What's different in PK of biologics?

Stephan Glund
Clinical PK/PD, Boehringer Ingelheim, Biberach

Disclosure

Full-time employee of Boehringer Ingelheim

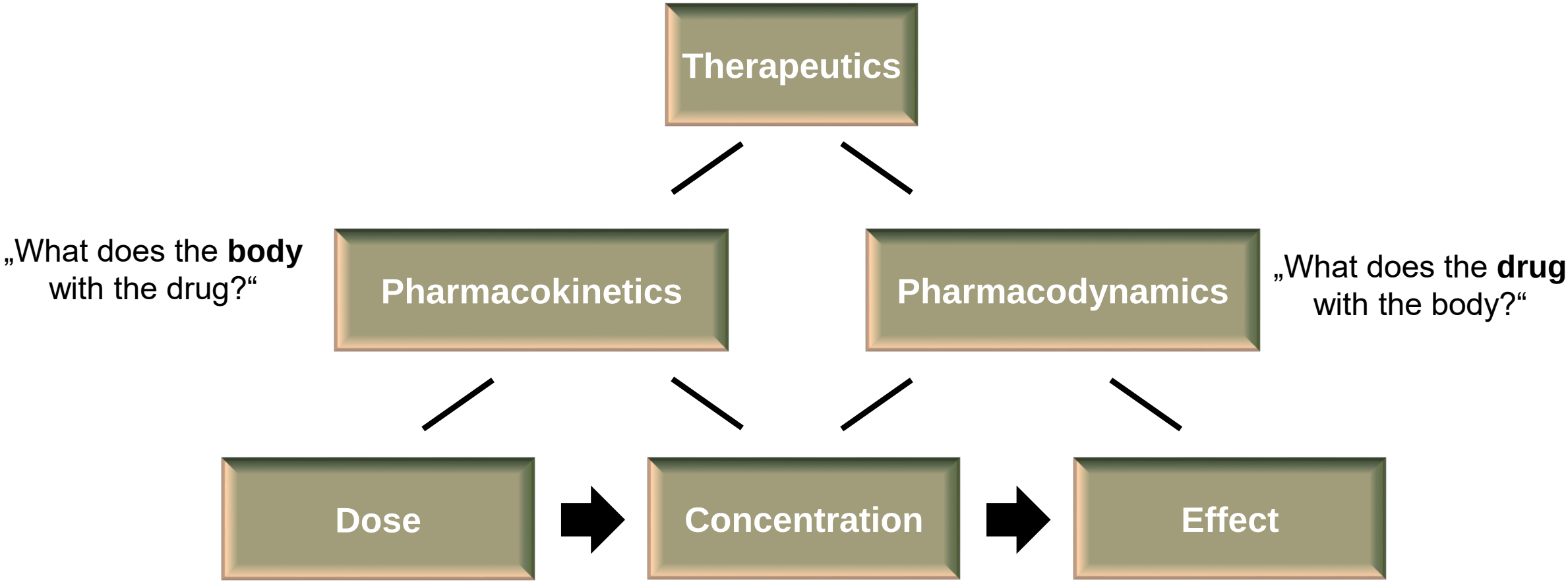
Agenda

- General introduction
- Bioanalytical aspects
- Immunogenicity
- ADME of mABs
- Drug-drug interaction
- Other aspects
- Considerations for clinical development / study design
- Comparability

Agenda

- General introduction
- Bioanalytical aspects
- Immunogenicity
- ADME of mABs
- Drug-drug interaction
- Other aspects
- Considerations for clinical development / study design
- Comparability

What´s Pharmacokinetics/ Pharmacodynamics?



Biological

Biopharmaceutical; NBE = New Biological Entity; Biologic(al) Medicinal Product; Therapeutic Protein

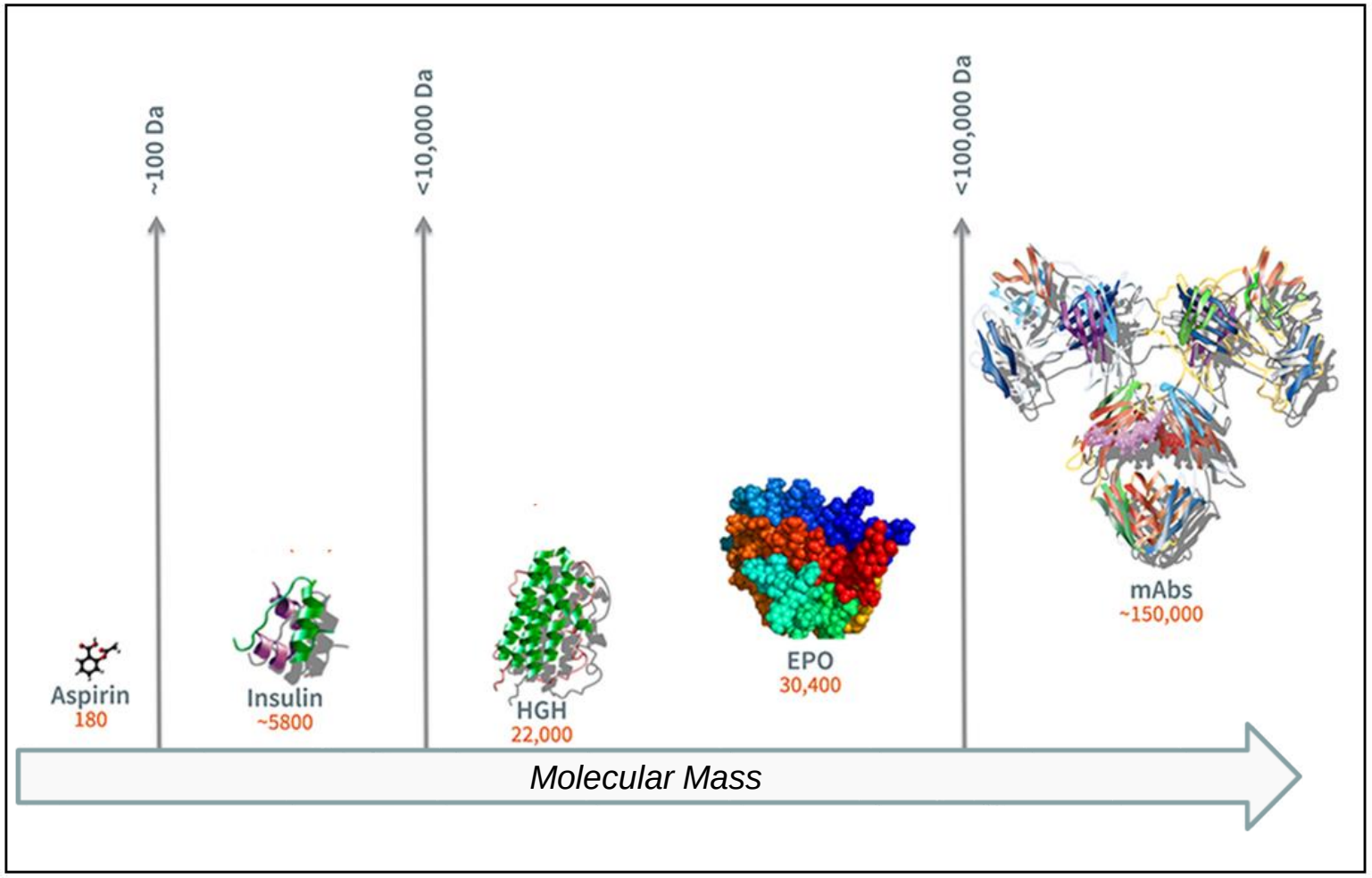
Any pharmaceutical drug product manufactured in, extracted from, or semisynthesized from biological sources.

Biologicals can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living cells or tissues.

Focus in this presentation:

monoclonal Antibodies (mAbs) & Antibody fragments (Fabs)

Biologics: size & complexity



Comparison of Biologics and Small Molecules

	Small molecule drugs	Biologics
Structure	• (relatively) simple and well-defined	• Complex (heterogeneous)
Manufacturing	• Defined chemical synthesis • Identical copy can be made	• Produced in living cells • Control of process challenging • Identical copy not possible
Characterization	• Product easy to characterize	• Complete characterization not possible
Stability	• Stable	• Sensitive to external conditions (heat, light, agitation, …)
Immunogenicity	• (Usually) not immunogenic	• Immunogenic

Biologics are not just „big chemicals“!

Top 5 drugs by sales in 2018

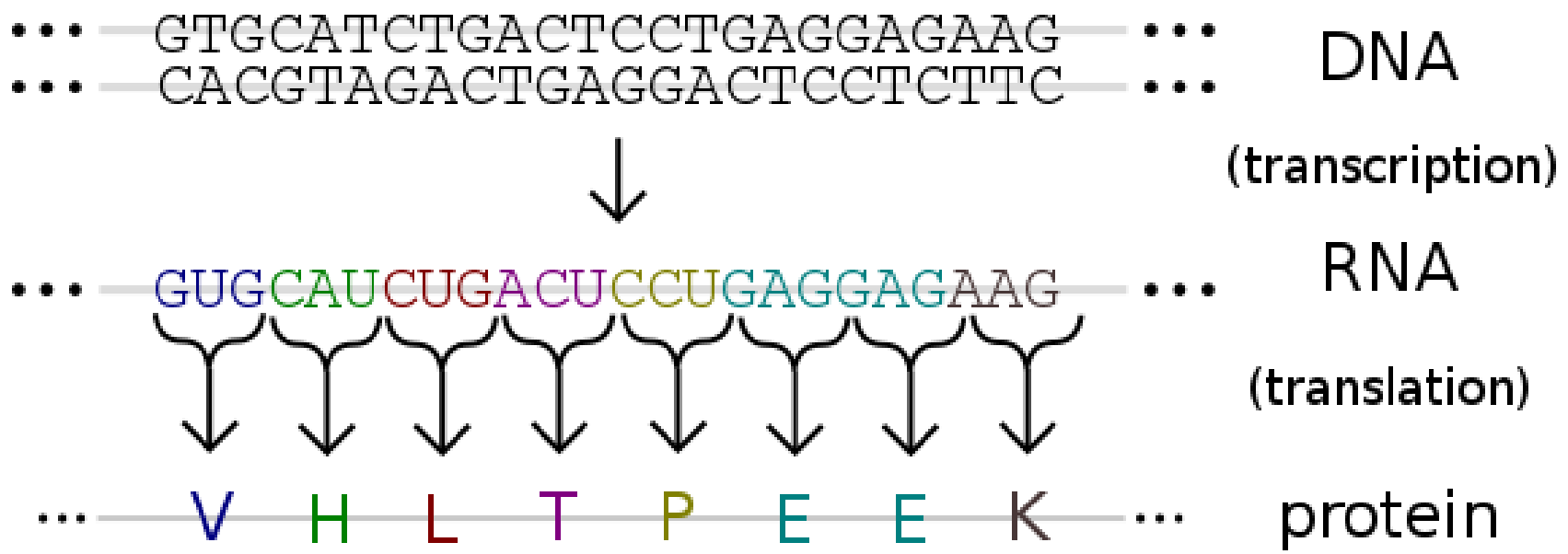
Rank	Drug	Trade name	Type	Main indications	Company	Sales (B$/year)
1	Adalimumab	Humira	Biologic	Rheumatoid arthritis	AbbVie Inc.	19.9
2	Lenalidomid	Revlimid	Small molecule	Multiple myeloma	Celgene	9.7
3	Pembrolizumab	Keytruda	Biologic	NSCLC	Merck & Co.	7.2
4	Trastuzumab	Herceptin	Biologic	Breast cancer	Roche	7.1
5	Bevacizumab	Avastin	Biologic	Colorectal cancer	Roche	7.0

Major kinds of biopharmaceuticals include:

Blood factors, thrombolytic agents, hormones, haematopoietic growth factors, interferons, interleukins, vaccines, mAbs

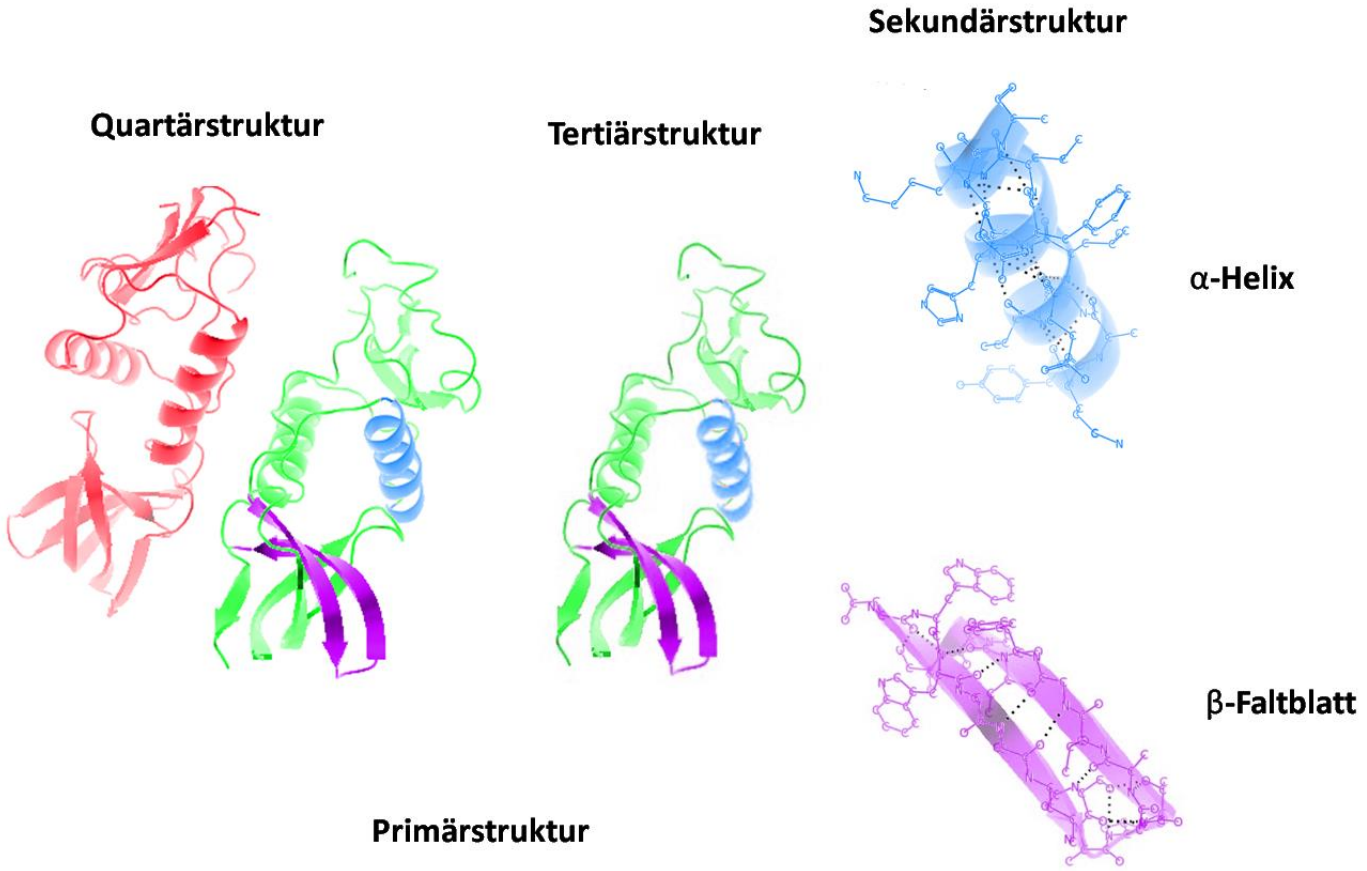
https://www.nature.com/articles/d41573-019-00049-0

