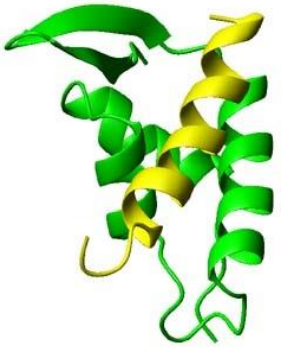

EUFEMED Conference, Brussels, Belgium, May 21, 2015

Drug-Drug Interactions between Biologicals and Small Molecules

Bernd Meibohm, PhD, FCP

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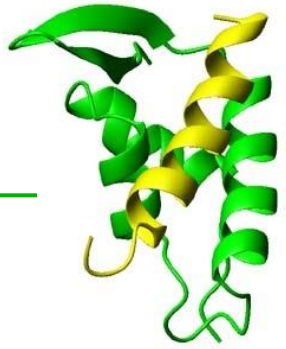
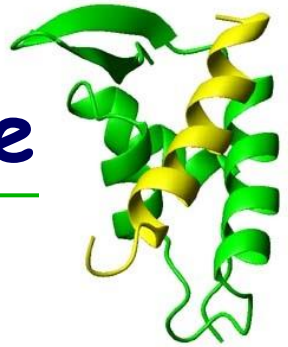
Interim Chair, Department of Pharmaceutical Sciences
College of Pharmacy
The University of Tennessee Health Science Center
Memphis, TN, U.S.A.

Undesired PK DDIs



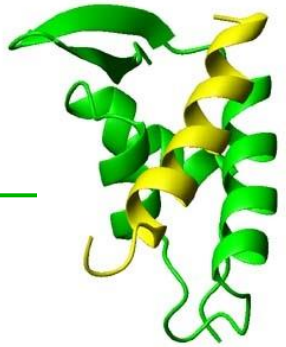
- In the age of polypharmacy, drugs are regularly administered in fixed (therapeutically defined) or random (patient/HCP defined) combinations.
- DDI can be desired or undesired, and can be related to pharmacokinetics (PK) or pharmacodynamics (PD).
  - ✓ In the following, the focus will be on undesired PK DDIs.
- Since therapeutic protein (TP) are predominantly administered by the IV, IM or SC route, absorption related DDI are usually a non-issue.
  - ✓ DDI affecting drug clearance and thus systemic exposure are the focus of concern.

Appreciation of TP DDIs over Time

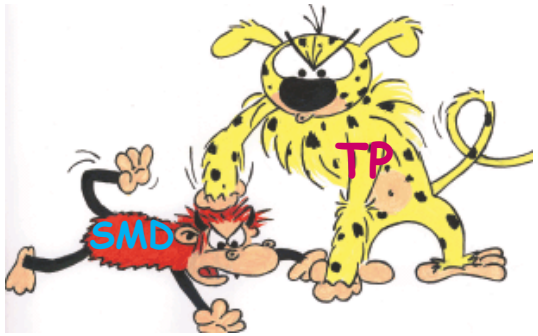


- Past
  - ✓ DDI for TPs are unlikely and potential mechanisms are unclear
  - ✓ DDI studies may not be required for regulatory approval
- Present
  - ✓ DDI for TPs are well documented
  - ✓ Knowledge about potential mechanisms is evolving
  - ✓ DDI study program is often required for regulatory approval

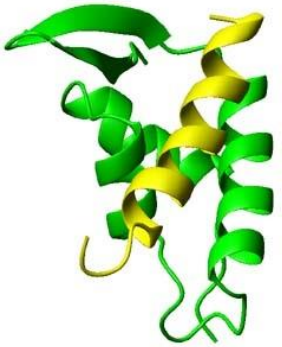
DDI Scenarios for TPs



1. The TP is the perpetrator and the small molecule drug (SMD) is the victim (TP → SMD)



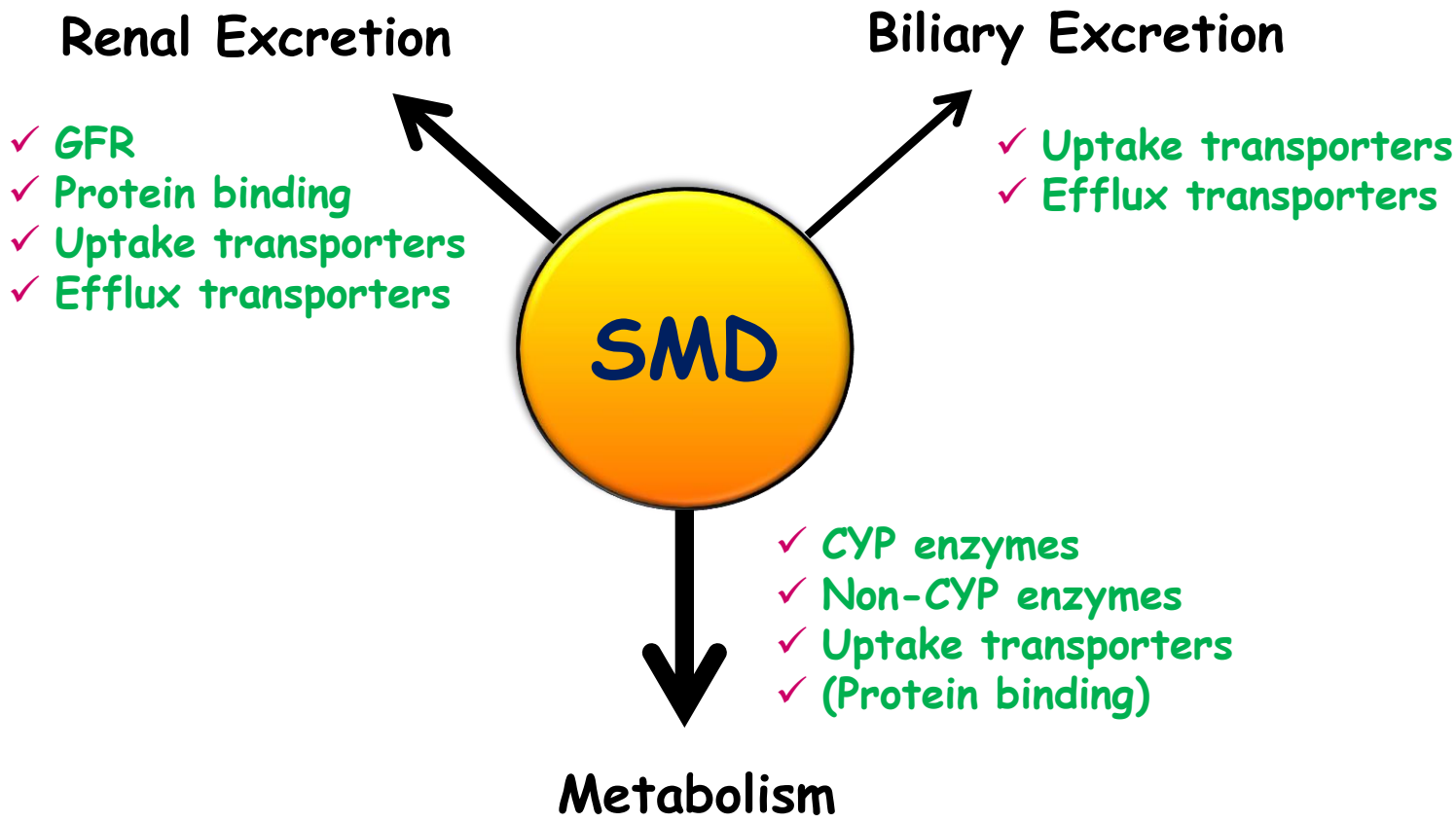
2. The SMD is the perpetrator and TP is the victim (SMD → TP)



