

Pharmacokinetics and pharmacodynamics of peptide and protein drugs

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Learning outcomes

- Overview of PK/PD
- PK: elimination of protein therapeutics
- PK: distribution of protein therapeutics
- PD: models for protein therapeutics
- PD/PK link models

Receptor theory



"Ligand"

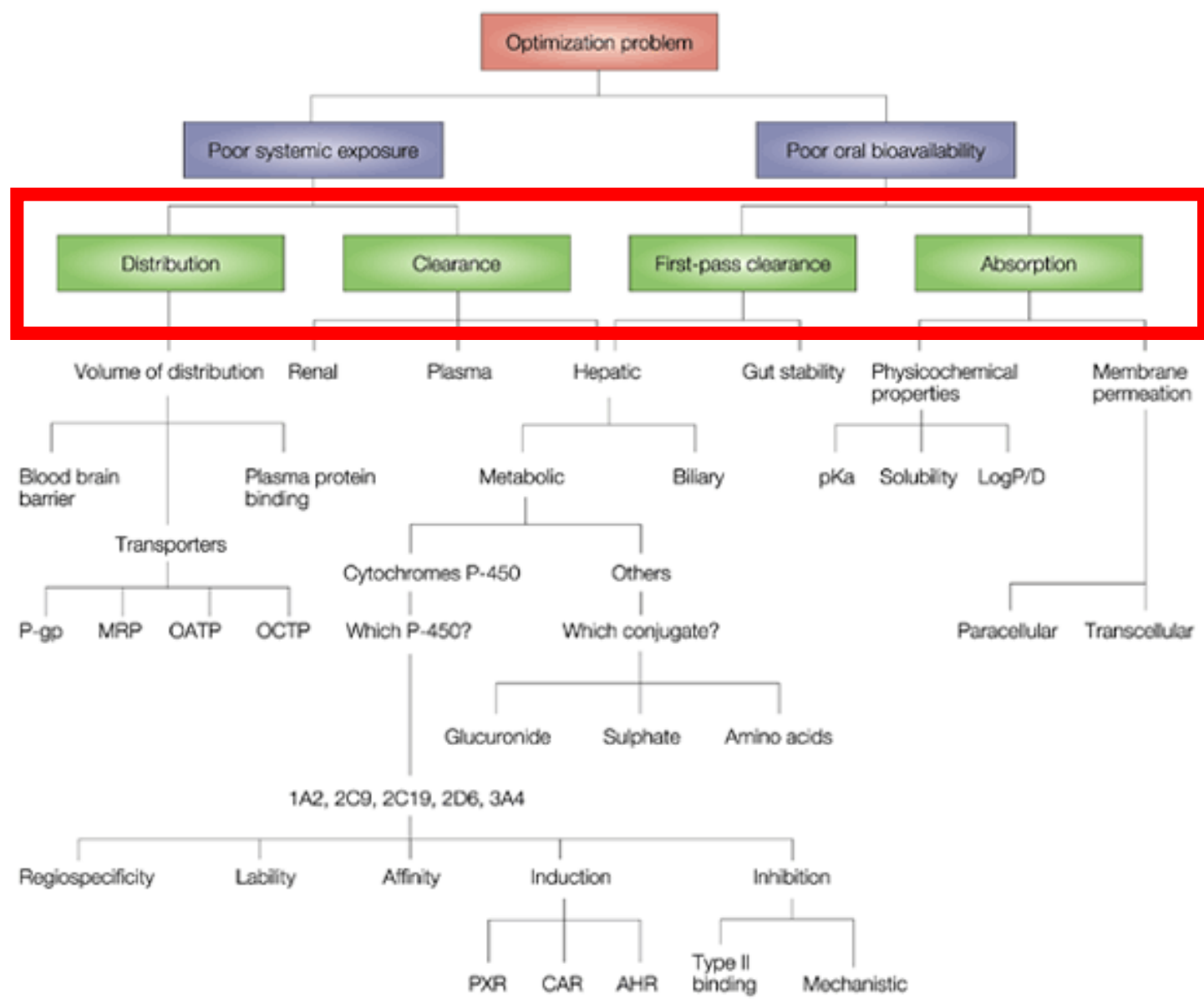


"Ligand"

1878 Langley – Ehrlich 1909

"PK – PD"

- What do these terms mean?
 - PK is what the body does to the drug
 - PD is what the drug does to the body



