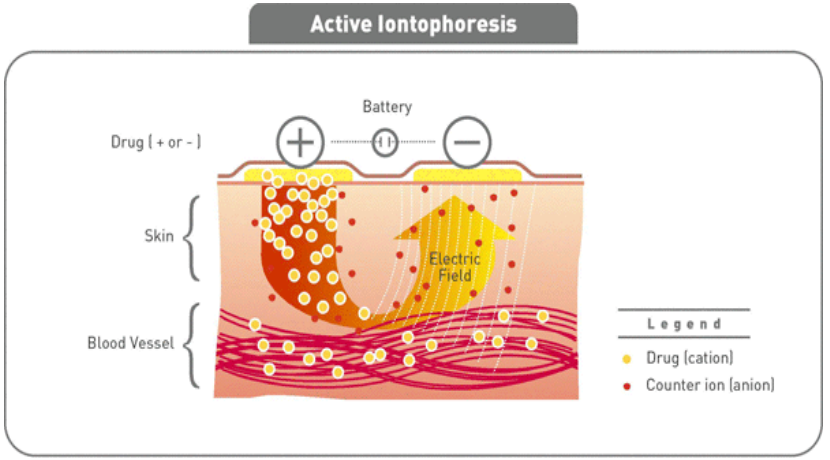
Nano capsules



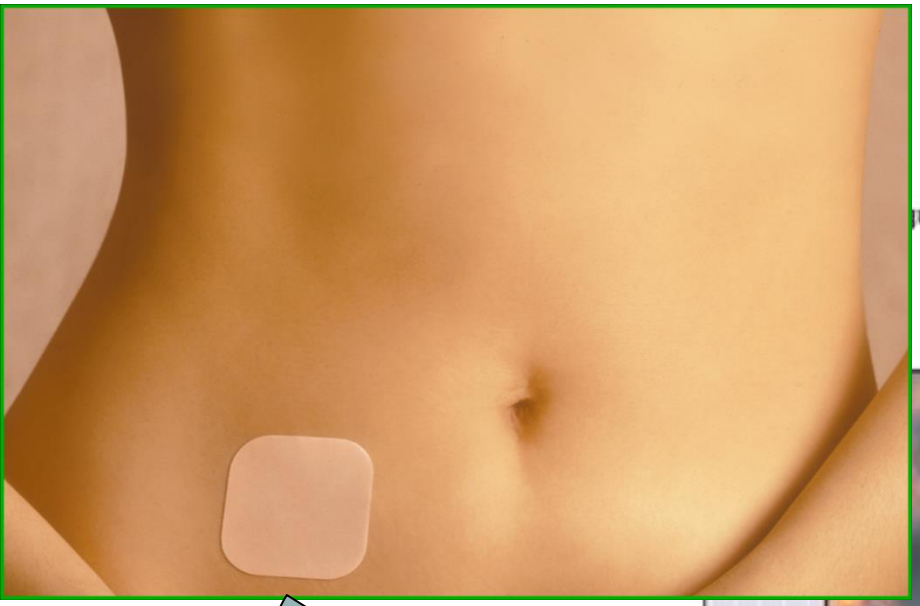
Artificial Islet Cells - Tejal Desai (UI)

Iontophoresis





Transdermal Patches



raph of an array of microneedles in 3M's Microstructured Transdermal