TP → SMD

Potential DDI Mechanisms for SMDs

Clearance Mechanisms for Small Molecule Drugs



Potential DDI Mechanisms for SMDs

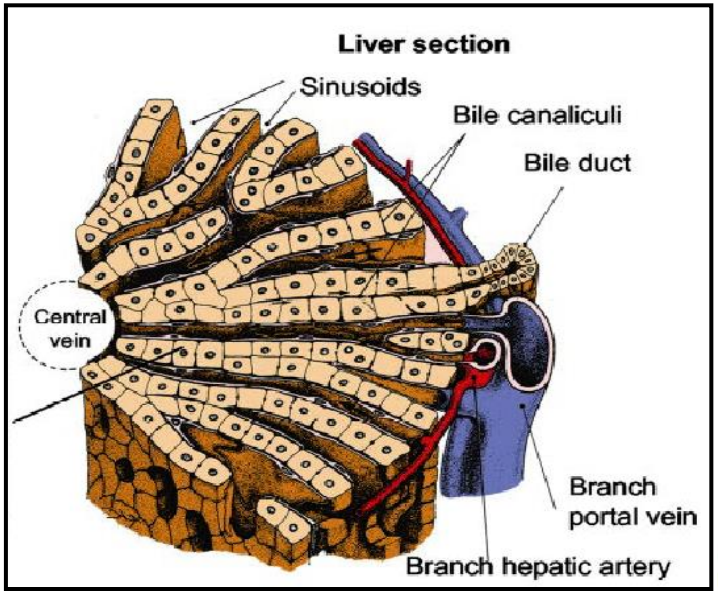
Inhibition of DME

1. Direct inhibition of drug metabolizing enzymes (CYPs, UGTs) by therapeutic protein
   - ✓ Rarely reported
   - ✓ Observed usually *in vitro* only
     - o G-CSF:
       - ✓ no significant effect on CYP3A;
       - ✓ 20% suppression of CYP1A2 and CYP2B6
   - ✓ *In vivo*: Anatomic hindrance:
     - o Intracellular localization of most DMEs
       - ✓ CYPs in the endoplasmatic reticulum
       - ✓ Phase II enzymes in cytosol
     - o Low permeability of large therapeutic proteins through biomembranes
       - ✓ High molecular weight
       - ✓ Highly charged
     - o Proteins enter cells in endosomes/vesicles and are not freely available in the cytosol

Known or Potential DDI Mechanisms

Inhibition of Transporters

2. Direct inhibition of drug transporters (uptake and export) by therapeutic protein
   - ✓ Not reported
   - ✓ All known direct inhibitors of transport proteins for P-gp and MRP2 are structurally completely different from large proteins and have not been described with molecular weights larger than 1000 Da
   - ✓ Anatomic hindrance:
     - o May only be relevant for transporters on membranes in contact with bloodstream
     - o ABC export transporters (e.g. MRP2, P-gp) in the bile canalicular membrane would require protein therapeutic to cross enter intracellular space for interaction