Protein biosynthesis



https://en.wikipedia.org/wiki/Protein#/media/File:Genetic_code.svg

Protein structure



https://upload.wikimedia.org/wikipedia/commons/2/20/Protein-Struktur.png

Posttranslational modification

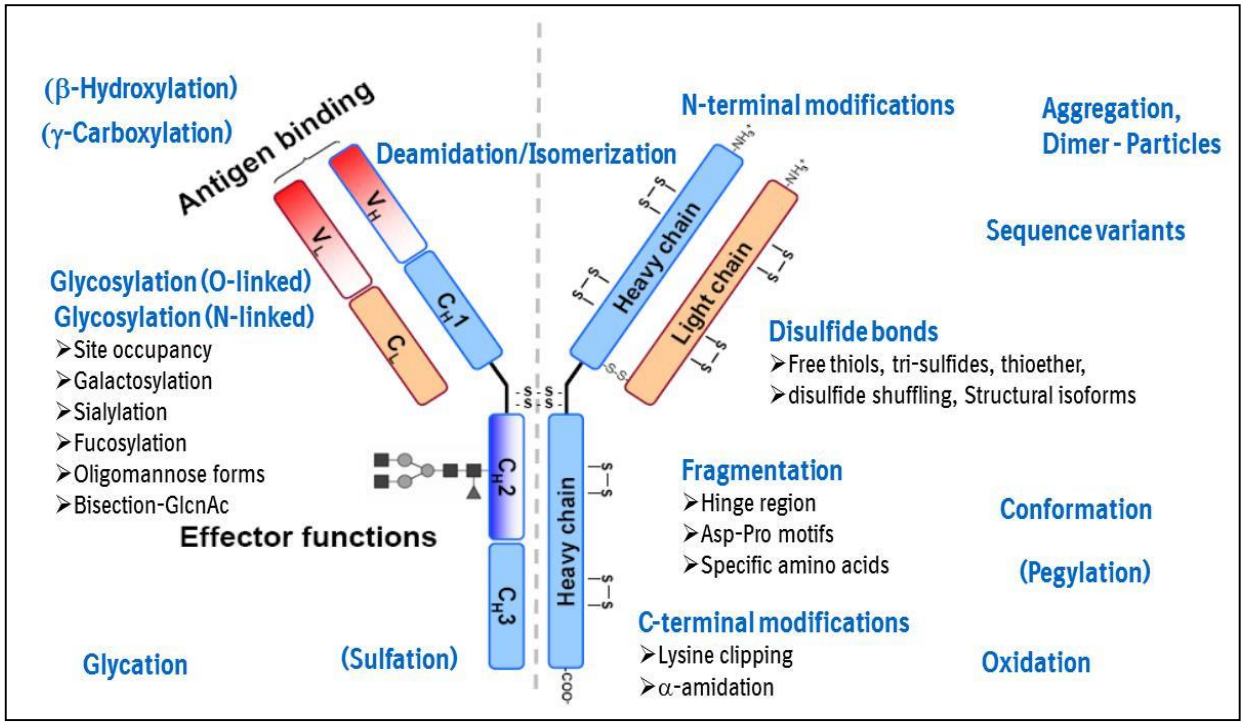
- Refers to the covalent and generally enzymatic modification of proteins following protein biosynthesis
- These modifications are important components, e.g., in cell signaling

Most common modifications include:

Phosphorylation
Acetylation
N-linked glycosylation
Amidation
Hydroxylation
Methylation
O-linked glycosylation
Ubiquitylation
Pyrrolidone Carboxylic Acid

Khoury, G. A., et al. Proteome-wide post-translational modification statistics: frequency analysis and curation of the swiss-prot database. *Sci. Rep.* 1, 90; DOI:10.1038/srep00090 (2011).

Micro-Heterogeneity



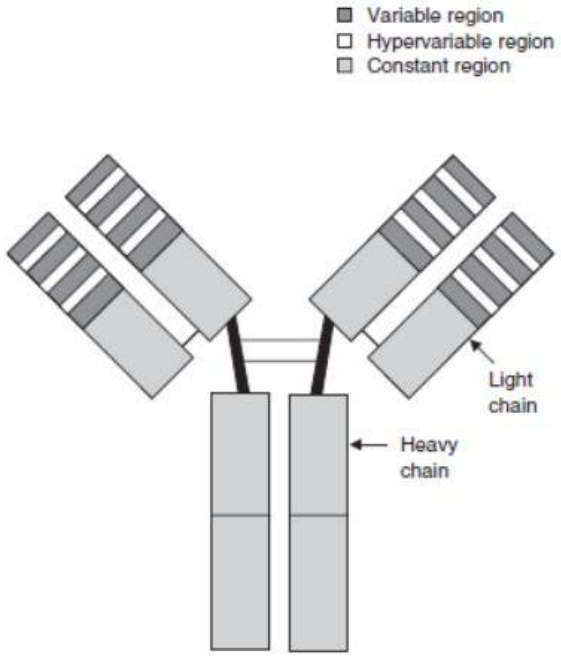
Micro-heterogeneity of mAbs: >10^8 potential molecular variants

The process determines the product

Advanced Drug Delivery Reviews 58 (2006) 707–722

Antibody / Fab - structure

- Antibodies (=Immunoglobulins; Ig), are large proteins (~**150kDa**)
- Important role in immune response
- There are 5 Ig isotypes (IgG, IgM, IgD, IgE, IgA) differentiated by types of Ig heavy chains. **All approved antibody drugs so far are IgGs.**



Fab: fragment antigen binding

Fc: fragment cristalyzable

Clin Pharmacokinet 2010; 49 (8): 493-5-7

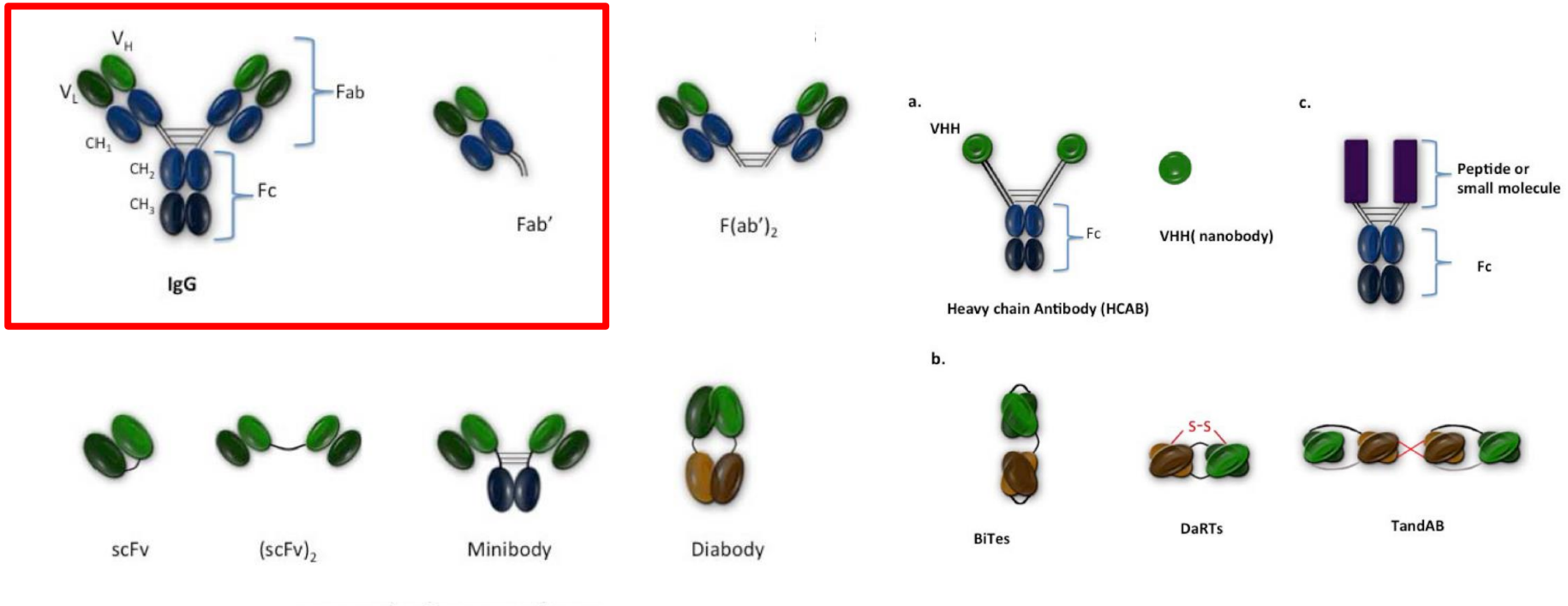
Properties of Ig classes

TABLE 2. *Physical, chemical, and biological properties of human heavy chain immunoglobulin classes*

Property	IgM	IgD	IgG	IgA	IgE
Molecular form	Pentamer, hexamer	Monomer	Monomer	Monomer, dimer	Monomer
Number of C region domains	4	3	3	3	4
Tailpiece	+	–	–	+	–
Accessory chains	J chain, SC	None	None	J chain, SC	None
Subclasses	None	None	G1,G2,G3,G4	A1,A2	None
Molecular weight	950 kD, 1150 kD	175 kD	150 kD	160 kD, 400 kD	190 kD
Carbohydrate content (%)	10	9	3	7	13
Percentage of total serum Ig	5–10%	0.3%	75–85%	7–15%	0.02%
Average adult free serum level (mg/ml)	0.7–1.7	0.04	9.5–12.5	1.5–2.6	0.0003
Synthesis rate (mg/kg/d)	7	0.4	33	65	0.016
Serum half-life (d)	5	3	23	6	2.5
Antibody valence	10, 12	2	2	2, 4	2
Bacterial lysis	+	?	+	+++	?
Placental transfer	–	–	+	–	–
Mast cell/basophil binding	–	–	–	–	+
Macrophage binding	–	–	+	+	–
Classical complement activation	++	–	+	–	–
Alternate complement activation	–	+	+	A1+,A2–	–
Other biological properties	Primary Ab responses; Secretory immunoglobulin	Unknown; Useful as a B cell marker	Hallmark of secondary immune responses	Main secretory immunoglobulin	Allergic and anti-parasite responses

Frazer and Capra: Fundamental Immunology, 1999
Chapter 3: Immunology: Structure and Function

NBE complexity – protein/peptide constructs



- Large variety of new concepts/constructs
- Each construct is associated with specific PK/PD properties

➢ *Focus on mAB and Fab*

J Clin Pharmacol. 2015 March ; 55(0 3): S4–S20

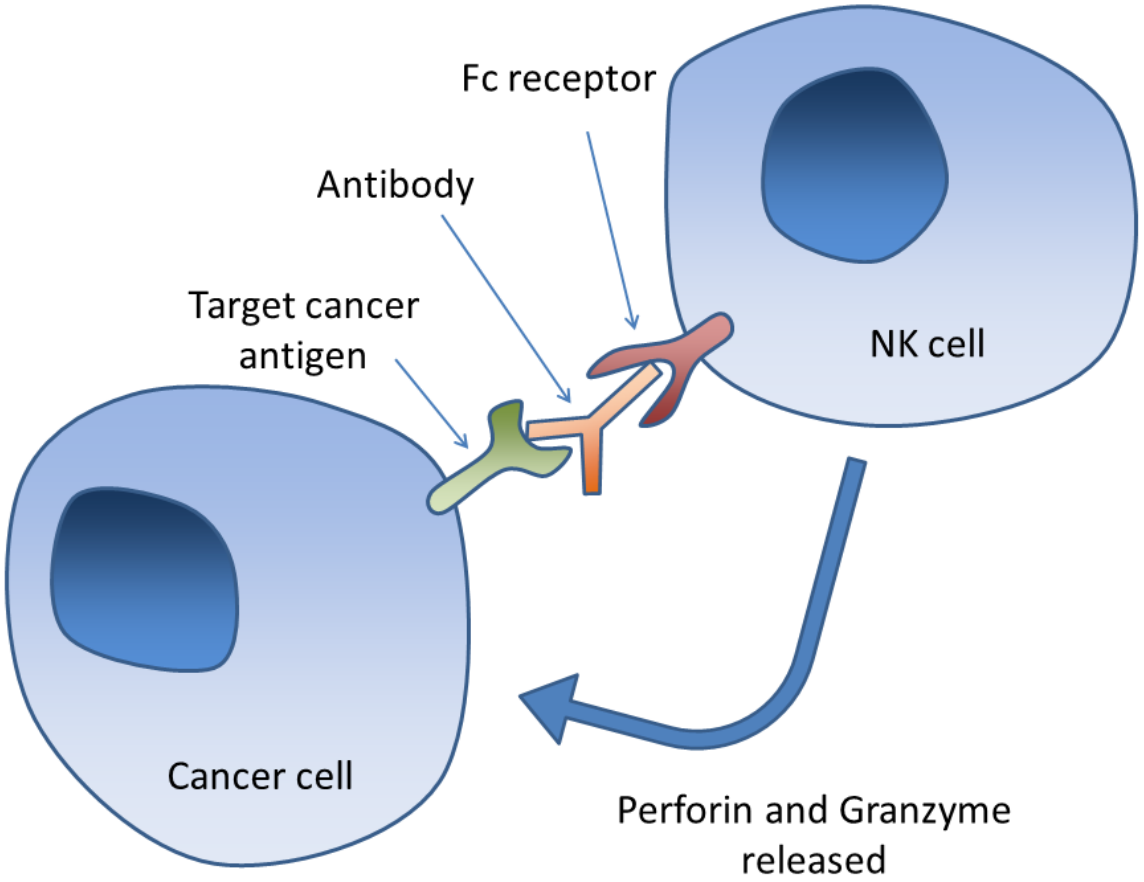
Modes of Action

Due to their high selectivity and affinity for the drug target, therapeutic mAbs are considered to be very close to the concept of a „magic bullet“

postulated by Paul Ehrlich in the early 20th century

- Blockage of interaction by binding to ligand or receptor
- Antibody-Dependent Cellular Cytotoxicity (ADCC)
- Complement-Dependent Cytotoxicity (CDC)
- Conjugated mAbs
- T-cell engagers