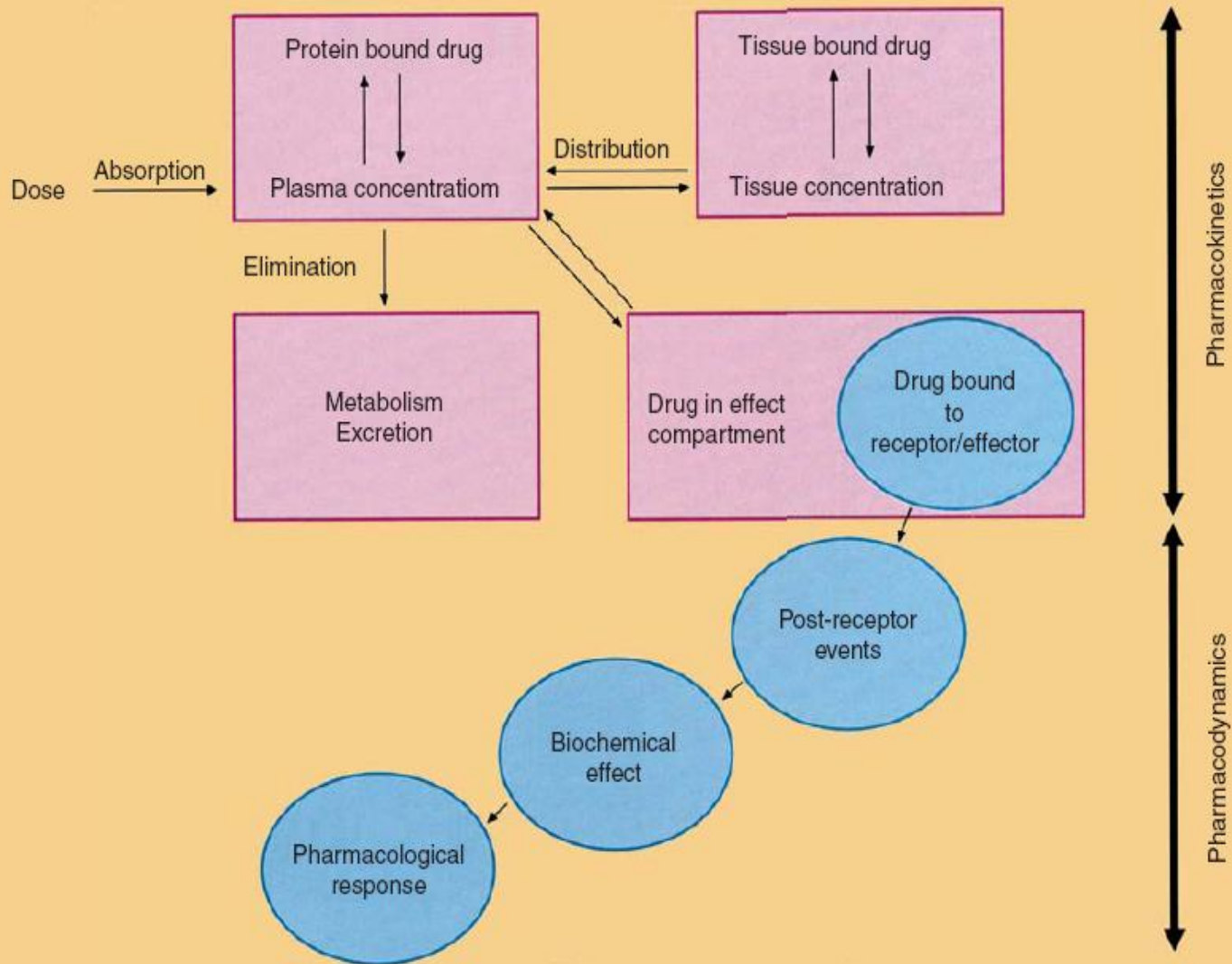
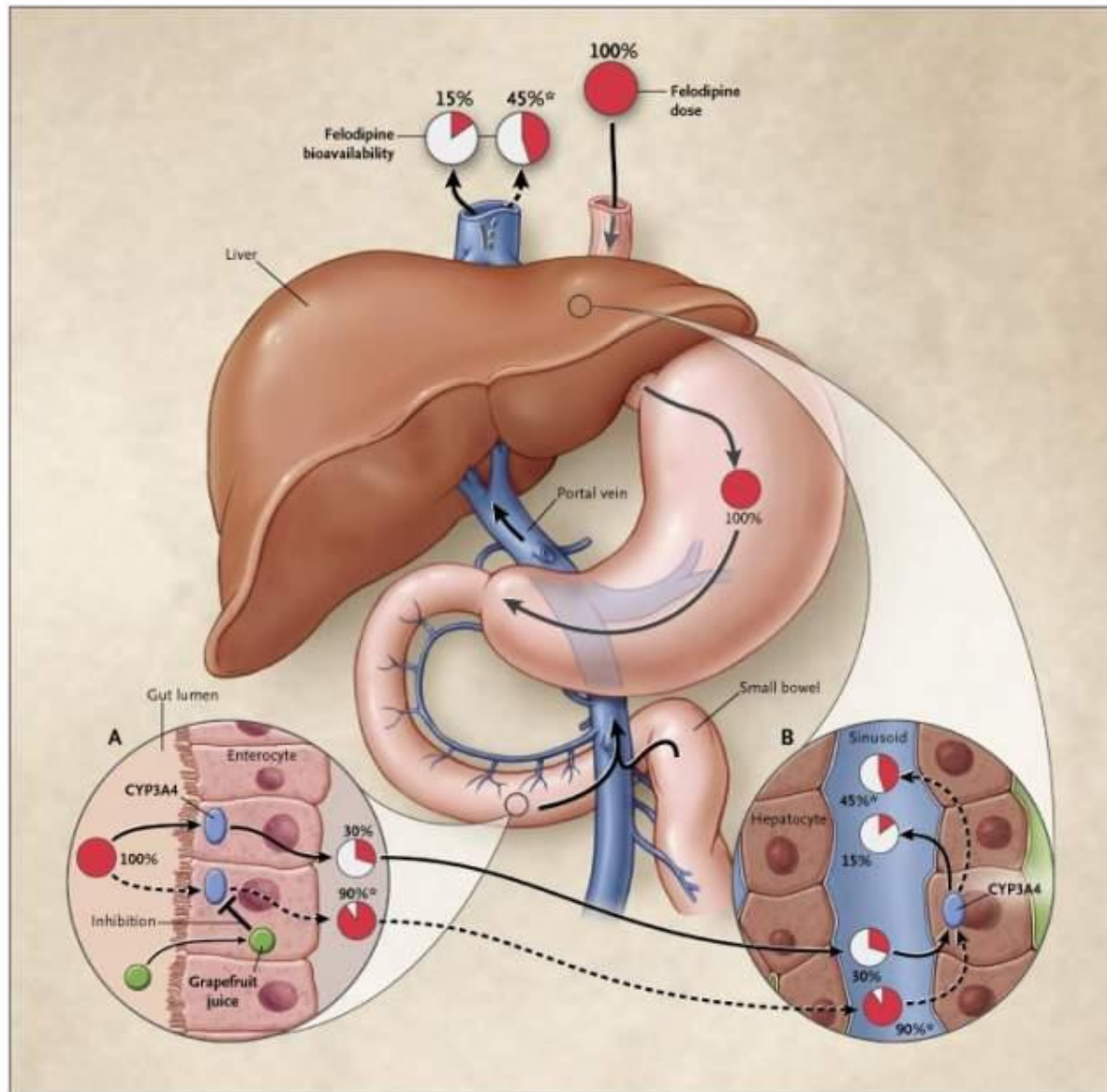


Figure 2 ■ Physiological scheme of pharmacokinetic and pharmacodynamic processes.



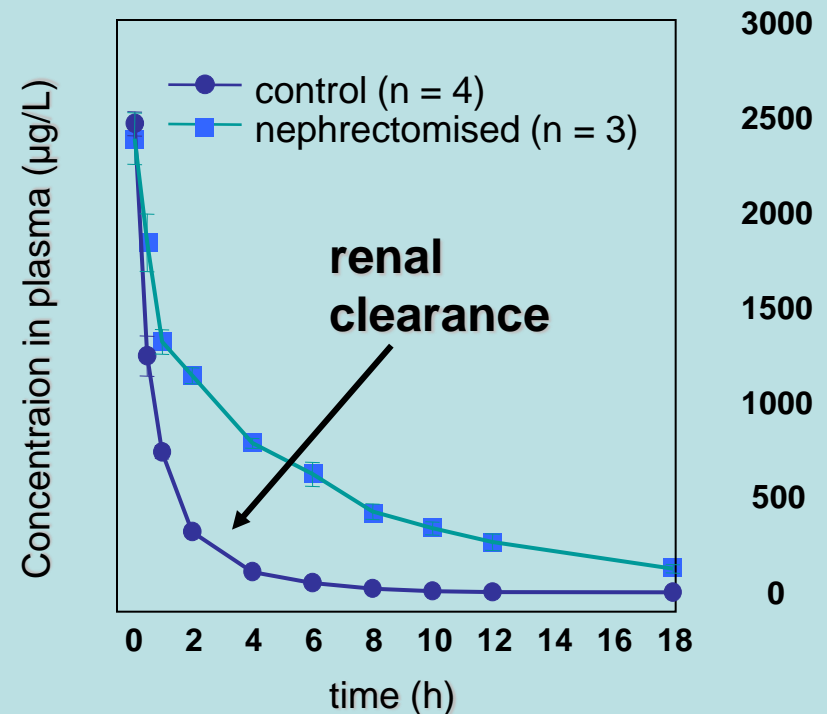
Filgrastim: dual mechanism of elimination