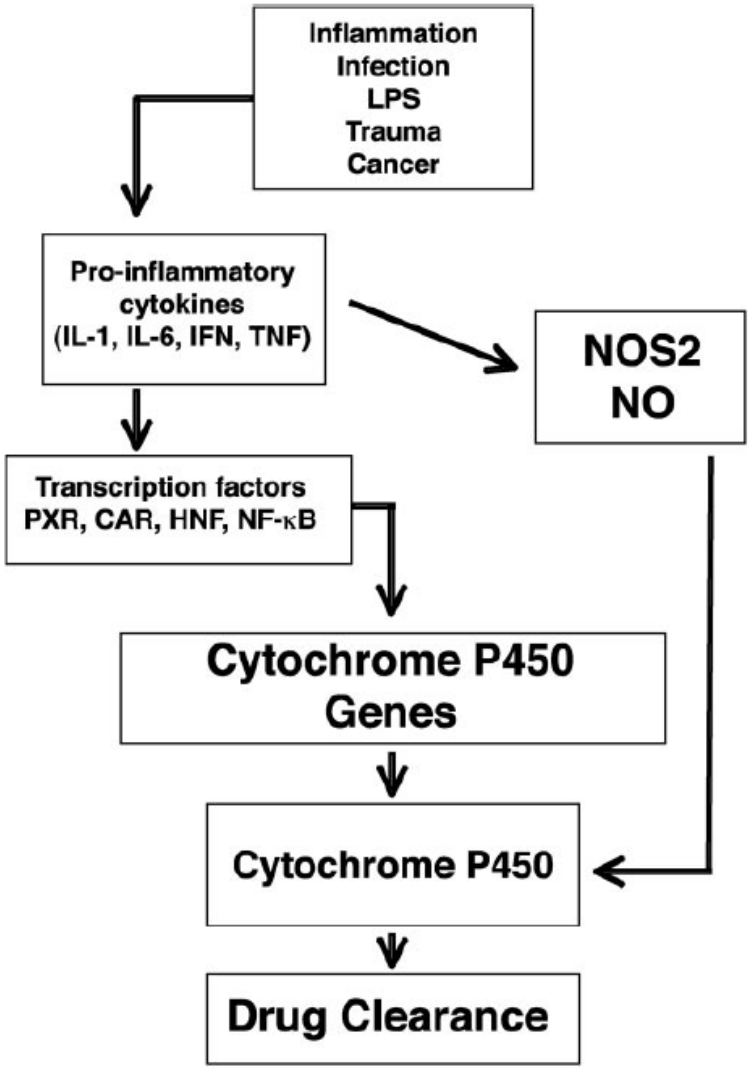
Potential DDI Mechanisms for SMDs

Change in Inflammatory Status

3. Indirect PK interactions by inflammatory/immune processes affecting DME and transporters
   - ✓ Most reported interactions are affecting the inflammatory status in the body (PD effect on immune system ⇨ Drug-disease interaction)
   - ✓ CYP enzymes are acute phase reaction proteins, and it is well-established that in acute inflammatory conditions, CYP enzyme expression and activity is downregulated
   - ✓ INF, IL-6 and TNF-α inhibit hepatic CYP enzymes and thus cause drug-cytokine interactions
   - ✓ Direct and indirect effects (interaction with regulators of their expression such orphan nuclear factors (e.g. PXR, CAR, FXR etc.).
     - o Variable for different CYP isozymes
     - o High-dose INF-α2b: no effect on some enzymes such CYP2E1, intermediate effect on CYP 2C19 and 2D6, and a substantial effects on CYP1A2 (-60% activity)

Potential DDI Mechanisms for SMDs

DME and Transporters as Acute Phase Reaction Proteins



Morgan et al.,
Drug Metab Disp 2008, 36, 205-16

Potential DDI Mechanisms for SMDs

Suppression and De-Suppression of DME and Transporters

Scenario 1:

Pro-inflammatory cytokine increases the inflammatory status

Downregulation of DME and transporters through dual interaction mechanism

- ⇨ Reduction in DME and transporter expression and activity (with delay based on turnover kinetics)
- ⇨ Reduced clearance and increased systemic exposure of affected small molecule drugs

Scenario 2:

Anti-inflammatory therapeutic protein decreases the inflammatory status

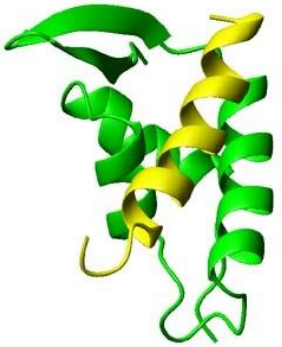
Upregulation of DME and transporters by re-establishing the normal homeostasis

- ⇨ Increase in DME and transporter expression and activity (with delay based on turnover kinetics)
- ⇨ Increased clearance and decreased systemic exposure of affected small molecule drugs

Potential DDI Mechanisms for SMDs

Change in Plasma Protein Binding

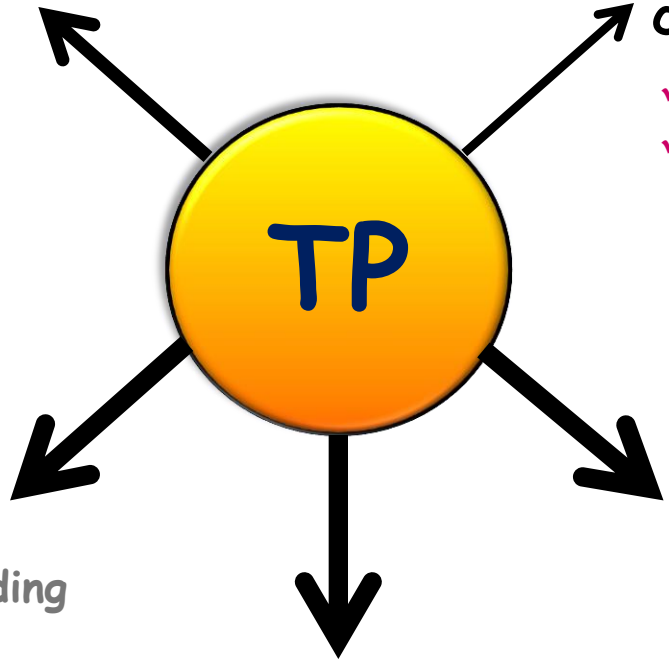
4. Indirect PK interactions by changing the concentrations of plasma proteins that serve as binding proteins for SMDs
   - ✓ α1-acid glycoprotein (AAG) is a 42 kDa plasma protein that serves as binding site for numerous SMDs
     - o e.g. phenytoin, saquinavir, amprenavir, imipramine, lidocaine
   - ✓ AAG is an acute phase reaction protein that is upregulated in with increased inflammatory status
   - ✓ Potential relevance for AAG upregulation:
     - o Reduced renal clearance secondary to reduced glomerular filtration by increased plasma protein binding
     - o Limited influence on SMDs with predominantly hepatic metabolism as elimination route
       - ✓ According to well-stirred hepatic clearance model (Benet and Hoener 2002)
       - ✓ Exception: Parenterally administered high hepatic extraction drugs