Antibody-dependent cell-mediated cytotoxicity (ADCC)



https://en.wikipedia.org/wiki/Cancer_immunotherapy#/media/File:Antibody-dependent_cell-mediated_cytotoxicity.png

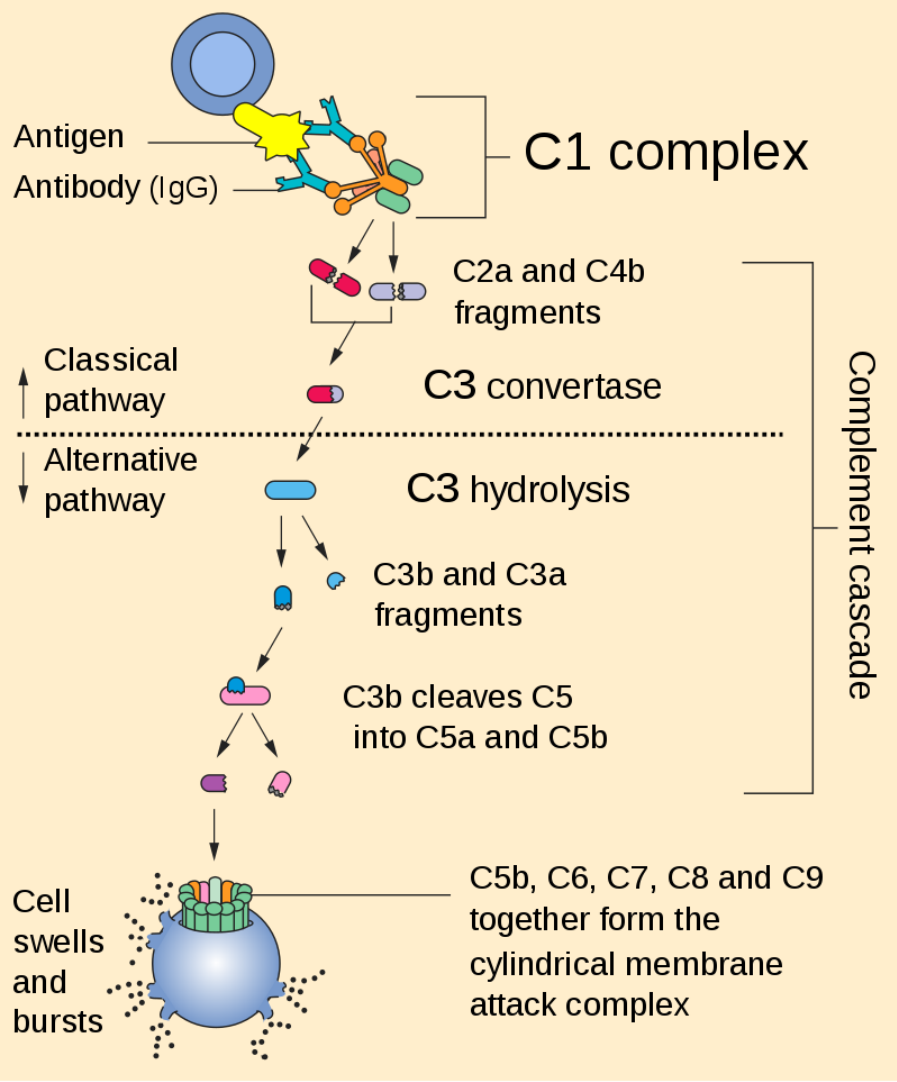
Modes of Action

Due to their high selectivity and affinity for the drug target, therapeutic mAbs are considered to be very close to the concept of a „magic bullet“

postulated by Paul Ehrlich in the early 20th century

- Blockage of interaction by binding to ligand or receptor
- Antibody-Dependent Cellular Cytotoxicity (ADCC)
- Complement-Dependent Cytotoxicity (CDC)
- Conjugated mAbs
- T-cell engagers

Complement-Dependent Cytotoxicity (CDC)



https://en.wikipedia.org/wiki/Classical_complement_pathway#/media/File:Complement_pathway.svg

Modes of Action

Due to their high selectivity and affinity for the drug target, therapeutic mAbs are considered to be very close to the concept of a „magic bullet“

postulated by Paul Ehrlich in the early 20th century

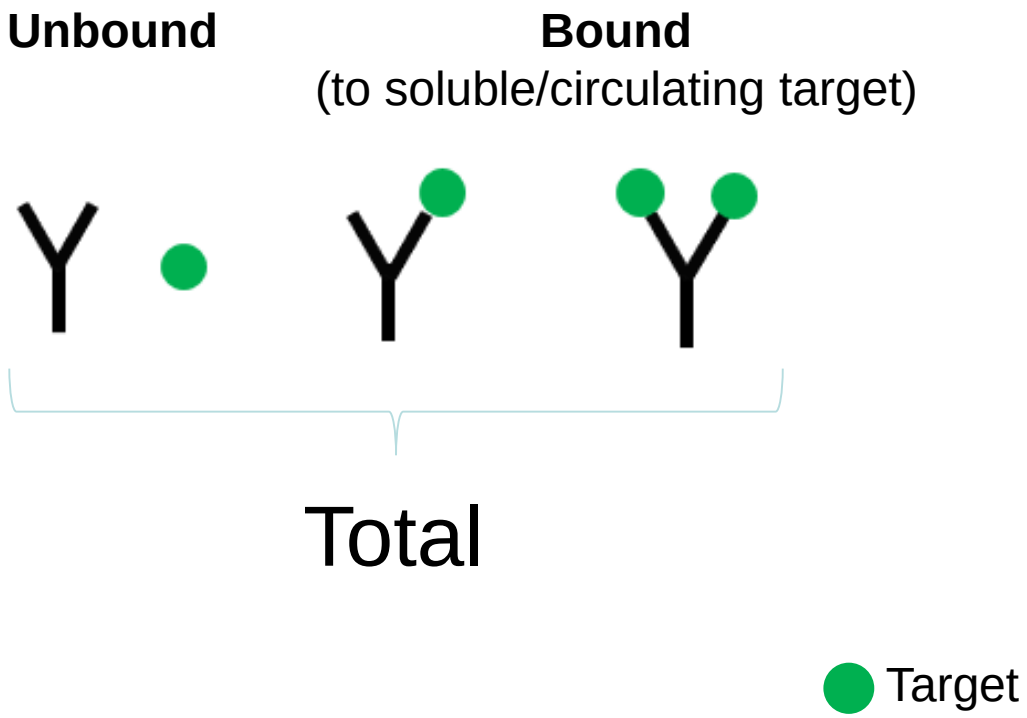
- Blockage of interaction by binding to ligand or receptor
- Antibody-Dependent Cellular Cytotoxicity (ADCC)
- Complement-Dependent Cytotoxicity (CDC)
- Conjugated mAbs
- T-cell engagers

Agenda

- General introduction
- Bioanalytical aspects
- Immunogenicity
- ADME of mABs
- Drug-drug interaction
- Other aspects (e.g. thorough QT)
- Considerations for clinical development / study design
- Comparability

Bioanalytical Aspects

- Which analyte/species is/should be detected?
- What is the influence of target concentration?
  - Healthy vs. patient
  - In patients with different diseases
  - Bispecific antibodies?



Bioanalytical Aspects (cont'ed)

- What assay format should be used (e.g., ELISA, Bioassay, LC-MS)

- Determination in complex matrices (e.g., plasma, whole blood, urine)

  Stability of analyte in matrix, specificity, accuracy, precision, lower and upper limit of quantification, limit of detection, concentration-response relationship, dilution linearity …

- Interference by anti-drug antibodies (ADA)?
- Interference by endogenous protein?
- Other interferences (e.g. degradation products)?

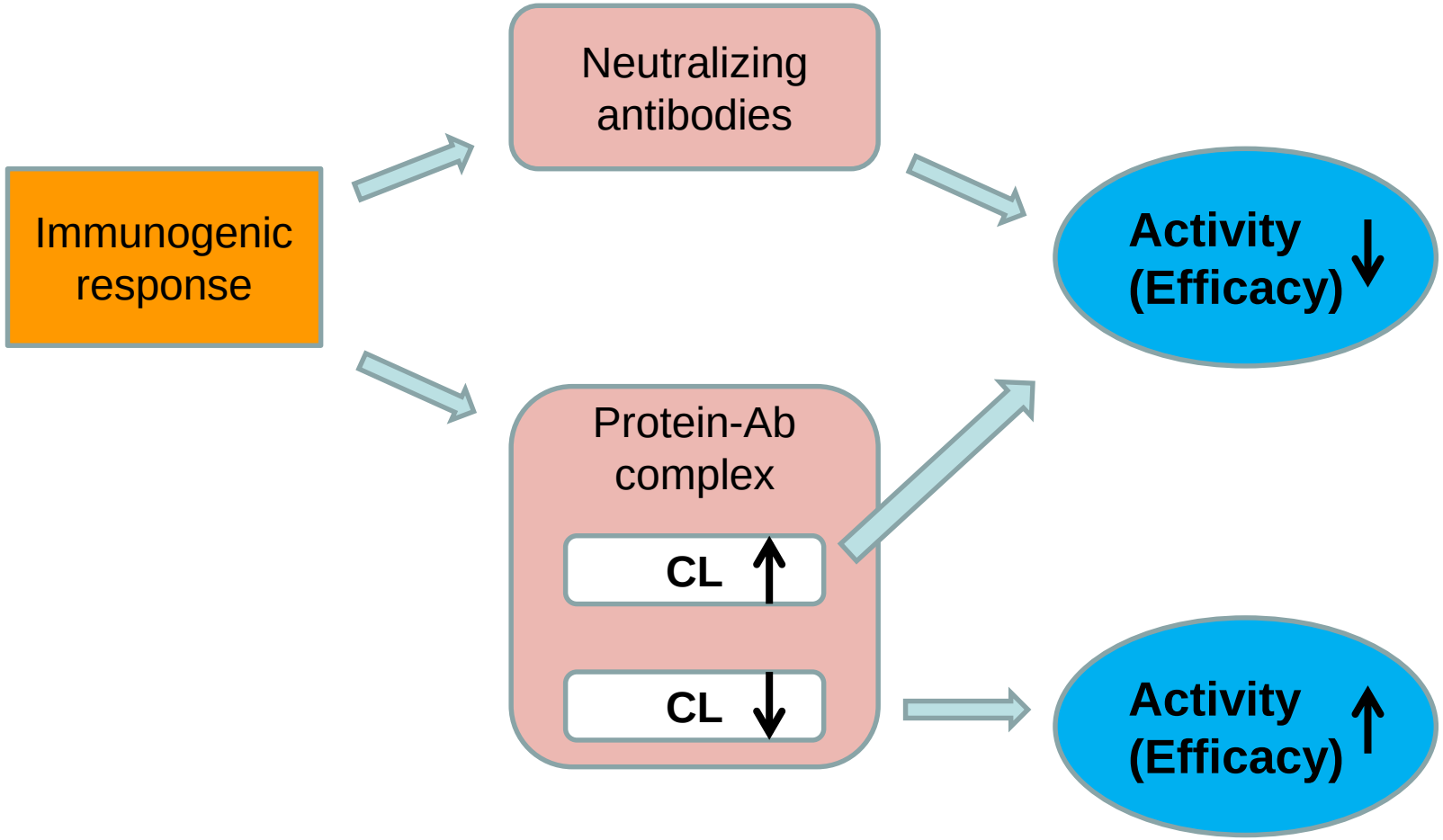
Sound bioanalytics are basis for successful pharmacokinetic analysis

Immunogenicity

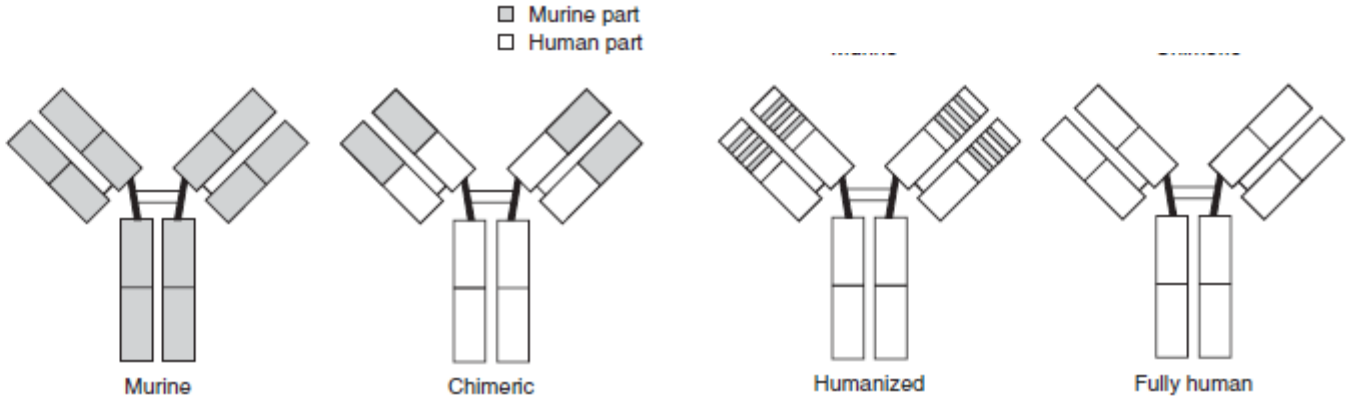
- A biologic can be an antigen itself and induce anti-drug antibody (ADA) in treated patients
  - All biological agents are (potentially) immunogenic
  - 25% out of 33 approved products by FDA in 2010 developed ADA[1]
  - Results are assay-dependent, not directly comparable between products
    - With method improvements, assay sensitivities improve -> *apparent* overall increase in prevalence of ADAs
- ADA might cause
  - Altered PK/PD with impact on efficacy (next slide)
  - Safety issues, incl.:
    - Infusion reaction
    - Anaphylaxis
    - Life threatening auto-immunity
  - "Nothing" (= no clinical impact detectable)