- **Renal clearance:**

- Rapid excretion via the kidneys
- Dependent on kidney function

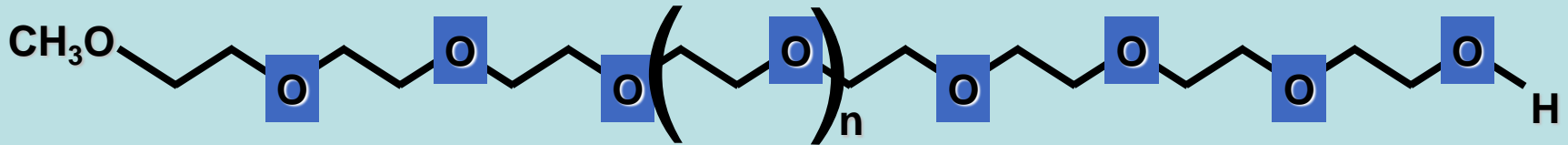
- **Neutrophil-mediated clearance:**

- Internalisation and degradation of the G-CSF / receptor-complexes in the cell
- Dependent of neutrophil count



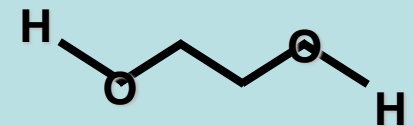
Pharmacokinetics in nephrectomised rats
Filgrastim 100 µg/kg

Properties of pegylation



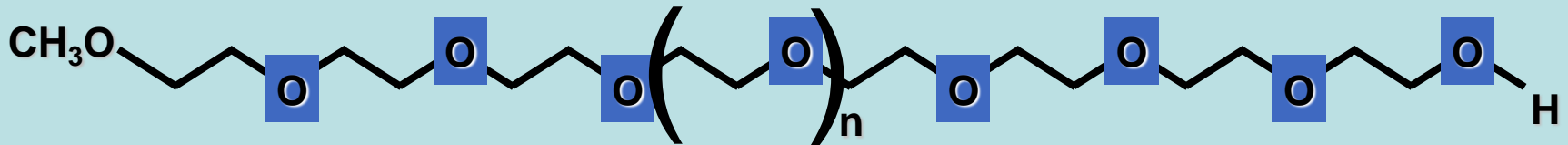
Properties of PEG

- Enhanced water solubility
- Physiologically inert
- Well tolerated, no immunogenicity
- Mainly neutrophil-mediated degradation
- Self-regulating via ANC



Ethylene glycol

Possible advantages of pegylation (PEG)



- Novel mechanism of elimination
- Enhanced molecular volume
- Changed PK
 - Renal clearance marginal
 - Mainly neutrophil-mediated degradation
- Self-regulating via ANC

Biological properties unchanged by PEG

- **Proliferation assays**
 - Similar stimulation of G-CSF–dependent cells
- **Receptor binding**
 - Comparable competitive binding affinity towards the G-CSF receptor
- **Neutrophil Response**
 - Dose-response relationship with regard to the rise of neutrophils
- **Functional studies of neutrophils**
 - No differences in release of superoxide and phagocytosis of *E. coli*

Molineux G, et al. *Exp Hematol*. 1999;27:1724–1734

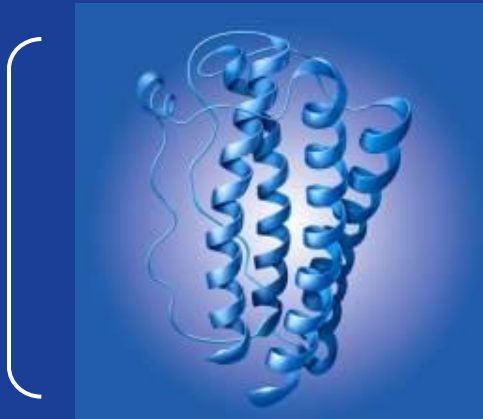
McKenna PJ, et al. *Blood*. 1998;92(suppl 1):379a

Allen RC, et al. *Blood*. 1999;94:172

Pegfilgrastim = pegylated filgrastim

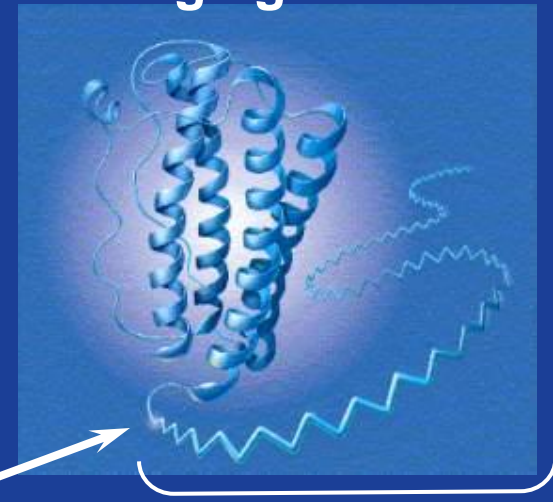
Filgrastim

Helical bundle



Pegfilgrastim

Helical bundle



N-terminal End

Polyethyleneglycol (PEG)