SMD → TP

Potential DDI Mechanisms for TPs

Clearance Mechanisms for Therapeutic Proteins



Renal Metabolism
- ✓ GFR
- ✓ Protein binding

Immunogenicity mediated clearance
- ✓ Immunoreactivity
- ✓ Immunosuppression

TMDD clearance
- ✓ Target receptors
  - ○ Membrane-standing

FcR-mediated clearance
- ✓ Fcγ expression
- ✓ FcRn expression

Unspecific proteolytic clearance
- ✓ Promiscuous membrane receptors
  - ○ LDLR
  - ○ LRP
  - ○ sugar-recognizing C-type lectin receptors

Potential DDI Mechanisms for TPs

Modulation in Receptor Expression

Indirect PK interactions by modulation of expression or competition for receptors involved in

1. Unspecific receptor-mediated endocytosis
2. Fc-receptors for mAbs or antibody fragments/fusion proteins
3. Target-mediated drug disposition

Potential DDI Mechanisms for TPs

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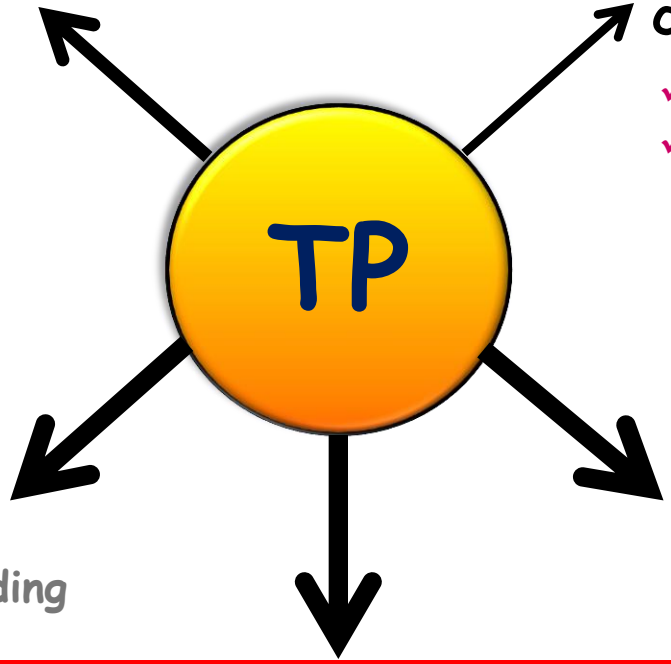

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Receptor-Mediated Endocytosis

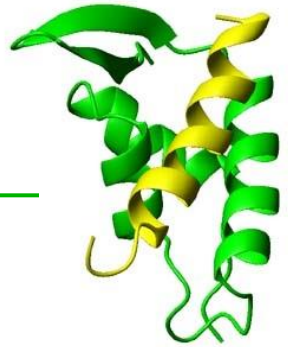
Hepatic Uptake Mechanisms for Proteins and Protein Complexes

Cell type	Uptake mechanism	Proteins/peptides transported
Hepatocytes	Anionic passive diffusion Carrier-mediated transport	Cyclic and linear hydrophobic peptides (<1.4 kDa; e.g., cyclosporins, CCK-8)
	RME: Gal/GalNAc receptor (asialoglycoprotein receptor)	N-acetylgalactosamine-terminated glycoproteins, galactose-terminated glycoproteins (e.g., desialylated EPO)
	RME: Low density lipo-protein receptor (LDLR)	LDL, apoE- and apoB-containing lipoproteins
	RME: LDLR-related protein (LRP receptor)	α_2-macroglobulin, apo-E-enriched lipoproteins, lipoprotein lipase (LpL), lactoferrin, t-PA, u-PA, complexes of t-PA and u-PA with plasminogen activator inhibitor type 1 (PAI-1), TFPI, thrombospondin (TSP), TGF-β and IL-1β bound to α_2-macroglobulin
	RME: Other receptors	IgA, glycoproteins, lipoproteins, immunoglobulins intestinal and pancreatic peptides, metallo- and hemoproteins, transferrin, insulin, glucagon, GH, EGF
	Nonselective pinocytosis (non-receptor-mediated)	Albumin, antigen–antibody complexes, some pancreatic proteins, some glycoproteins
Kupffer cells	Endocytosis	Particulates with galactose groups
Kupffer and endothelial cells	RME	IgG, N-acetylgalactosamine-terminated glycoproteins
	RME: Mannose receptor	Mannose-terminated glycoproteins (e.g., t-PA, renin)
	RME: Fucose receptor	Fucose-terminated glycoproteins
Endothelial cells	RME: Scavenger receptor	Negatively charged proteins
	RME: Other receptors	VEGF, FGF (?)
Fat-storing cells	RME: Mannose-6-phosphate receptor	Mannose-6-phosphate-terminated proteins (e.g., IGF-II)

Abbreviation: RME, receptor-mediated endocytosis.