[1] *Baker, M.P., Self Nonself, 1 (4), 314-322 (2010)*

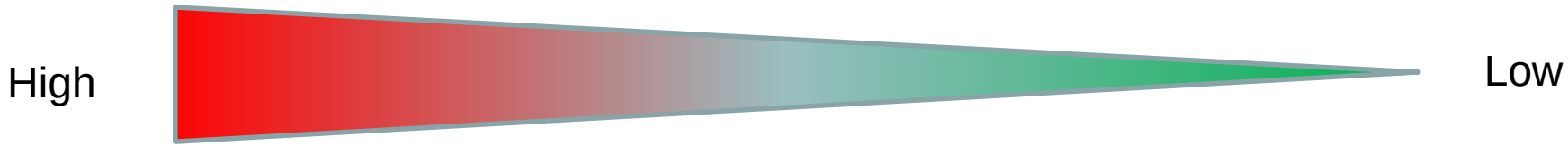
Possible effects of ADAs on PK/PD



Immunogenicity

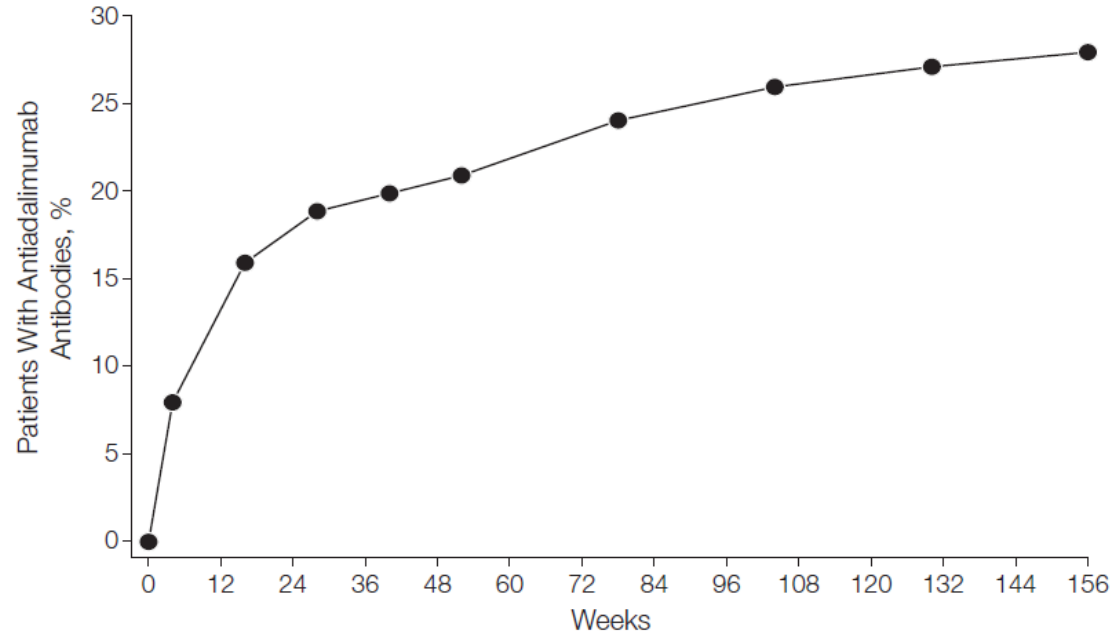


„-momab“	„-ximab“	„-zumab“	„-mumab“
Ibritumomab	Rituximab	Bevacizumab	Adalimumab
Muromomab	Infliximab	Trastuzumab	Panitumomab



Example Adalimumab

Figure 1. Percentage of Antiadalimumab Development Over Time



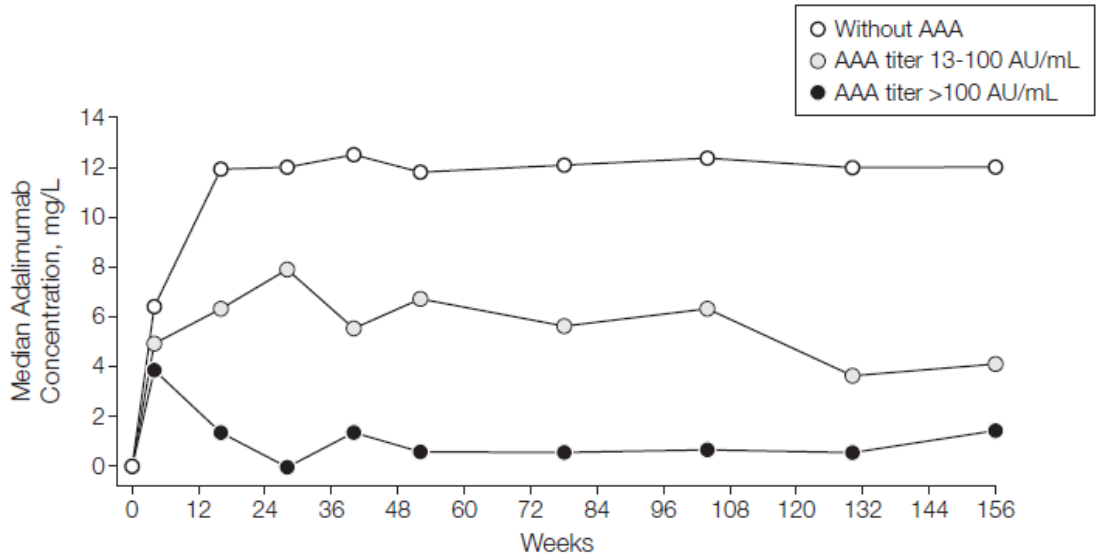
Week	0	4	16	28	40	52	78	104	130	156
No. of patients	272	261	247	228	201	192	175	156	137	118

Number of patients with available serum samples are shown.

JAMA. 2011 Apr 13;305(14):1460-8

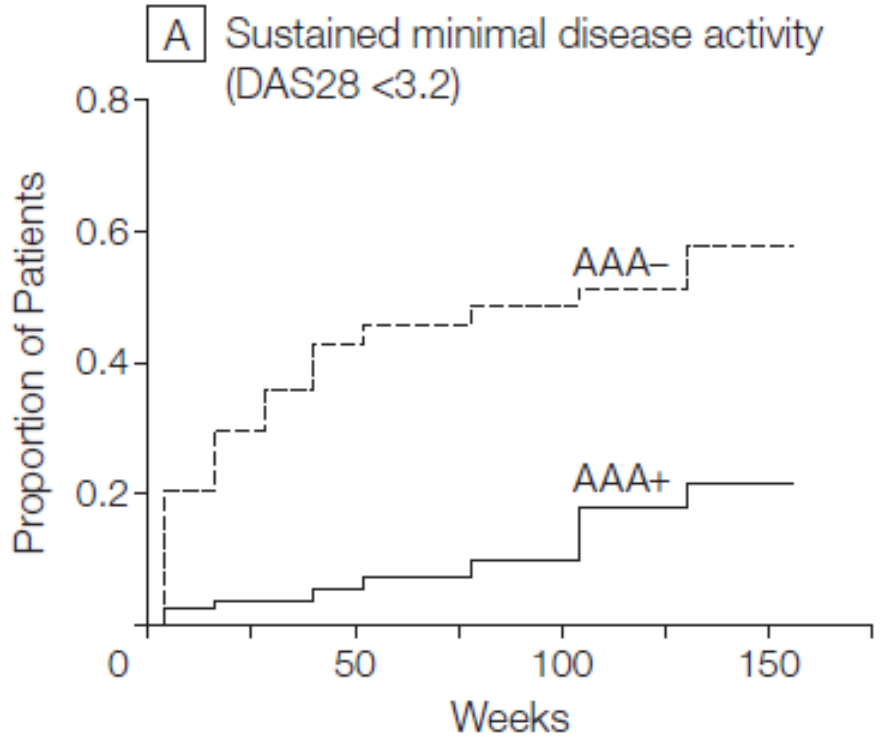
Example Adalimumab

Figure 2. Median Adalimumab Concentrations Over Time



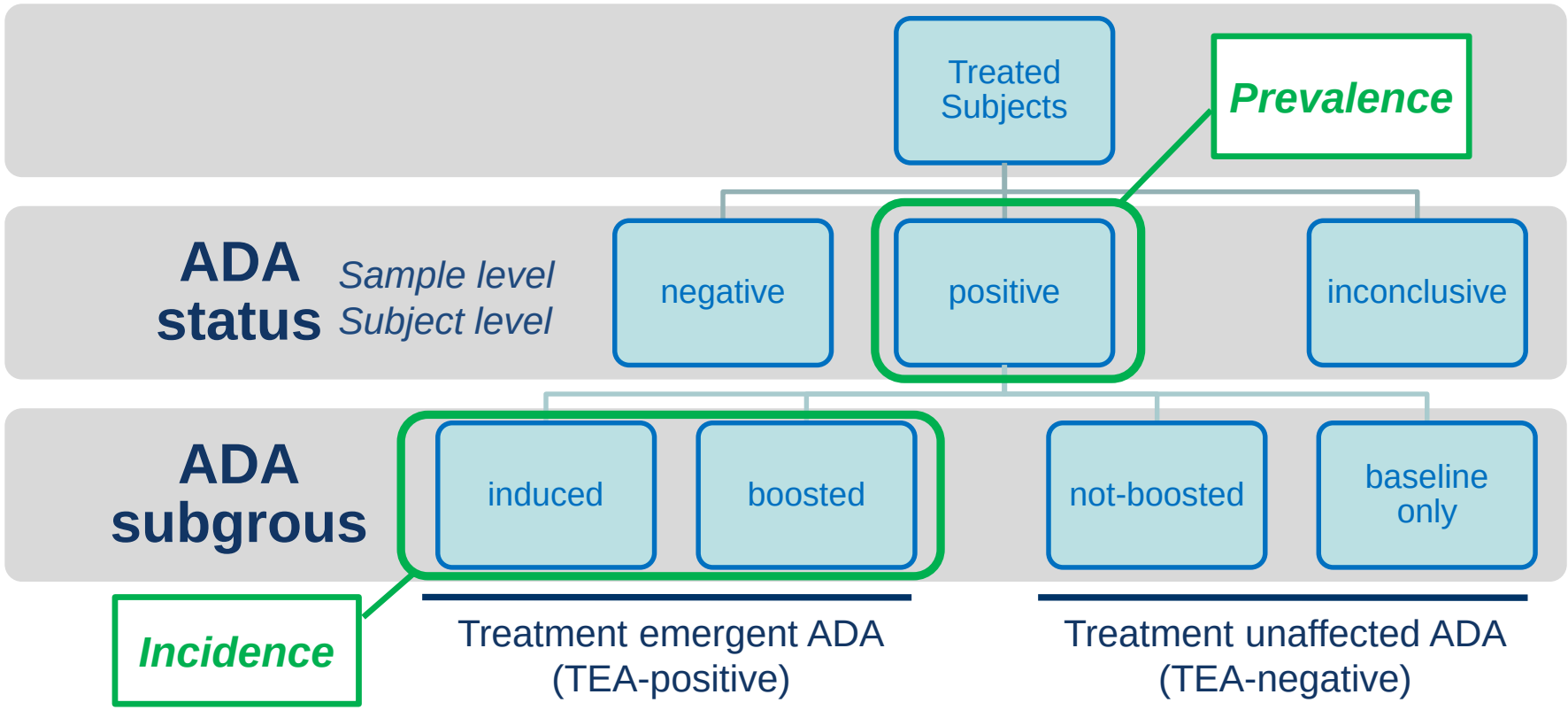
Week	0	4	16	28	40	52	78	104	130	156
No. of patients										
Without AAA	196	187	177	164	145	139	131	118	107	93
AAA 13-100 AU/ml	45	43	42	37	34	34	28	24	19	17
AAA >100 AU/ml	31	31	28	27	22	19	16	14	11	8

Sustained Minimal Disease Activity in patients with and without ADAs



JAMA. 2011 Apr 13;305(14):1460-8

Determination of ADA response



Titer distribution, neutralization potential, time course, persistence …

Clinical Impact

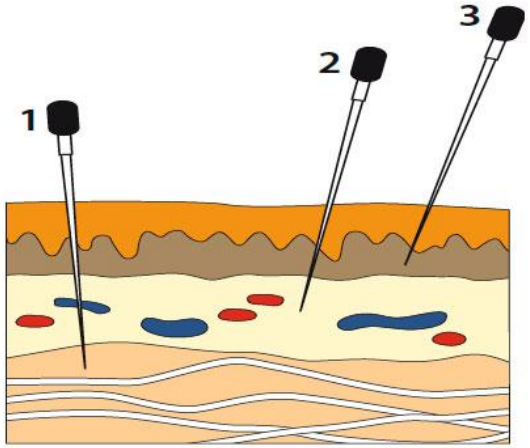
Based on:
The AAPS Journal
Vol. 16, No. 4, July 2014

Agenda

- General introduction
- Bioanalytical aspects
- Immunogenicity
- ADME of mABs
- Drug-drug interaction
- Other aspects
- Considerations for clinical development / study design
- Comparability