18.800 Daltons

Molecular weight

39.000 Daltonss

Renal

Primary pathway of elimination

Via neutrophils

Daily

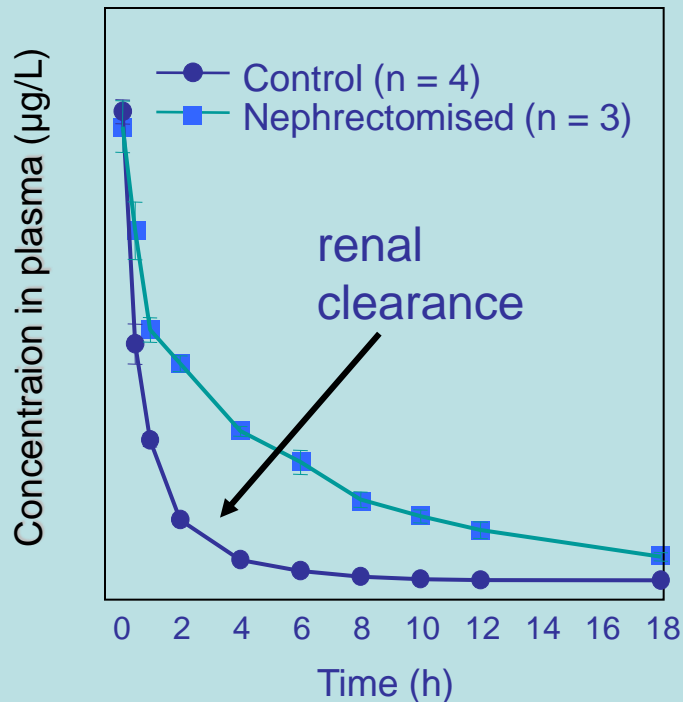
administration

1x / CT-cycle

Pegfilgrastim: neutrophil-mediated elimination

Pharmacokinetics: nephrectomised rats

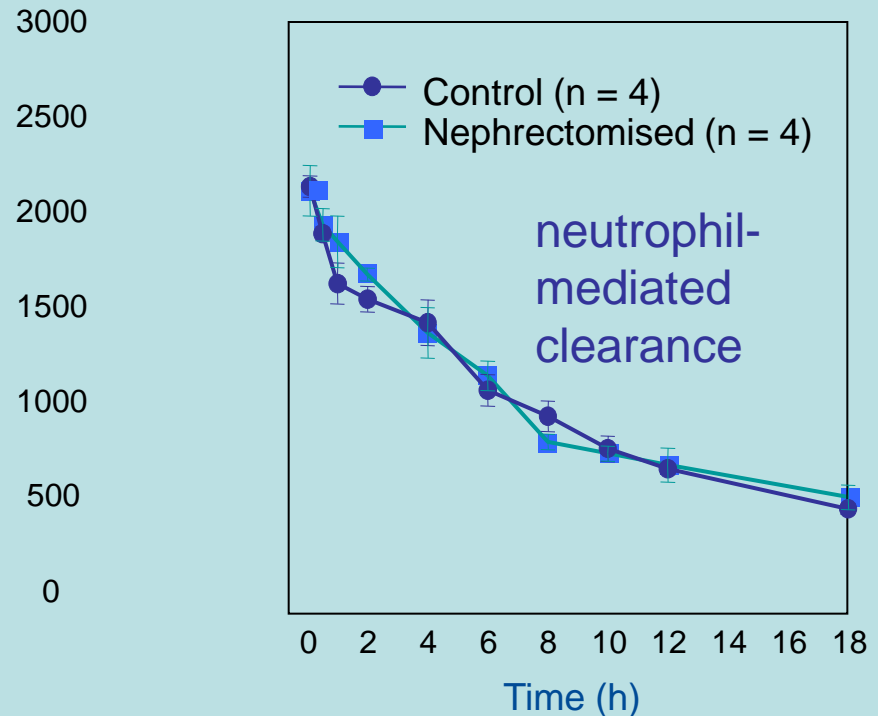
Filgrastim 100 µg/kg