Meibohm & Braeckman, In: Crommelin, Sindelar, Meibohm (eds.), Pharmaceutical Biotechnology, 3rd ed, Informa Healthcare 2007

Receptor-Mediated Endocytosis



Effect of Receptor Systems on t-PA Disposition

- Clearance of tissue-type plasminogen activator (t-PA) is mediated by hepatic receptor-mediated endocytosis
- Two involved receptor systems:
  - ✓ Low density lipoprotein receptor-related protein (LPR) on liver parenchymal cells
  - ✓ Mannose receptor on liver endothelial cells
- Inhibition of the mannose receptor and LPR results in a >30 fold increase in the terminal half-life for t-PA in mice

Narita et al., J Clin Invest 1995, 96, 1164-8

Potential DDI Mechanisms for TPs

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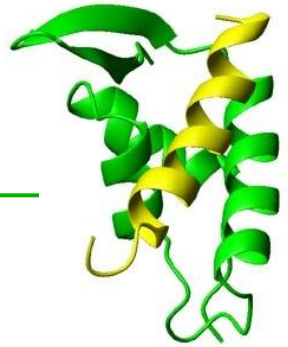
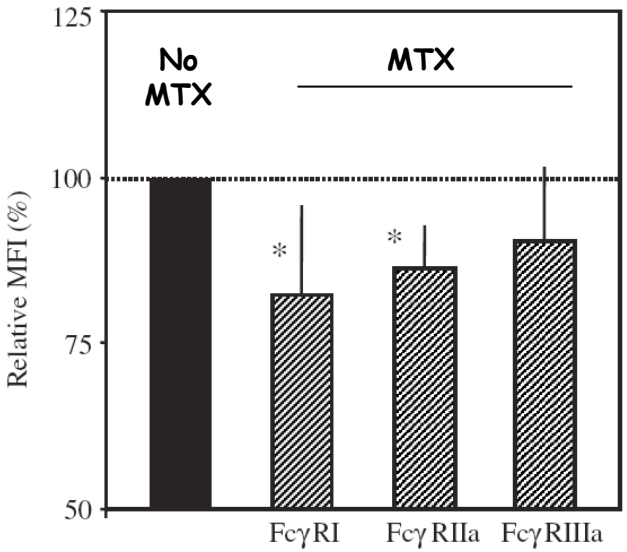
Fcγ-Receptors

Modulation of Fcγ Expression



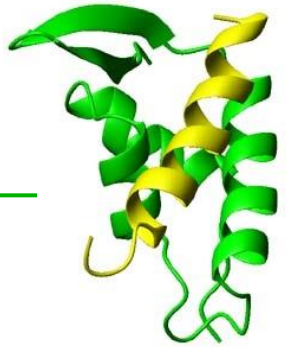
- Methotrexate is known to downregulate Fcγ receptors on monocytes
  - ✓ Potential decrease in the clearance of monoclonal antibody based therapeutics with high affinity to Fcγ receptors
  - ✓ Potential decrease in ADCC mediated efficacy
  - ✓ Potential mechanism for the reduced clearance of adalimumab under methotrexate therapy
    - Methotrexate decreases adalimumab (anti-TNFa) clearance by as much 29-44% in patients with rheumatoid arthritis
- Other Fc-receptors may potentially also be affected



Fcγ expression in monocytes cultured for 4 days in the absence or presence of MTX (10^{-6}M)

Wijngaarden et al.
Rheumatology 2005, 44, 729-34

Fcγ-Receptors



Modulation of Expression

- Macrophage Fcγ-receptors are modulated by dopaminergic drugs
  - ✓ Dopamin-agonists: Enhance expression of FcγR on splenic macrophages
    - o Bromocriptine, leuprolide, pergolide
  - ✓ Dopamin-antagoinsts: Inhibit expression of FcγR on splenic macrophages
    - o Chlorpromazine, metoclopramide, sulpiride, veralipride, alizapride, cisapride
- FcγRI was more sensitive than FcγRII
- Unclear clinical consequences

Gomez et al., Clin Immunol 1999, 90, 375-87

Potential DDI Mechanisms for TPs

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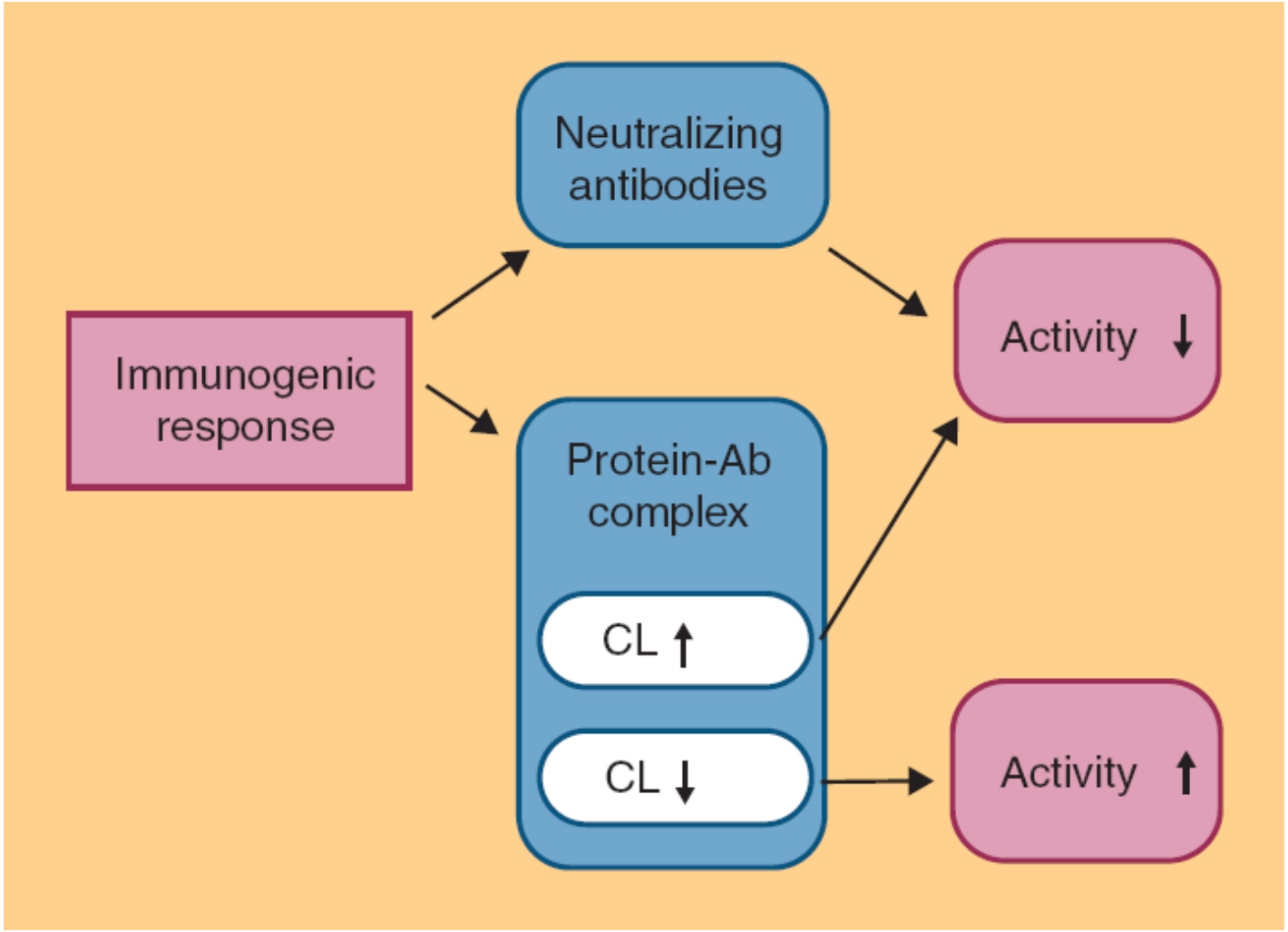
  - ○ sugar-recognizing C-type lectin receptors