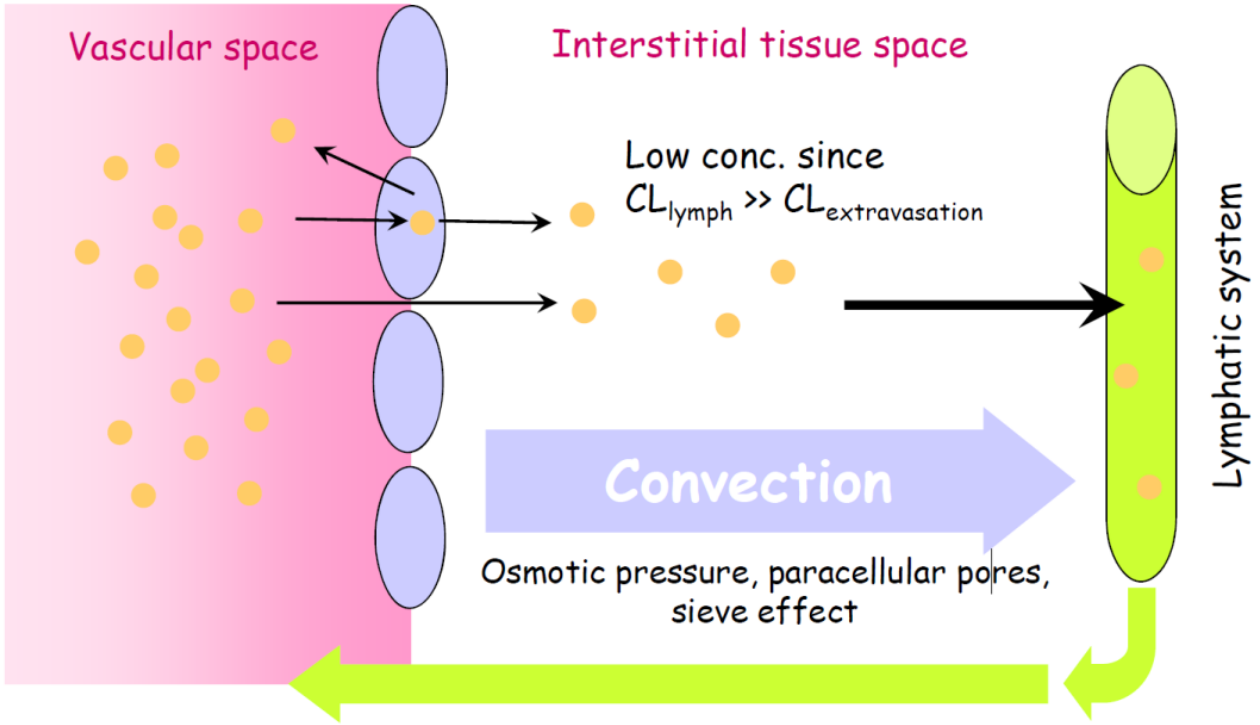
Absorption

- Administered usually i.v., s.c. or i.m.
  Low-to-no bioavailability when administered orally
- Bioavailability (s.c./i.m.) is generally high (40-100%); limited volume
- Absorbed via lymphatic system
- Absorption is a slow process;
  Tmax: 1-8 days after s.c. or i.m.



Distribution

- Limited due to usually large Molecular Weight; low volume of distribution
- Distribution mainly driven by convection (compared to diffusion for small molecules)
- Endocytosis (large surface of endothelial cells of blood vessels!)



Meibohm, B.: Pharmacokinetics and Pharmacodynamics of peptides and protein therapeutics; Pharmaceutical Biotechnology : Fundamentals and Applications; Springer-Verlag New York Inc. 2013

Absorption, Distribution, Metabolism, Excretion

Typical elimination for mABs:

- Non-specific elimination pathway
- Specific elimination pathway

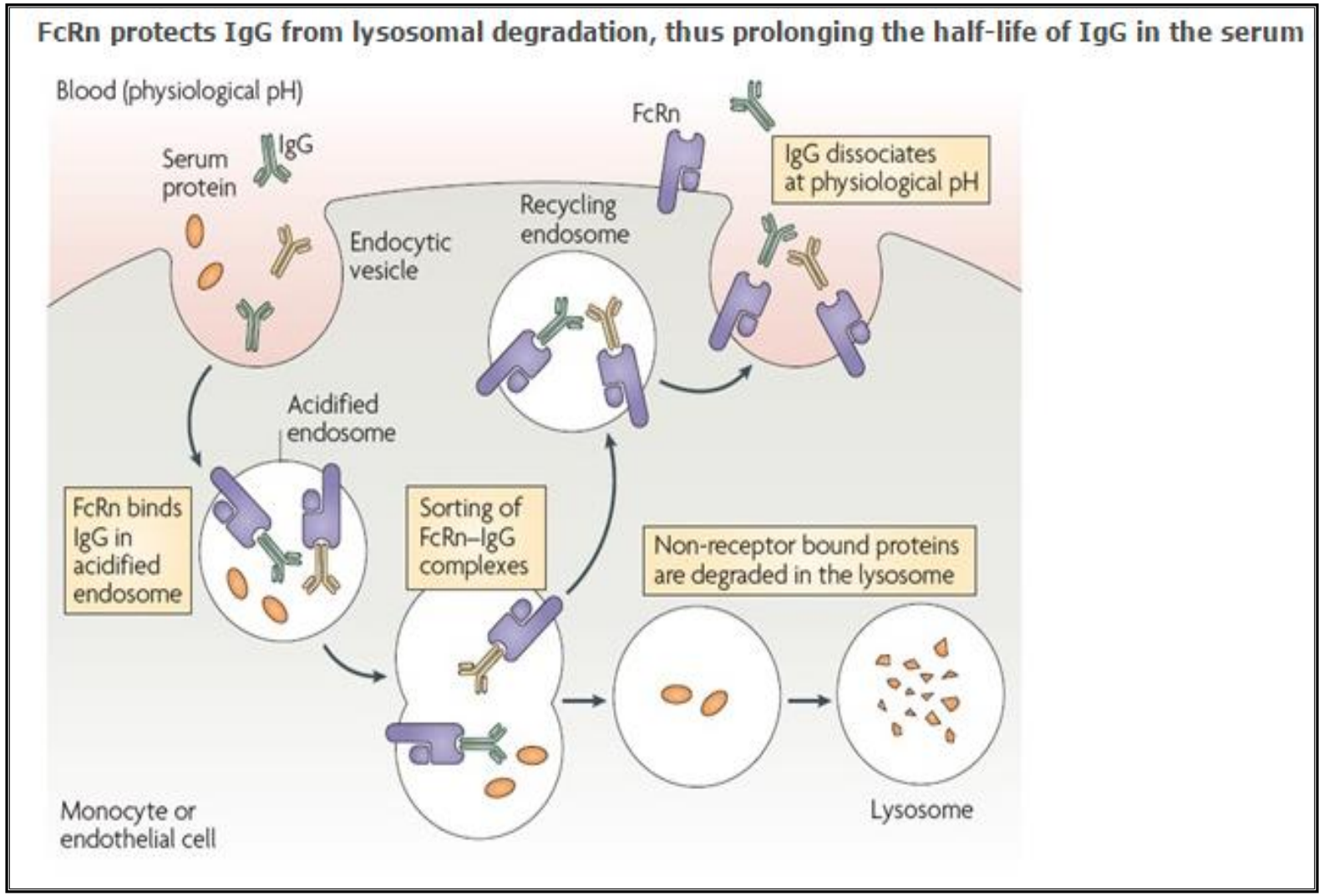
Elimination (1): Non-Specific Pathway

The primary route of elimination for larger proteins (e.g. mAbs) is cellular uptake followed by proteolytic degradation

- Interaction with FcRn (neonatal Fc receptor) protects IgG from lysosomal degradation

- Usually linear (FcRn not saturated)

FcRn Protection



Roopenianand Akilesh.Nature Reviews Immunology 2007; 7: 715

FcRn and PK variability

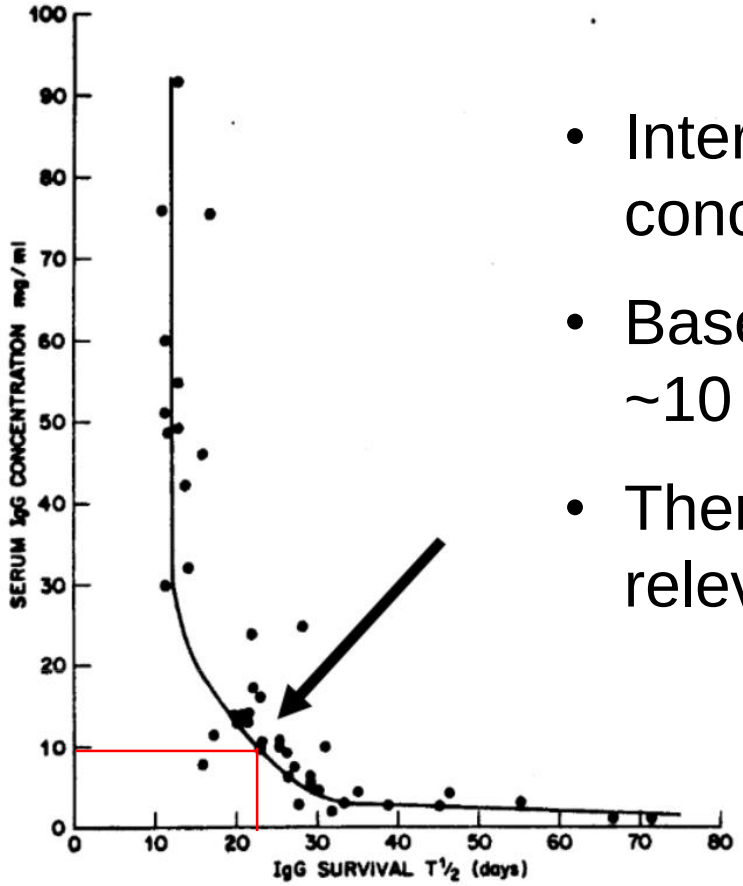


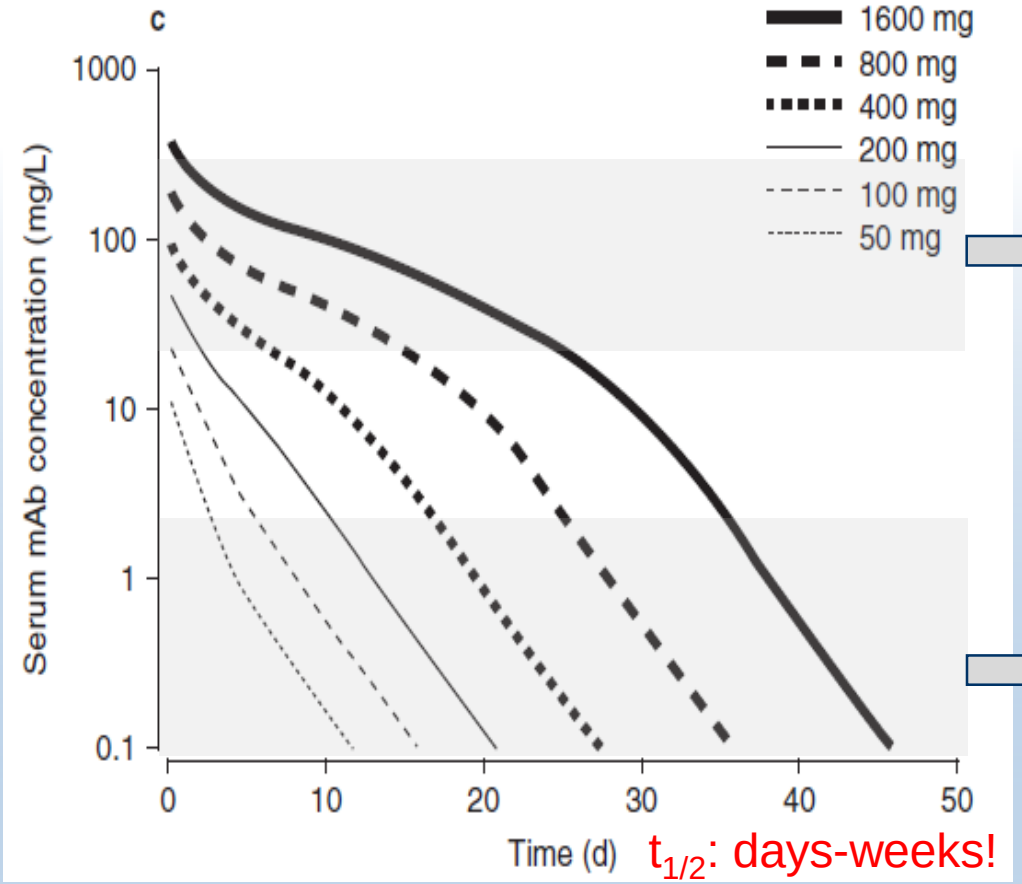
Fig. 8. The relationship between the survival T1/2 of I_gG and the serum I_gG concentration obtained from turnover studies performed in patients with a wide range of I_gG concentrations.