Rapid decrease of plasma concentration

→ Daily administration

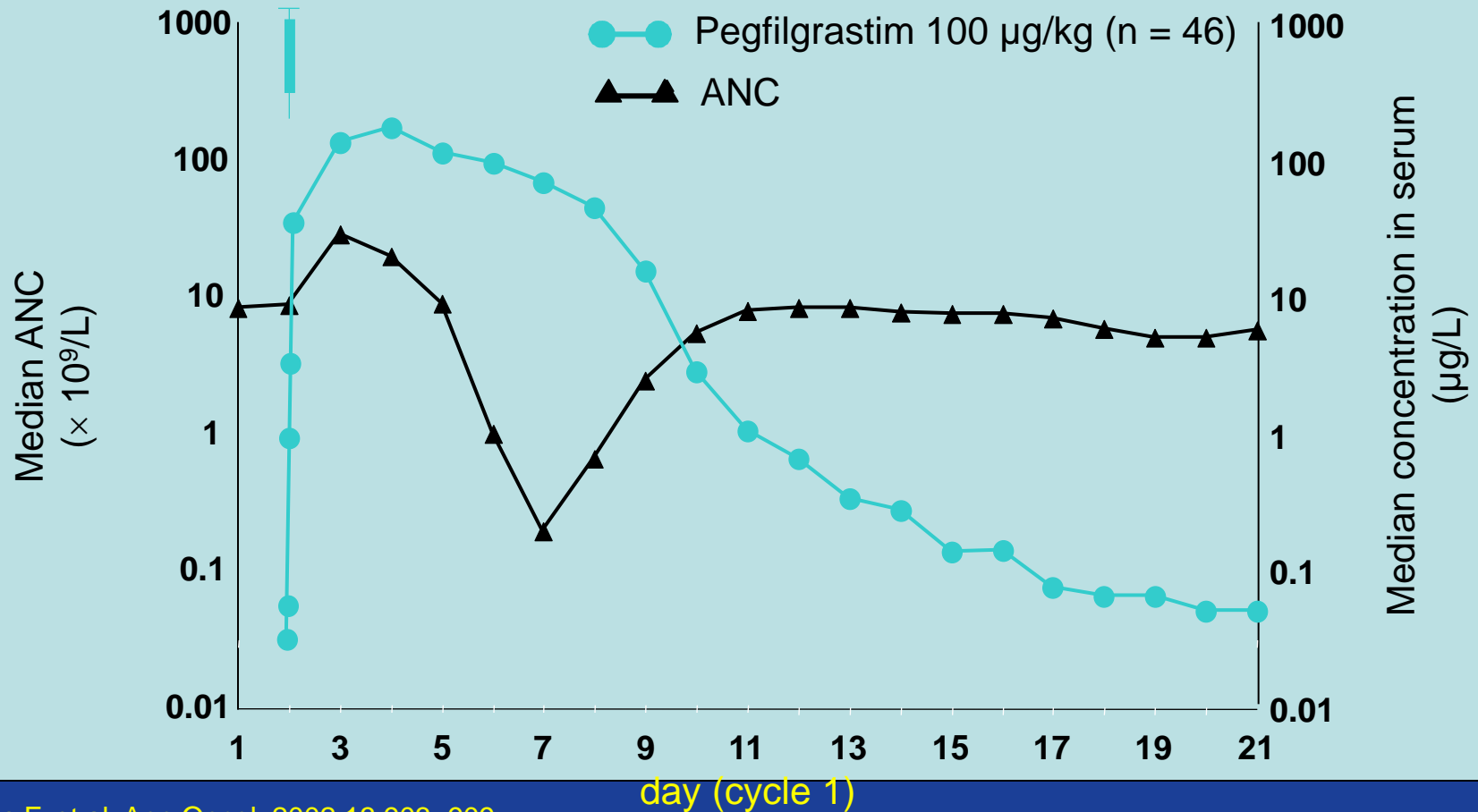
Pegfilgrastim 100 µg/kg



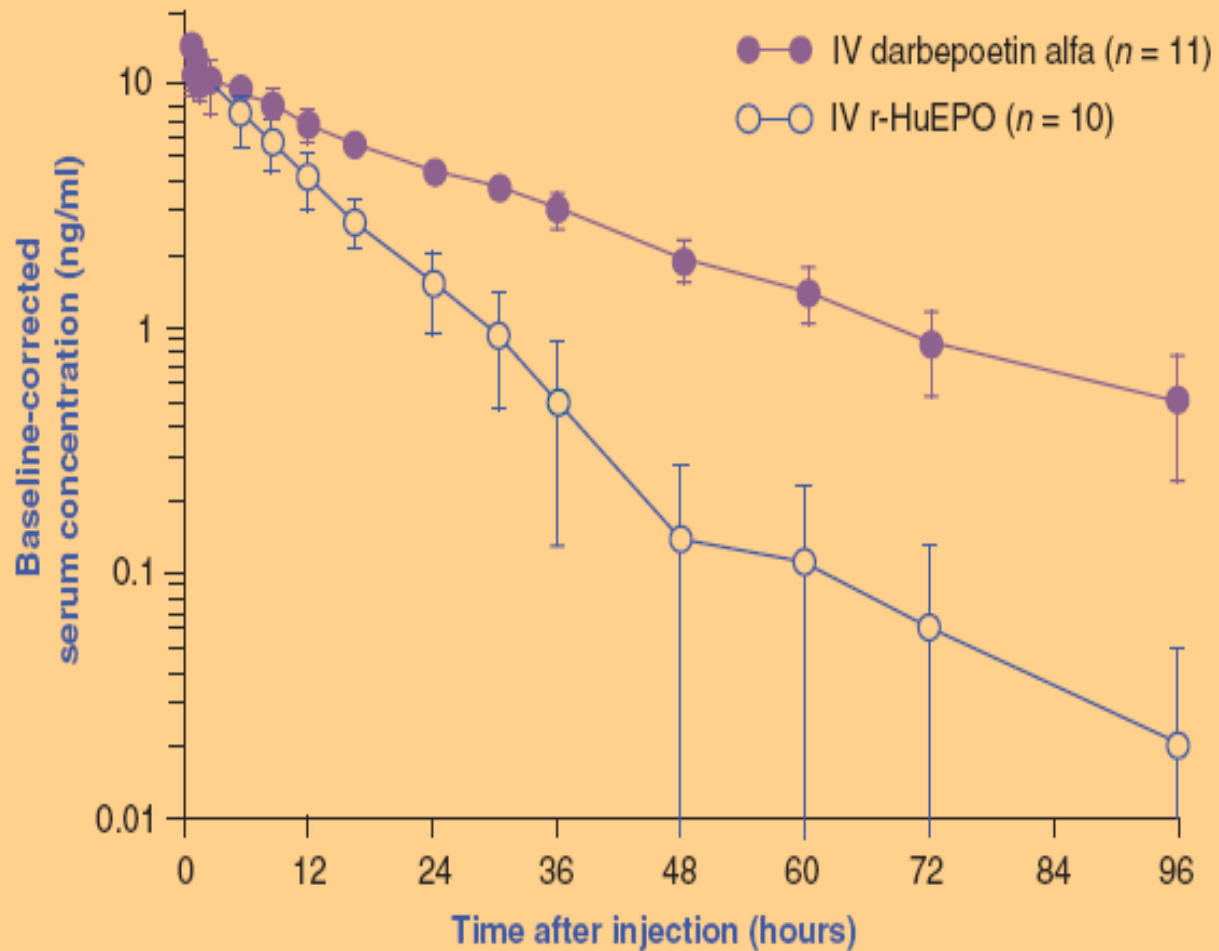
Longer half-life

→ Gavage only 1x/CT-cycle

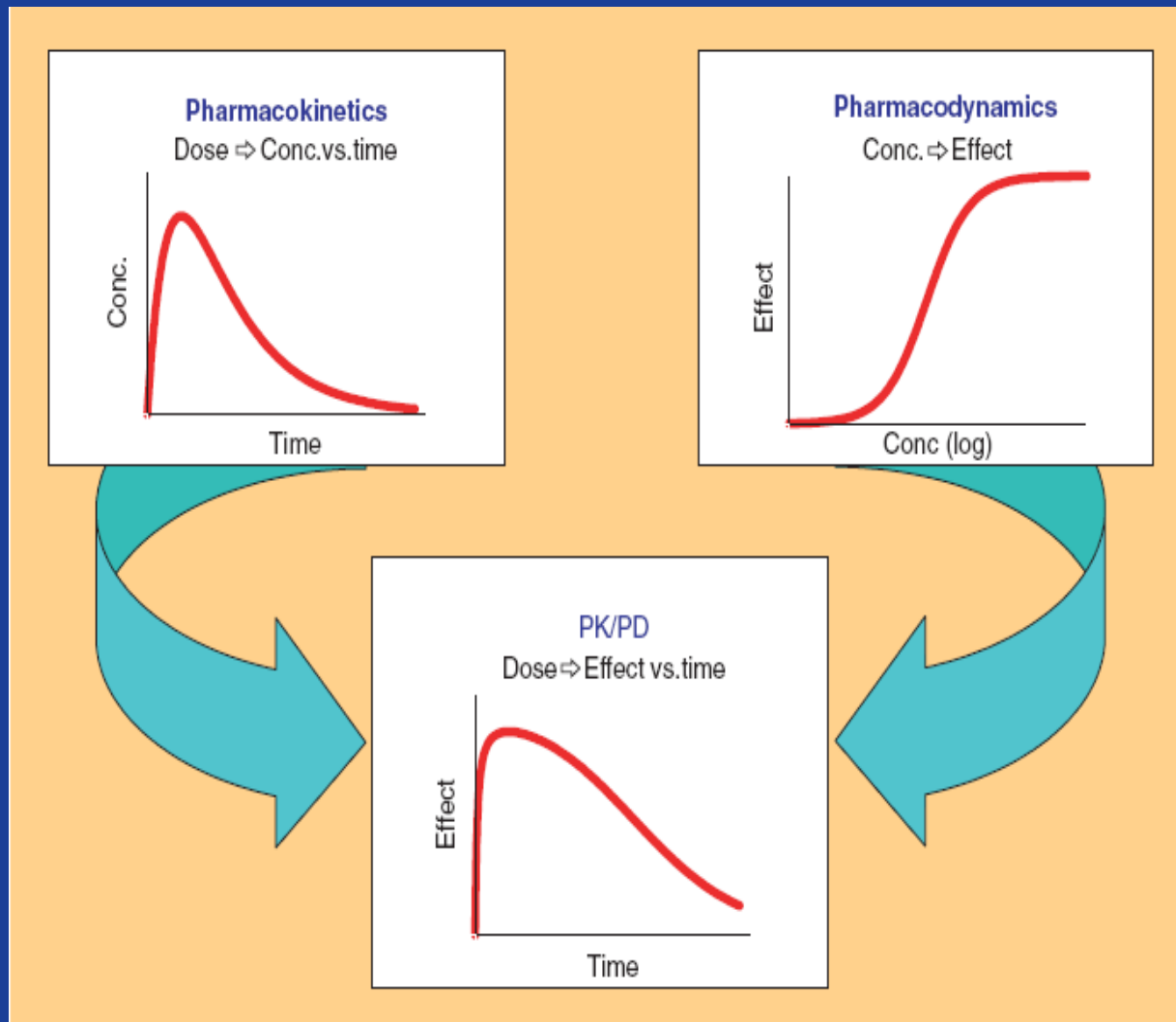
Self-regulation by Pegfilgrastim



PK: distribution of protein therapeutics