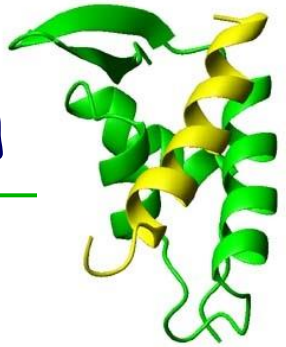
Anti-Drug Antibody Formation

Possible Scenarios



Meibohm & Braeckman, In: Crommelin, Sindelar, Meibohm (eds.), Pharmaceutical Biotechnology, 3rd ed, Informa Healthcare 2007

Anti-Drug Antibody Formation



DDI by ADA Modulation

- Coadministered immunosuppressive therapy may reduce/abolish the effect of clearing or sustaining ADA
  - ✓ E.g. methotrexate, cyclosporine
  - ✓ Reduced clearance and increased systemic exposure for TP affected by clearing ADA
  - ✓ Enhanced clearance and decreased systemic exposure for TP affected by sustaining ADA

Potential DDI Mechanisms for TPs

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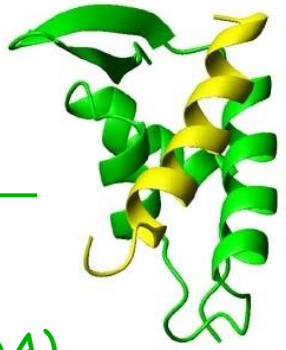
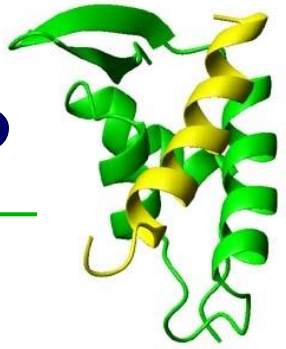
Protein Binding of TPs



- Specific binding proteins for many protein therapeutics
  - ✓ Binding proteins, soluble receptors, anti-drug antibodies (ADA)
  - ✓ Determines unbound, pharmacologically active fraction
  - ✓ Prolongs the protein circulation time by acting as a storage depot or it may enhance the protein clearance
  - ✓ Example: Growth hormone
    - o Protein binding substantially reduces elimination with a tenfold smaller clearance of total compared to free growth hormone, but also decreases its activity via reduction of receptor interactions.
- Modulation of protein binding as a DDI mechanism
  - ✓ Change in degree of TP-binding protein interaction affecting renal clearance
    - o E.g. sustaining ADA
  - ✓ Palifermin (recombinant human keratinocyte growth factor) interaction with heparin
    - o Potential mechanism: Heparin displaces palifermin from its epithelial cell surface receptors
    - o Concomitant administration causes a five-fold increase in the systemic exposure of palifermin