- Interpatient variability in baseline concentration may lead to variability in PK
- Baseline IgG concentration ~10 mg/mL
- Therapeutic doses of mAb usually do not relevantly affect IgG concentration

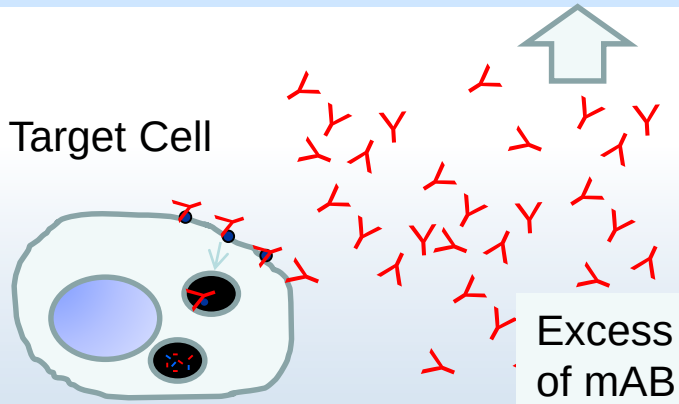
*Prog Allergy. 1969;**13**:**1**-110.*

Elimination (2): Specific pathway: **Target-mediated drug disposition**

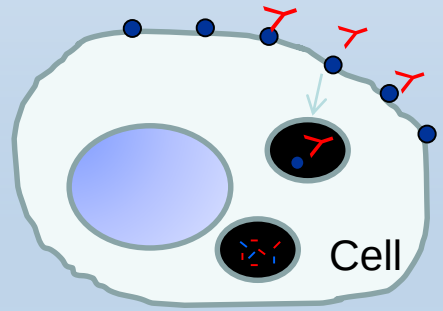
PK highly dependent on amount of target and dose



Non-specific (linear) elimination



Target mediated (specific) elimination



Example: anti-HER2 mAb

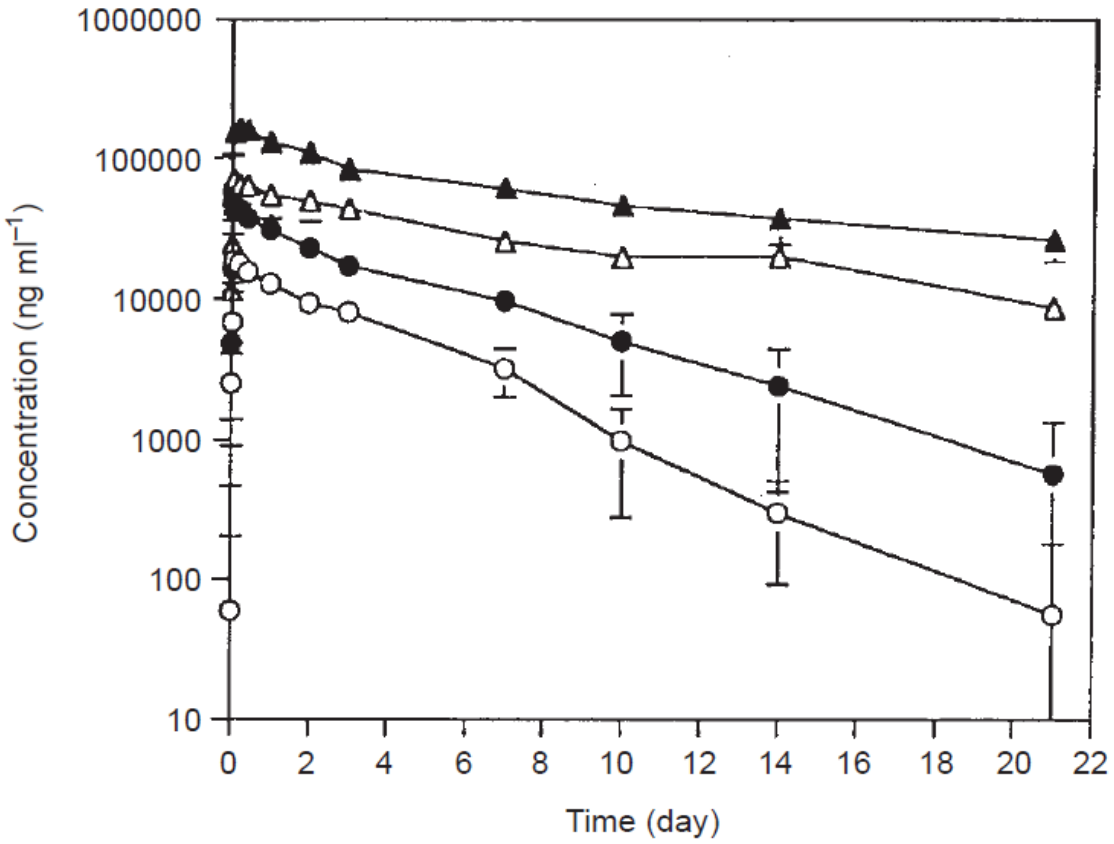


Figure 1 Serum concentration-time profiles of MKC-454 after first administration. The values of serum concentration at a dose level of 1 mg kg^{-1} (open circle), 2 mg kg^{-1} (closed circle), 4 mg kg^{-1} (open triangle), or 8 mg kg^{-1} (closed triangle) represent mean ± s.d.

Dose [mg/kg]	CL [ml/day/kg]
1	14.1
2	11.1
4	6.4
8	5.6

$$CL = \frac{Dose}{AUC}$$

Dose escalation and pharmacokinetic study of a humanized anti-HER2 monoclonal antibody in patients with HER2/*neu*-overexpressing metastatic breast cancer

British Journal of Cancer (1999) ***81****(8), 1419–1425*

Elimination: Impact of target location

Target on cell membrane

- Receptor-mediated endocytosis followed by degradation
- Variable target expression
- Both linear and non-linear pathway involved

Soluble target

- Generally low target expression
- Often unspecific (linear) pathway dominant
- Antibody:target complex may be cleared via elimination pathway of target
- Example: FG-3019, a mAb against connective tissue growth factor

Pharm Res. 2016 Aug;33(8):1833-49

Biologicals vs. Small Molecules

- Due to the significant target-mediated clearance at the site of action, concentrations of biologics at the site of action are not simply related to plasma concentrations of unbound drug

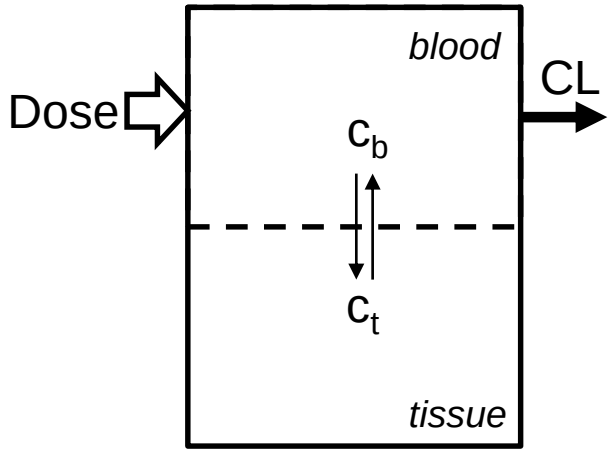
- The drug concentration at the site of action often are dependent on access to tissue (blood perfusion, vascular porosity) as well as target expression and turnover

-> These often show high variability

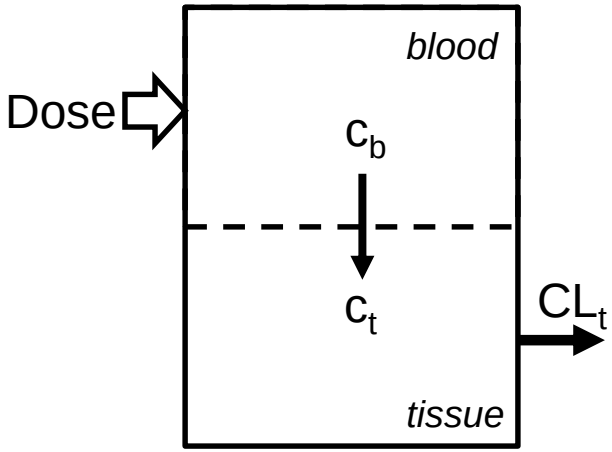
  - Between species (i.e. animal vs. humans)
  - Between patients
  - Within patients (e.g. targets expressed in different sites)

Effect of tissue metabolism on V_{ss}

(Most) small molecule drugs



(Many) mAbs



- Assumptions for non-compartmental analysis:

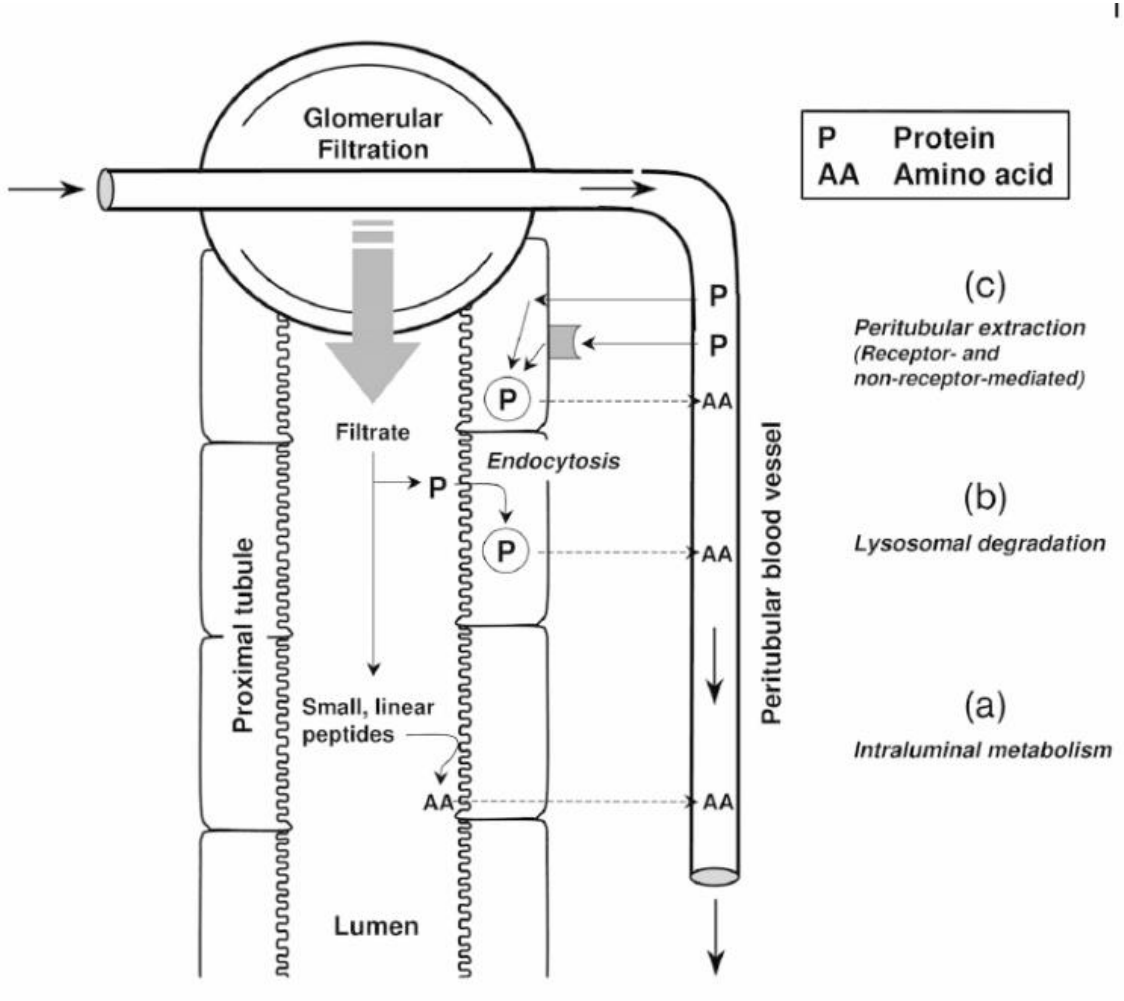
  Linear PK & rapid equilibrium between blood and tissues
- This is not true for many mAbs
- NCA calculations for V_{ss} may underestimate the drug‘s true distribution
- Consider modelling approaches

Absorption, Distribution, Metabolism, Excretion

Renal elimination/ excretion:

- Only relevant for proteins with MW <~60kDa
  -> NOT for mAb
- Usually glomerular filtration rate-limiting step

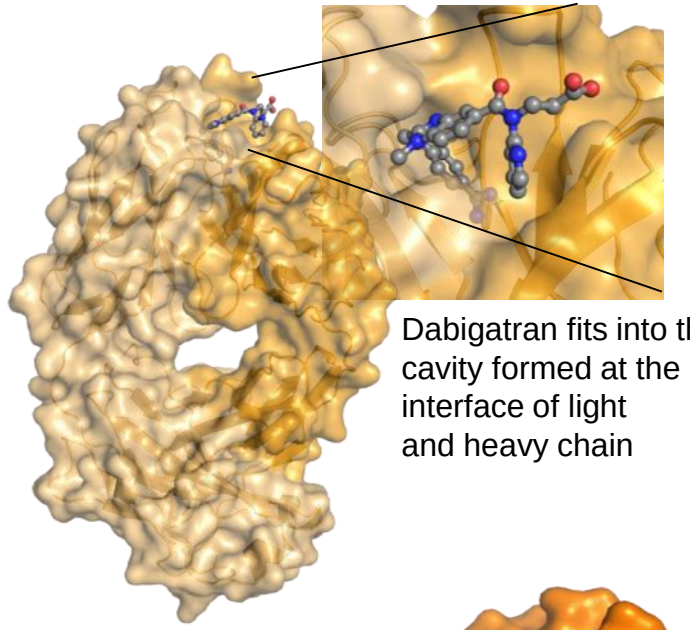
- Examples
  - a) angiotensin I and II; glucagon
  - b) growth hormone, insulin, idarucizumab
  - c) insulin



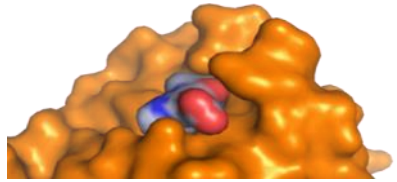
Meibohm, PK/PD of Biotech Drugs, Wiley 2012

Rationale for Anti-Dabigatran Fab Approach

- Safe restoration of coagulation:
  - High binding affinity
  - High specificity
    - Off-target binding is not expected
    - No activated coagulation expected
  - Shorter half life than full mAb
- Easy and rapid administration:
  - Intravenous, immediate onset of action
- Low risk of adverse reactions:
  - Humanized
  - No Fc receptor binding