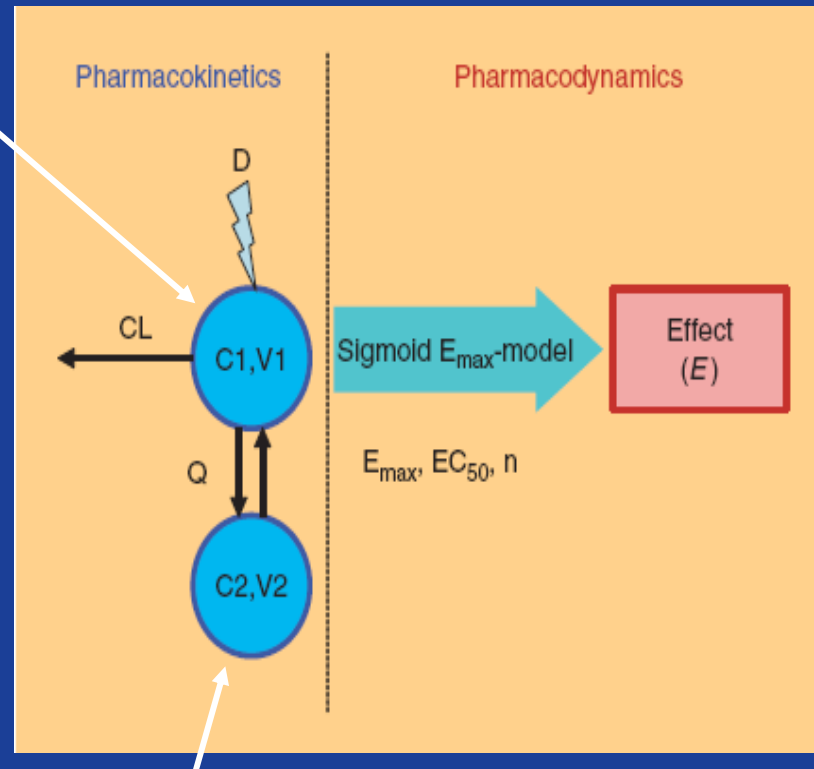


Indirect-direct effects



PK/PD link model

Central compartment

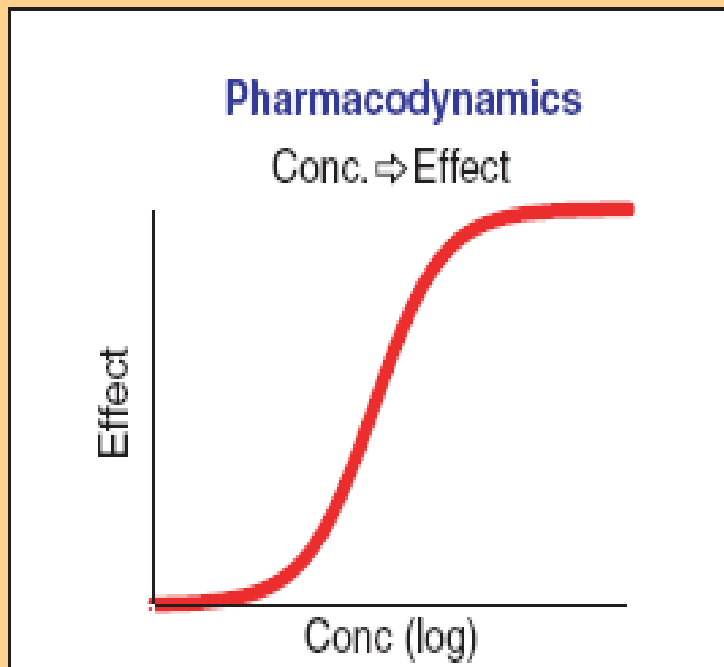


Peripheral compartment

PD: models for protein therapeutics

Indirect effect models

P



Pharmacodynamics

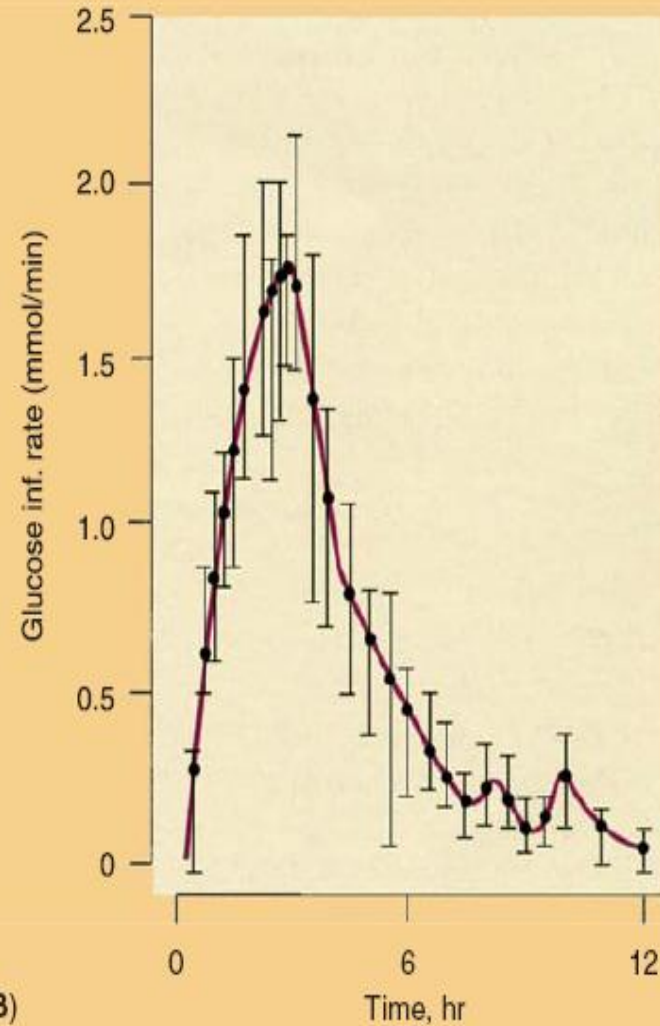
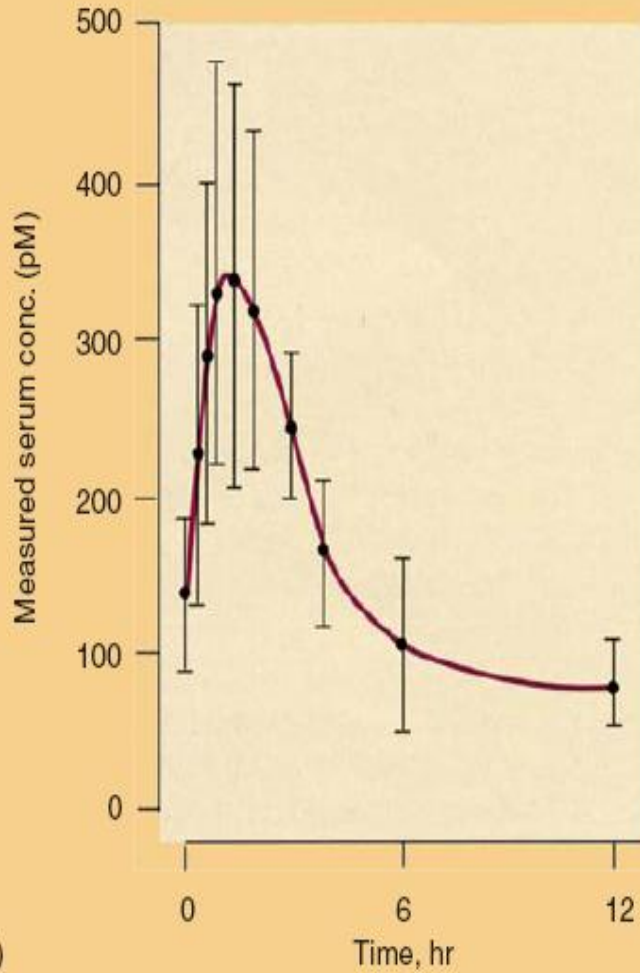
max-model