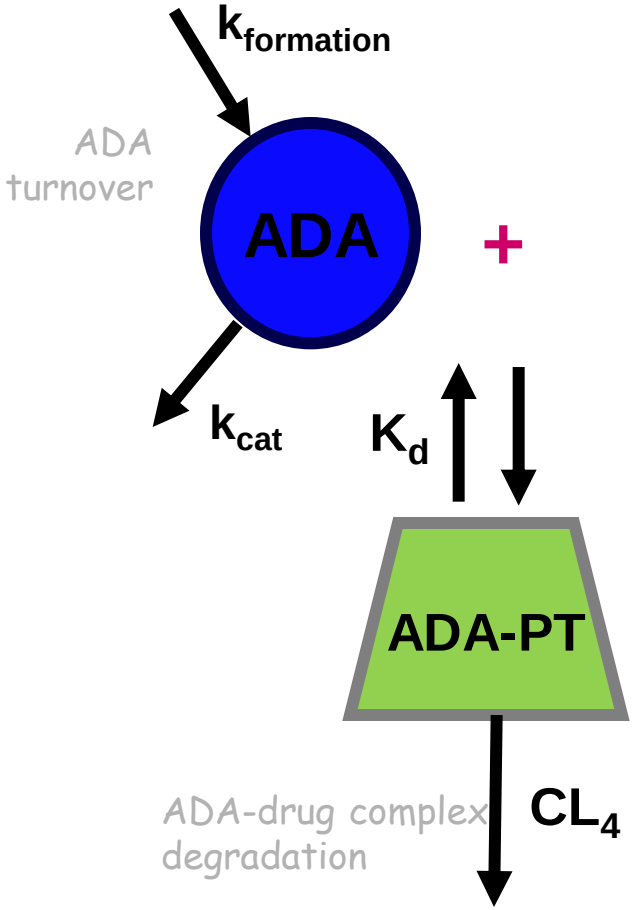
Mechanistic Basis of DDI with TP

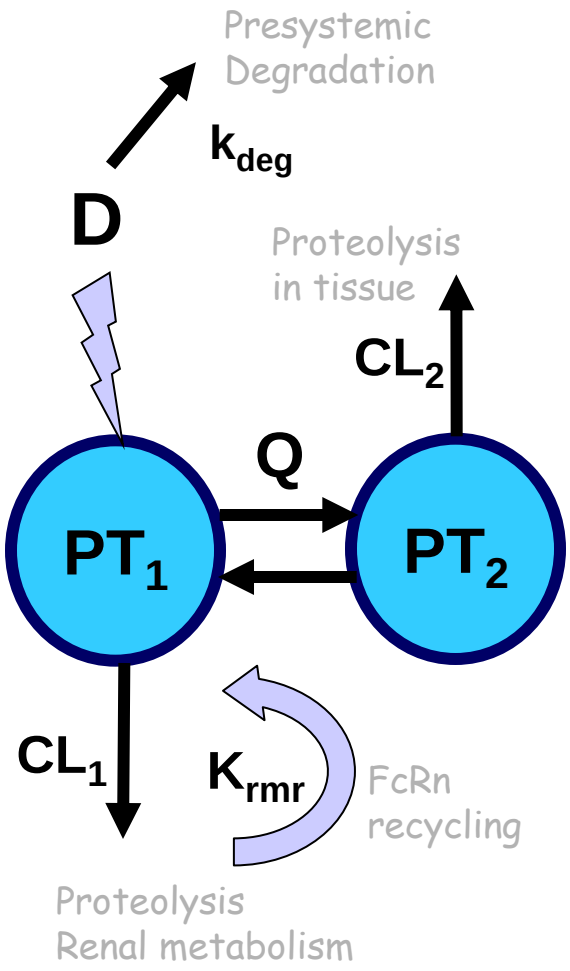


Take Home Messages

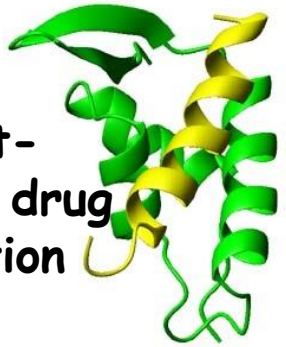
- Therapeutic proteins exhibit DDI similar to small molecules
  - ✓ **The occurrence is usually less frequent**
  - ✓ **The effect magnitude is usually less extensive**
- The knowledge about the mechanistic basis of DDI for TPs is evolving
- Assessment of the DDI potential for TPs needs to be an integral part of the clinical pharmacology development program
- An in-depth understanding of the clearance pathways involved on the disposition of a TP are a necessary prerequisite for the development of a meaningful DDI assessment plan

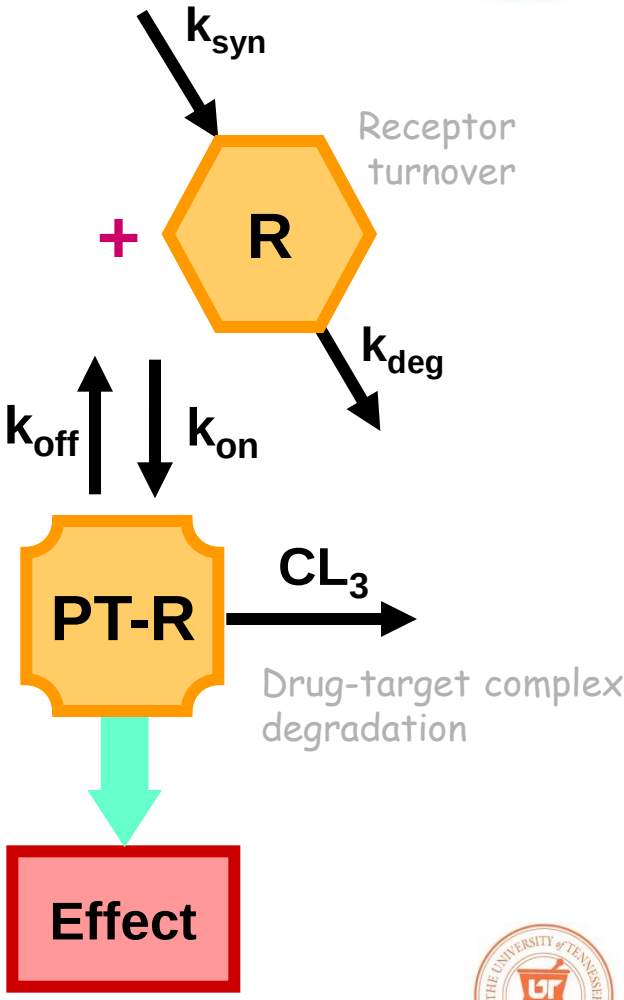
ADA immune complex formation & disposition





Target-mediated drug disposition





Chirmule, Jawa, Meibohm, AAPS J 2012, 14, 296-302

Literature on PK/PD of Biologics

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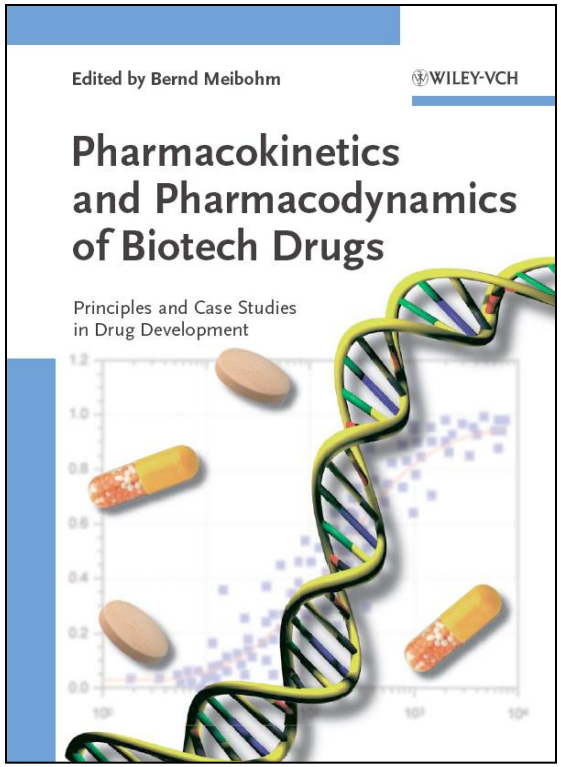