Dabigatran fits into the cavity formed at the interface of light and heavy chain



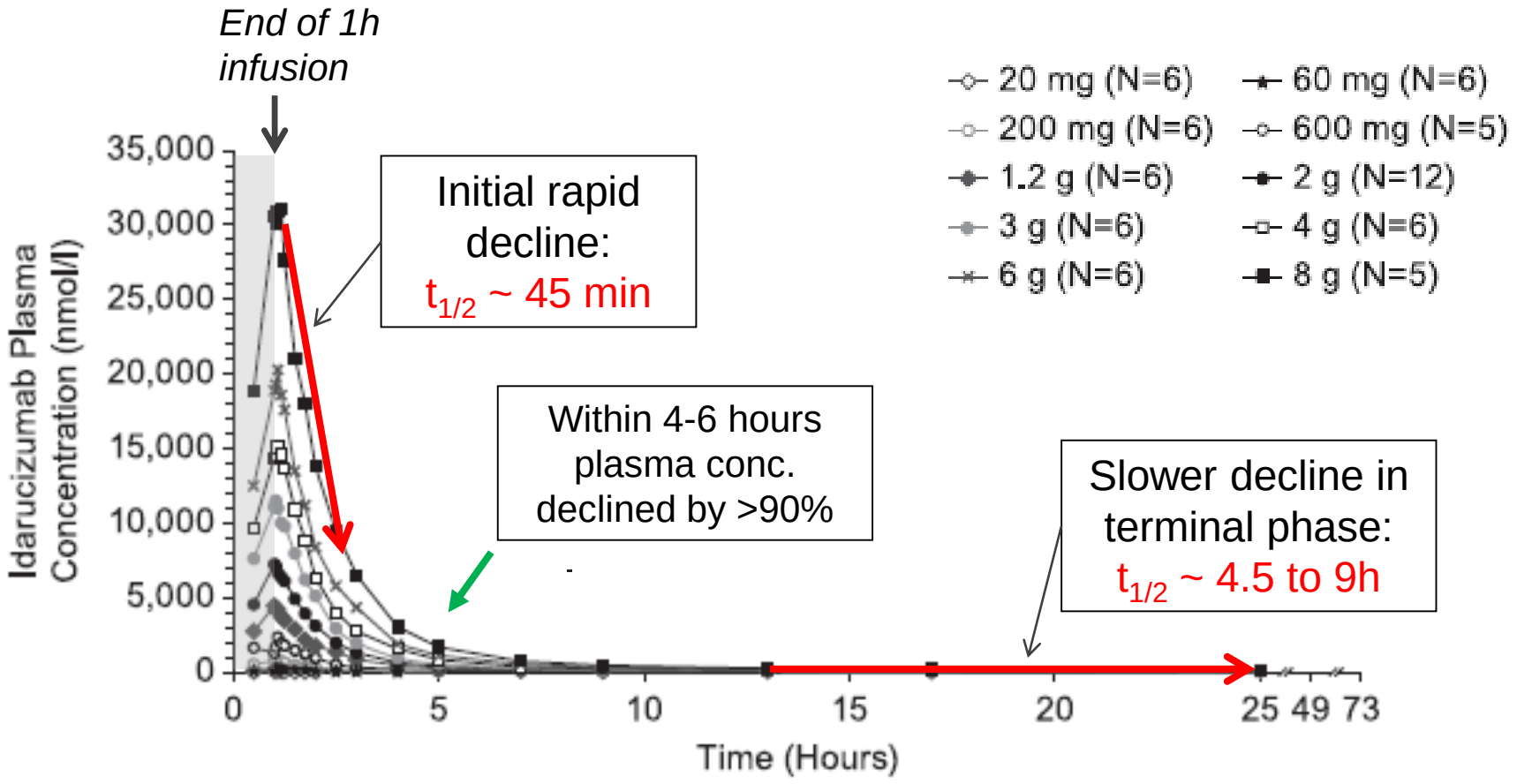
No protruding moieties

Blood 121:3554-3562, 2013

Fc = fragment crystallizable; mAb = monoclonal antibody

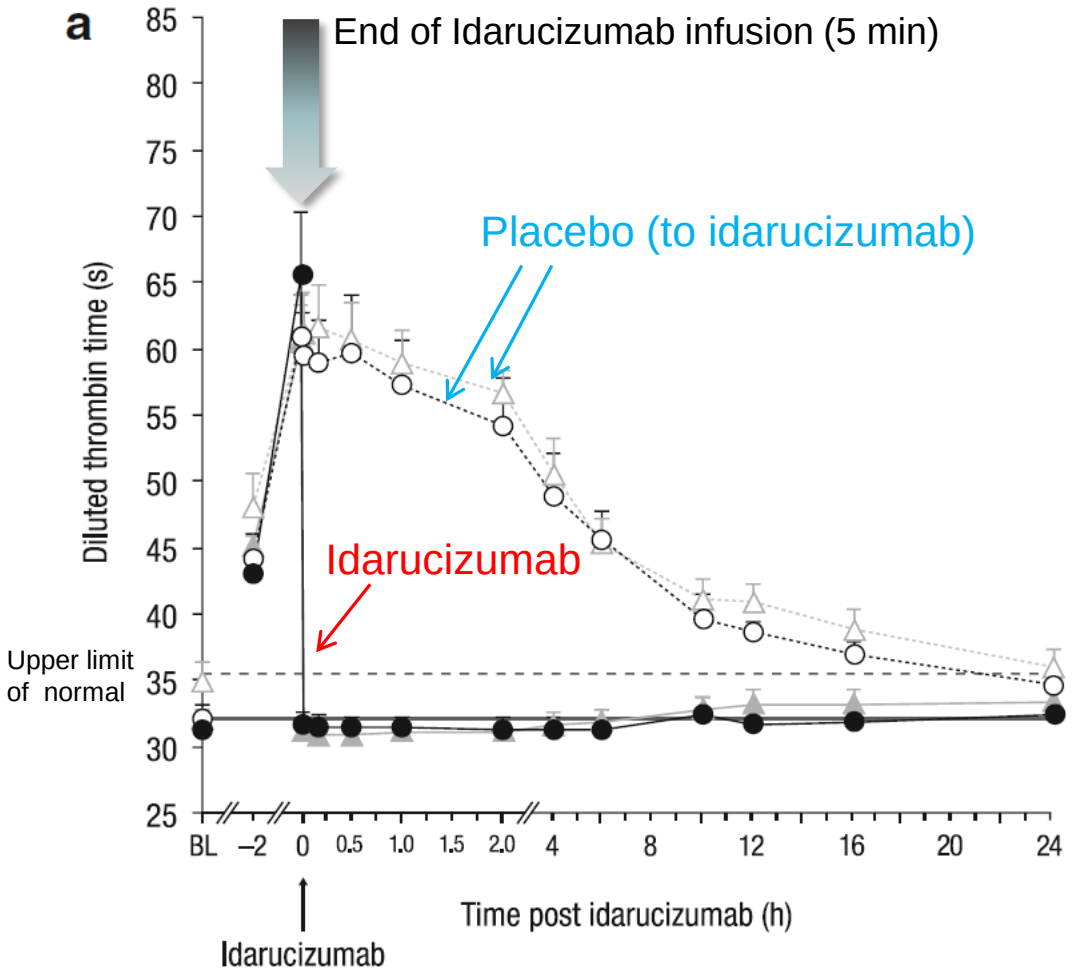
Example Fab: Idarucizumab

Thromb Haemost. 2015; 113(5):943-51



- Low volume of distribution (V_{ss} = 6-8 L)
- Elimination: substantial contribution of renal excretion and catabolism

Example Fab: Idarucizumab



- Dabigatran dosed to steady state (last dose 2h prior to idarucizumab)
- Immediate efficacy due to i.v. administration of idarucizumab
- Re-administration of dabigatran possible after 24 h due to short $t_{1/2}$ of idarucizumab

45–64 y, 220 mg DE/5 g idarucizumab
45–64 y, 220 mg DE/placebo (5 g)
45–64 y, 220 mg DE/2.5 g idarucizumab
45–64 y, 220 mg DE/placebo (2.5 g)

Clin Pharmacokinet. 2017 Jan;56(1):41-54
J Am Coll Cardiol. 2016 Apr 5;67(13):1654-1656

PK parameter comparison: Fab vs IgG

	Idarucizumab 5000 mg i.v.	Adalimumab 40 mg s.c.
t_{max} [h]	**End of infusion**	**5.5 d**
$t_{½}$ [h]	**0.75**	**14.7-19.3 d**
fe [%]	**32.1**	**n.d.**
CL [mL/min]	**47.0**	**0.15-0.20***
V_z [L]	**8.9 §**	**5.1-5.8***

**For s.c. administration, Vz/F and CL/F*

§ V_{ss} for idarucizumab

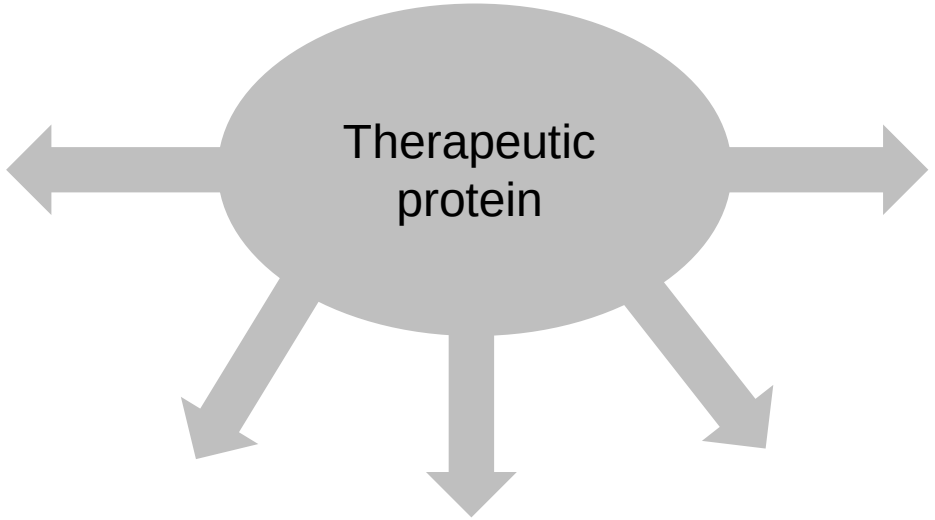
Monoclonal IgG Antibodies

Name	Binding target	Apparent volume of distribution	Clearance	Half-life
Adalimumab	TNFa	5.1-5.8 L	9-12 mL/h	14.7-19.3 d
Bevacizumab	VEGF	3.0 L	8-11 mL/h	20 d
Cetuximab	EGFR	3.5-5.2 L	35-140 mL/h	4.8 d
Gemtuzumab	CD33	NA	265 mL/h	1.9-2.5 d
Infliximab	TNFa	NA	NA	9.5 d
Rituximab	CD20	NA	NA	9.4 d
Trastuzumab	HER2	3.6-5.2 L	16-41 mL/h	2.7-10 d

Agenda

- General introduction
- Bioanalytical aspects
- Immunogenicity
- ADME of mABs
- Drug-drug interaction
- Other aspects (e.g. thorough QT)
- Considerations for clinical development / study design
- Comparability

Considerations for Drug-Drug Interactions (DDI)



Can co-administered drugs impact the PK and/or PD of therapeutic proteins (or vice versa)?

PK-based DDI

Overall: uncommon

- TP with SMD:
  No overlapping clearance pathways
  - *SMDs:*
    renal, hepatic, biliary clearance
  - *TPs:*
    nonspecific proteolysis, immunogenicity, TMDD
    (no CYPs and uptake/efflux transporters involved)
- TP with other TP
  Nonspecific proteolytic clearance pathways usually unsaturable at therapeutic concentrations

TP	*Therapeutic protein*
SMD	*Small molecule drug*

PD-based DDI

Overall: possible

- TP is perpetrator
  - SMD: If TP has immunomodulatory function (cytokine/cytokine modulator) and thereby affects CYP/transporter expression
    Example: IL-1ß, IL-6 and TNF are potent inhibitors of P450 enzymes
  - TP: immunomodulation can theoretically also affect other TP via ADA formation
- TP is victim
  - SMD: - If SMD (by its MoA) modulates the expression of the TP´s target (…and TMDD contributes significantly to the clearance of the TP)
    - If SMD has immunosuppressive function (… and immunogenicity (ADA) contributes significantly to clearance of the TP)
    Example: Methotrexat effect on adalimumab
- If TP and SMD/other TP bind the same target
- Due to overlapping/cumulative PD effects (not necessarily with associated changes in exposure)

Limited clinical relevance in most cases

- Caution should be taken with respect to narrow therapeutic index drugs

TP *Therapeutic protein*
SMD *Small molecule drug*

Agenda

- General introduction
- Bioanalytical aspects
- Immunogenicity
- ADME of mABs
- Drug-drug interaction
- Other aspects
- Considerations for clinical development / study design
- Comparability

Thorough QT studies

- Usually not done
- Cardiac channels (e.g., hERG) need interaction on intra-cellular domain, not reached by larger biologics
- Indirect effects may be possible (e.g. target on cardiomyocytes)

- Intense safety pharmacology on CV-system
- Extended ECG measurements in early clinical studies
  - ➢ Intensify QT assessment in case signal is picked up

- tQT recommended per ICH E14 for smaller peptides or ADC drugs

Covariates (1): Renal/hepatic impairment

Renal impairment studies?

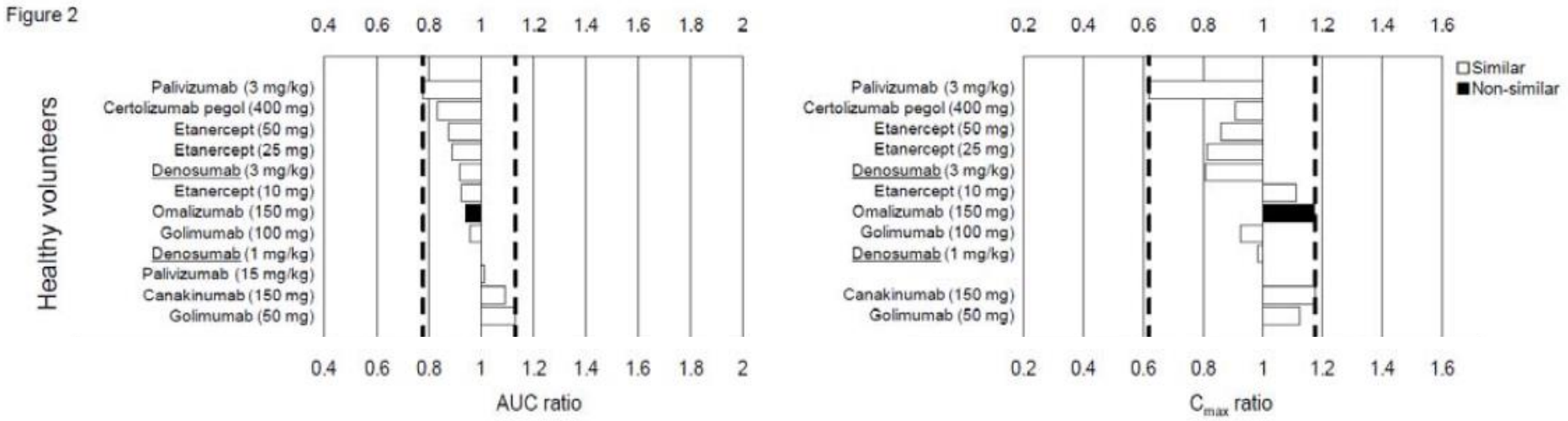
- Cutoff for glomerular filtration ~60 kDa -> larger proteins not impacted
- Dedicated studies for proteins that undergo glomerular filtration

Hepatic impairment studies?