max, EC_{50}

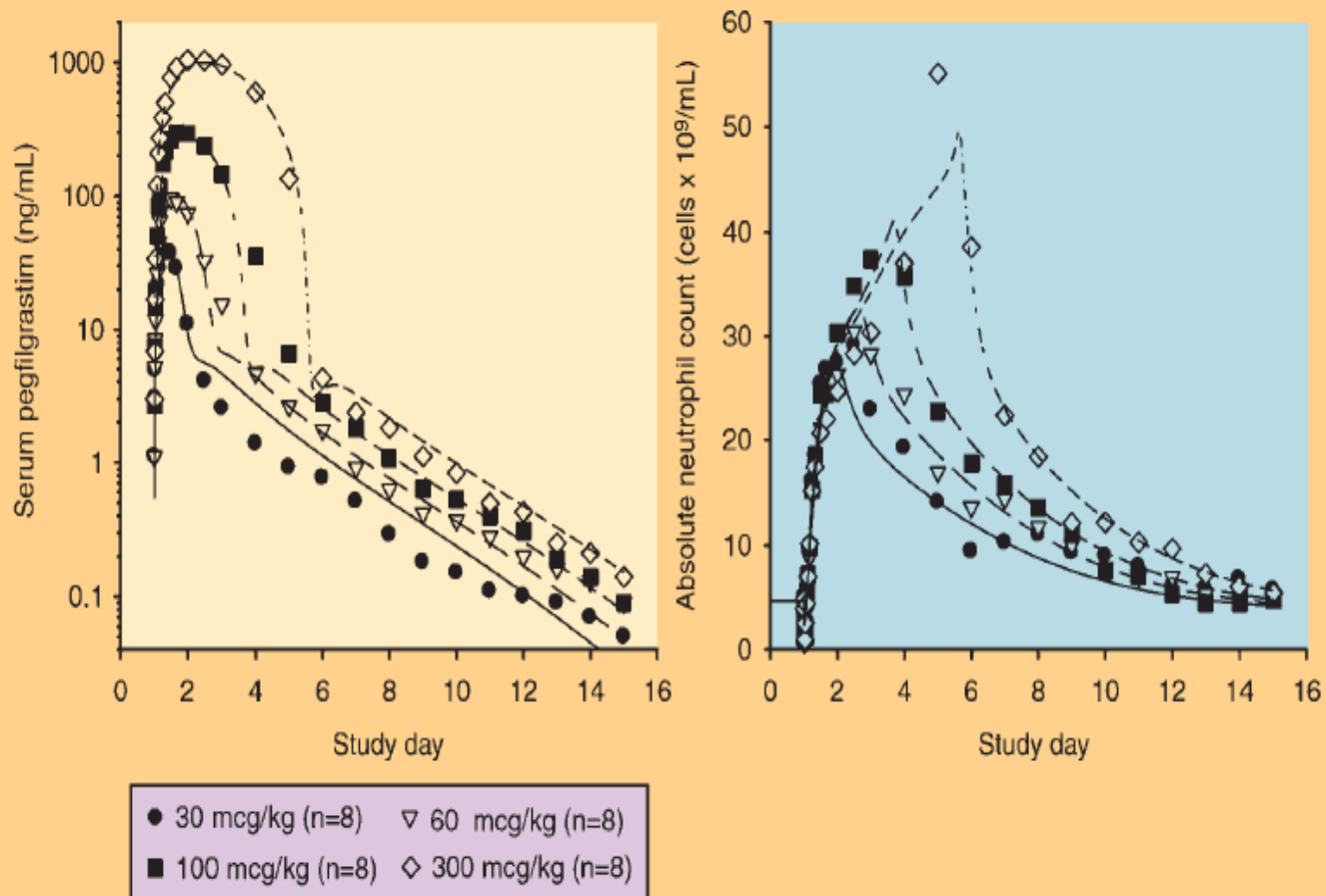
ment

Effect
(E)