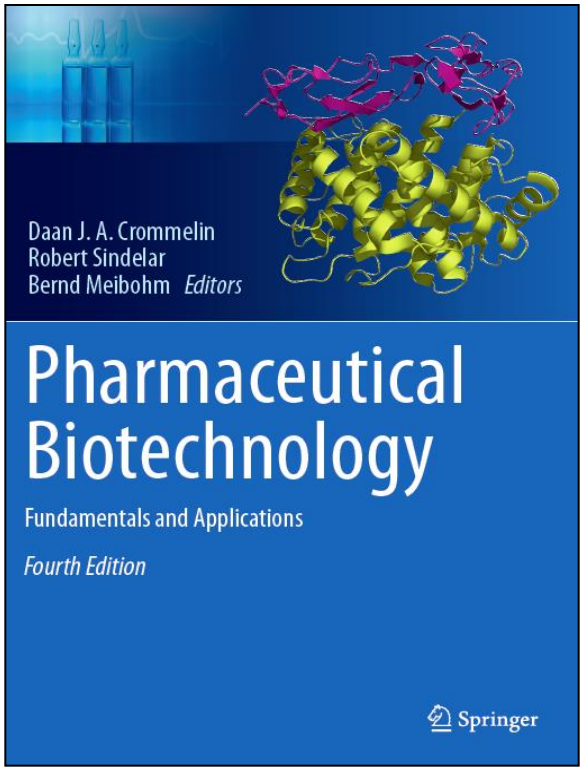

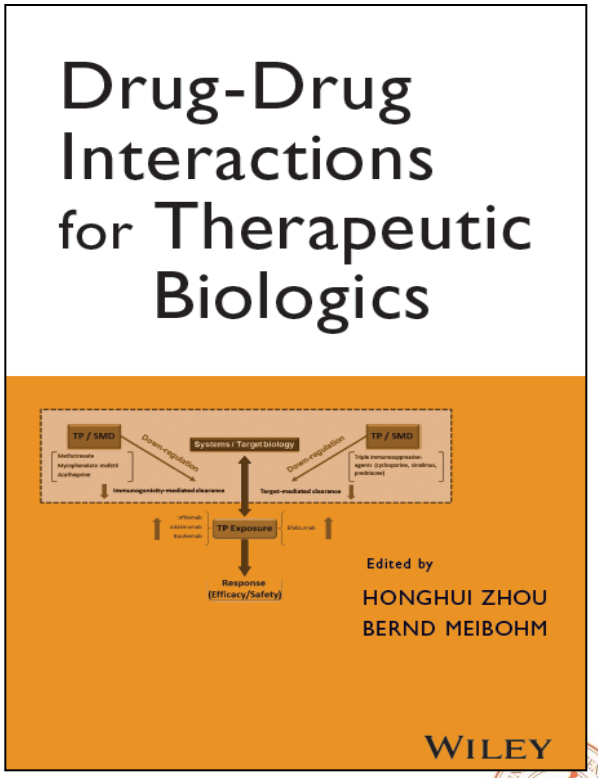

www.PKPDofProteinTherapeutics.com

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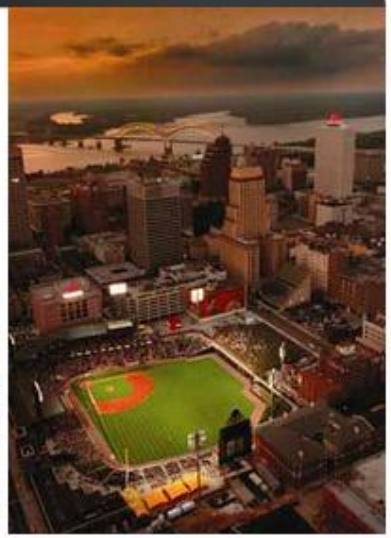
6th *Introductory Pharmacometric Training Course*

Pharmacokinetics & Pharmacodynamics of Protein Therapeutics

- Concepts and Hands-On Modeling and Simulation -



Course Directors:
Bernd Meibohm, University of Tennessee
Johan Gabrielsson, Swedish University of Agricultural Sciences

The 5-day course will introduce participants to basic principles in the pharmacokinetic and pharmacodynamic evaluation of novel protein therapeutics and provide opportunities for hands-on PK and PK/PD modeling and simulation examples relevant for protein drugs. Topics include target-mediated drug disposition, tissue and tumor penetration, interspecies scaling, first-in human dose selection, immunogenicity, model-based drug development, disease progression modeling, and drug-drug interactions. Hands-on data analysis will be performed individually and in small groups using several software packages.

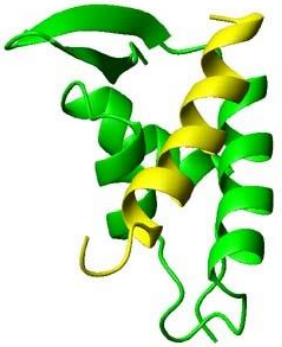
Location: **University of Tennessee College of Pharmacy, Memphis, TN, USA**

Time: April 11-15, 2016

Last updated: May 30, 2012

Click here First Announcement Flyer

Participants of the 2nd 'PKPD of Protein Therapeutics' pharmacometric training course, April 2012



April 11-15, 2016

sity of Tennessee