- Limited direct elimination of biologics through hepatic pathway
- Dedicated studies usually not done

Covariates (2): Ethnic differences

AUC and Cmax ratio between Japanese and Caucasian (Data from 8 mAb)



J. Clin. Pharmacol 2013
http://onlinelibrary.wiley.com/doi/10.1002/jcph.231/pdf

- No apparent PK ethnic difference observed in healthy volunteers
  - Observed differences could mostly be attributed to body weight and target expression levels
- The target expression in HV is usually not different between populations
- Proposal in manuscript: consider waiver for Phase I studies with mAbs that look at ethnic differences in PK

Covariates affecting PK of mAb

Covariates often reported as significant:

- ***Target expression***
- ***Body size***
- ***Immunogenicity***
- ***Renal function (for smaller proteins)***

Covariates often reported as NOT significant:

- ***Hepatic impairment***
- ***Age***
- ***Gender***
- ***Ethnicity***

Agenda

- General introduction
- Bioanalytical aspects
- Immunogenicity
- ADME of mABs
- Drug-drug interaction
- Other aspects
- Considerations for clinical development / study design
- Comparability

ClinPharm studies NCEs vs. NBEs

Type of study	Small Molecule	mAbs
Single-dose PK/PD (HV or patients)	✓	✓
Multiple-dose PK/PD (HV or patients)	✓	✓
Absolute bioavailability	✓	✓
Bioequivalence / Comparability	✓	✓
ADME	✓	X
CYP450 mediated DDI	✓	X / ✓
PK in hepatic or renal impairment	✓	X
PK in geriatric patients	✓	✓
Thorough QTc study	✓	X
Immunogenicity investigation	X	✓
Population PK investigation	✓	✓

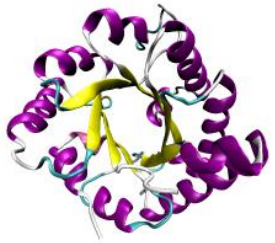
General considerations for ClinPharm studies

Small molecule drugs	Biologics
Often healthy volunteer	Healthy volunteer or patients
Usually oral dosing	Usually parenteral dosing (i.v., s.c.)
No ADA assessment	ADA assessment
Cross-over design possible	Long half-life limits cross-over design
Short duration	Longer study duration
Limited drug storage and preparation requirements	Often specific storage and preparation requirements (e.g. refrigerated or frozen)
May need extensive ClinPharm characterization	Usually requires less studies

Agenda

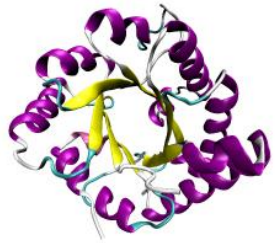
- General introduction
- Bioanalytical aspects
- Immunogenicity
- ADME of mABs
- Drug-drug interaction
- Other aspects
- Considerations for clinical development / study design
- Comparability

What is comparability?
What triggers comparability ?



Before change

Process change?
Formulation change?



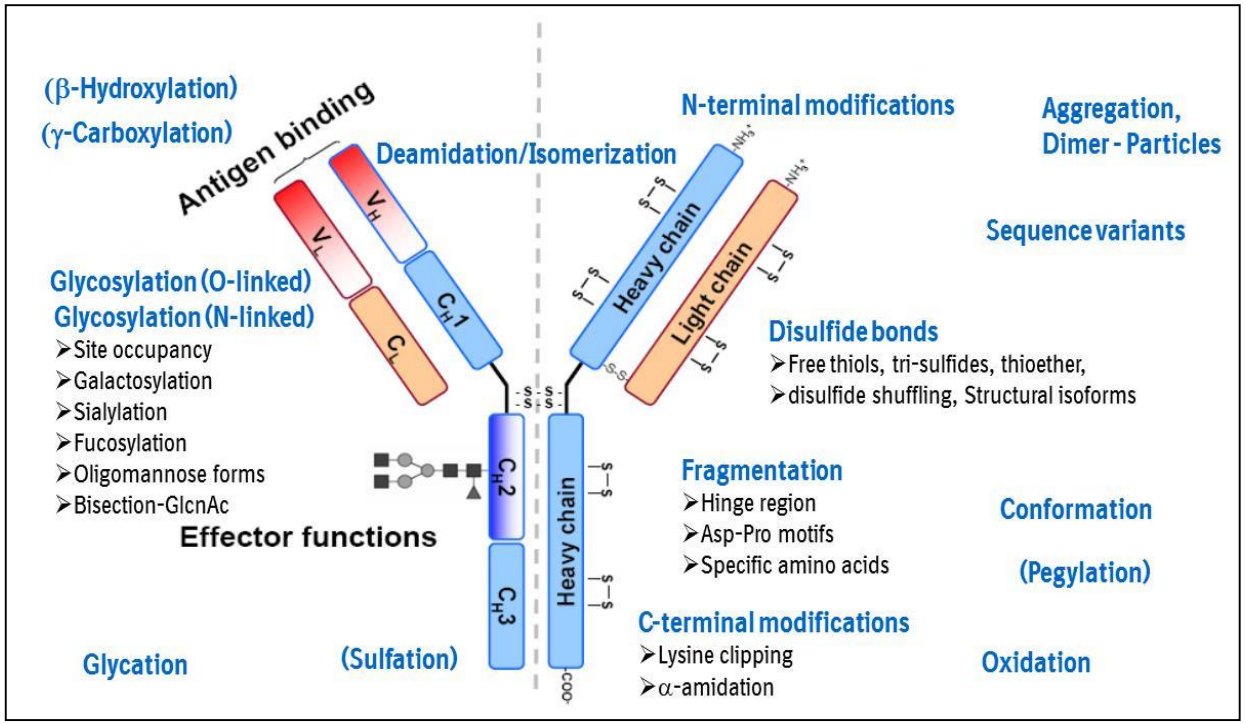
After change

The **goal of the comparability exercise is to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process**, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes.

The demonstration of comparability **does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar** and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

ICHQ5E; https://en.wikipedia.org/wiki/Protein#/media/File:Proteinviews-1tim.png

Micro-Heterogeneity

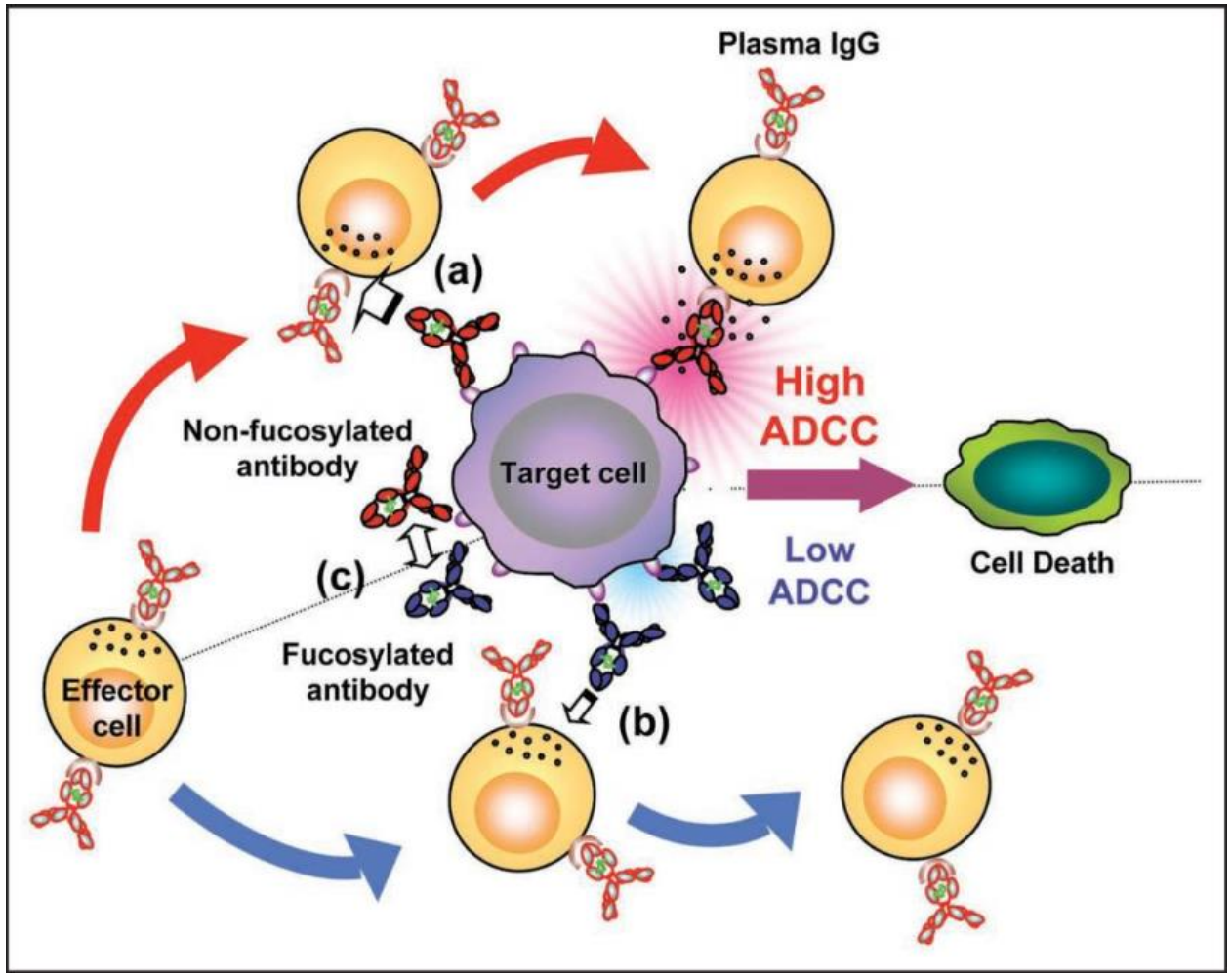


Micro-Heterogeneity of mAb: >10^8 potential molecular variants

The process determines the product

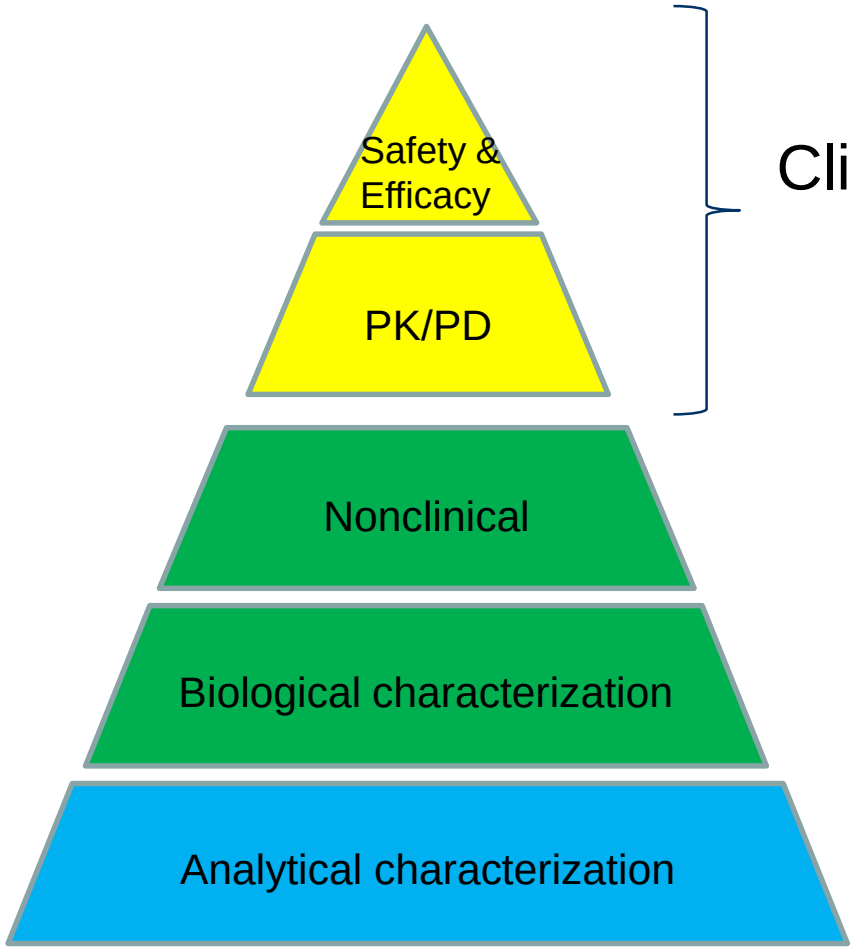
Advanced Drug Delivery Reviews 58 (2006) 707–722

Effect of fucosylation on ADCC



MAbs. 2009 May-Jun; 1(3): 230–236.

Comparability exercise



Clinical evaluations possible

ICH Q5E:

"A determination of comparability can be based on a combination of analytical testing, biological assays, and, ***in some cases,*** *nonclinical and clinical data."*

Comparability exercise

Extent of characterization depends on development stage of drug and severity of change

e.g. pre-clinical vs. late stage change

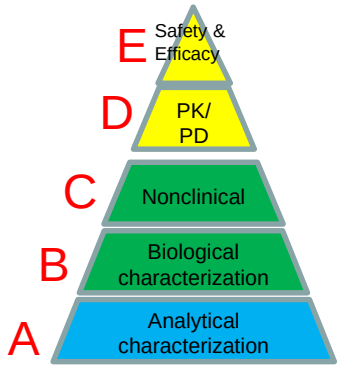


Table 3. Categories of proposed comparability assessments for process changes occurring late in development (during and after pivotal trials) of mAbs

Process change	Category[a]
Cell culture changes, no changes in characteristics	A+B[b] if mAb with no cell killing
	A+B if mAb depletes cells
Recovery changes, no changes in characteristics	A+B[b] if mAb with no cell killing
	A+B if mAb depletes cells
Cell culture or recovery changes, with changes in charge distribution	A+B+C
Cell culture changes, with changes in Fc glycan distribution	A+B[b] if mAb with no cell killing
	A+B if mAb depletes cells
	A + B + C for both cases if magnitude of change is high
Switch from lyophilized to liquid form, new excipients	A+B+C+D
Switch from lyophilized to liquid form, increased minor forms, specification changes	A+B+C+E
Formulation changes in concentration of active pharmaceutical ingredients (API)	A+B+C+D
New cell line, derived from original master cell bank	A+B+C+D
New cell line, derived from new transfection or host	A+B+C+E

Trends in Biotechnology 2010 (28) 509–516

Summary

Biologics …

- are not just „big chemicals“
- have favourable PK/PD attributes, including slow clearance, highly selective target binding with low risk for off-target toxicity

Challenges for clinical pharmacology include:

  - TMDD
  - Effect of disease on PK/PD
  - Translation animal to human
  - ADA effects on PK/PD
  - Risk for DDI

Thank you!