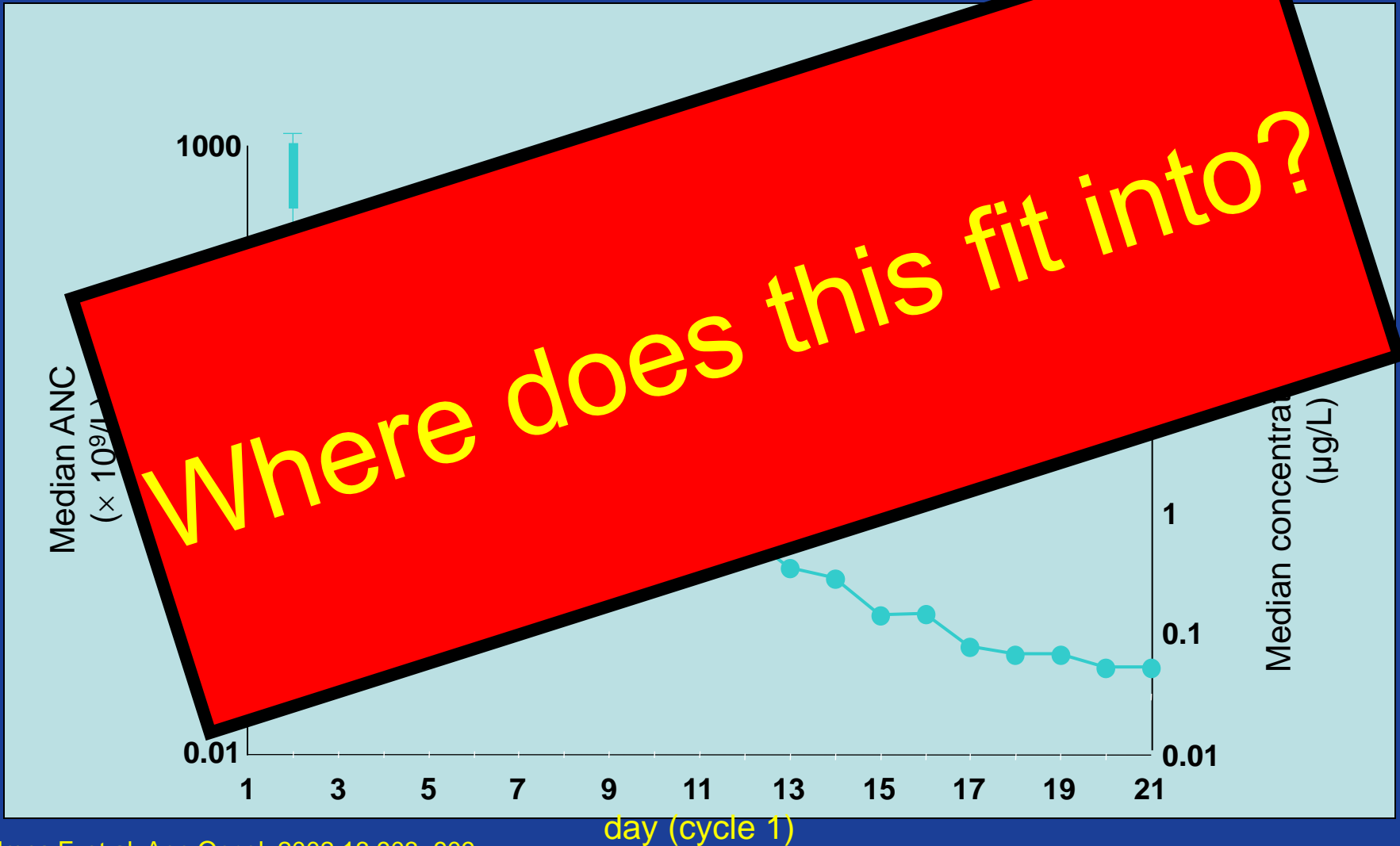
PK/PD link model



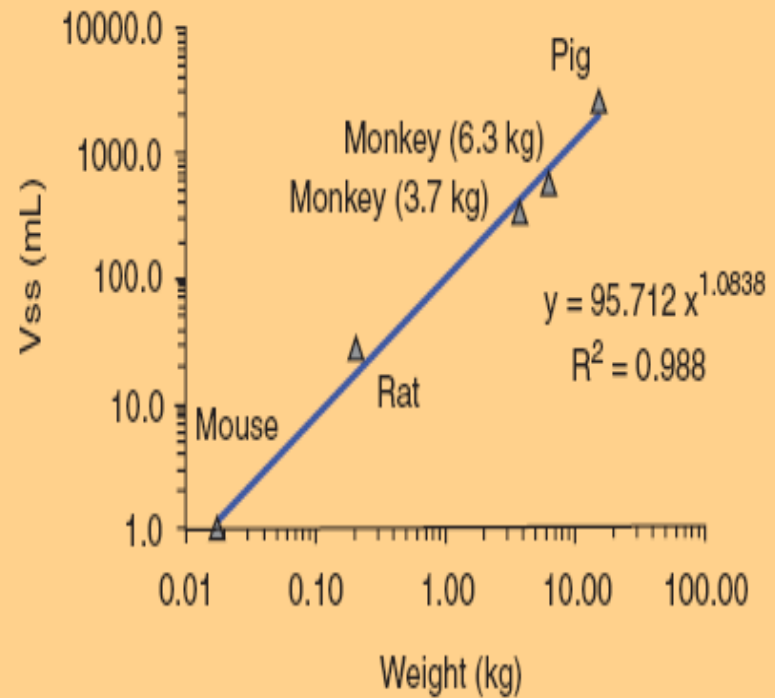
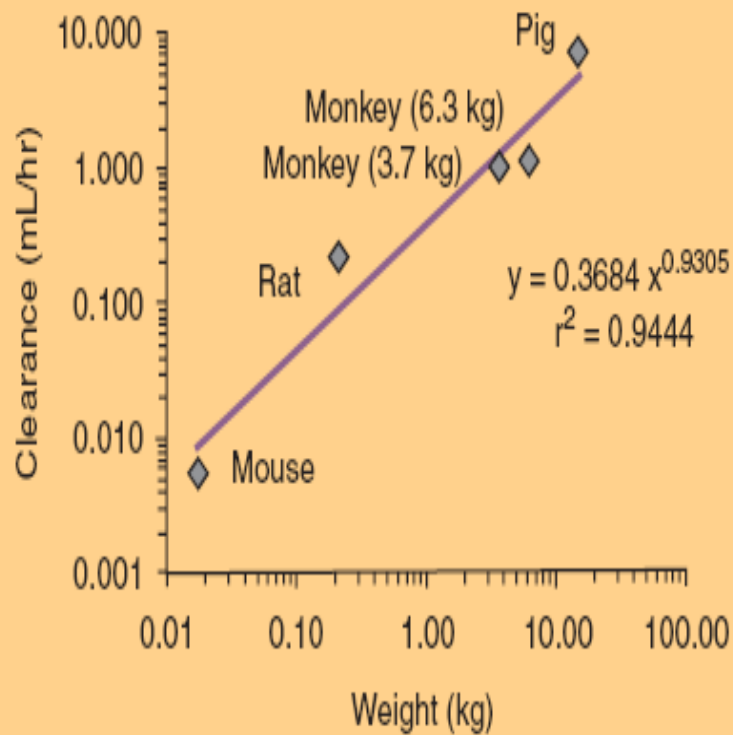
DR- and CR-curves are useful predictors for clinical trials



Self-regulation by Pegfilgrastim



Scaling techniques are used for inter-species prediction of PK curves



Conclusion slide

- Overview on PK/PD
 - What does PK/PD mean for drug/body?
- PK: elimination of protein therapeutics
 - To degrade or not degrade... that is...
- PK: distribution of protein therapeutics
 - Binding to the plasma proteins or what?
- PD: models for protein therapeutics
- PD/PK link models
 - Dry matters