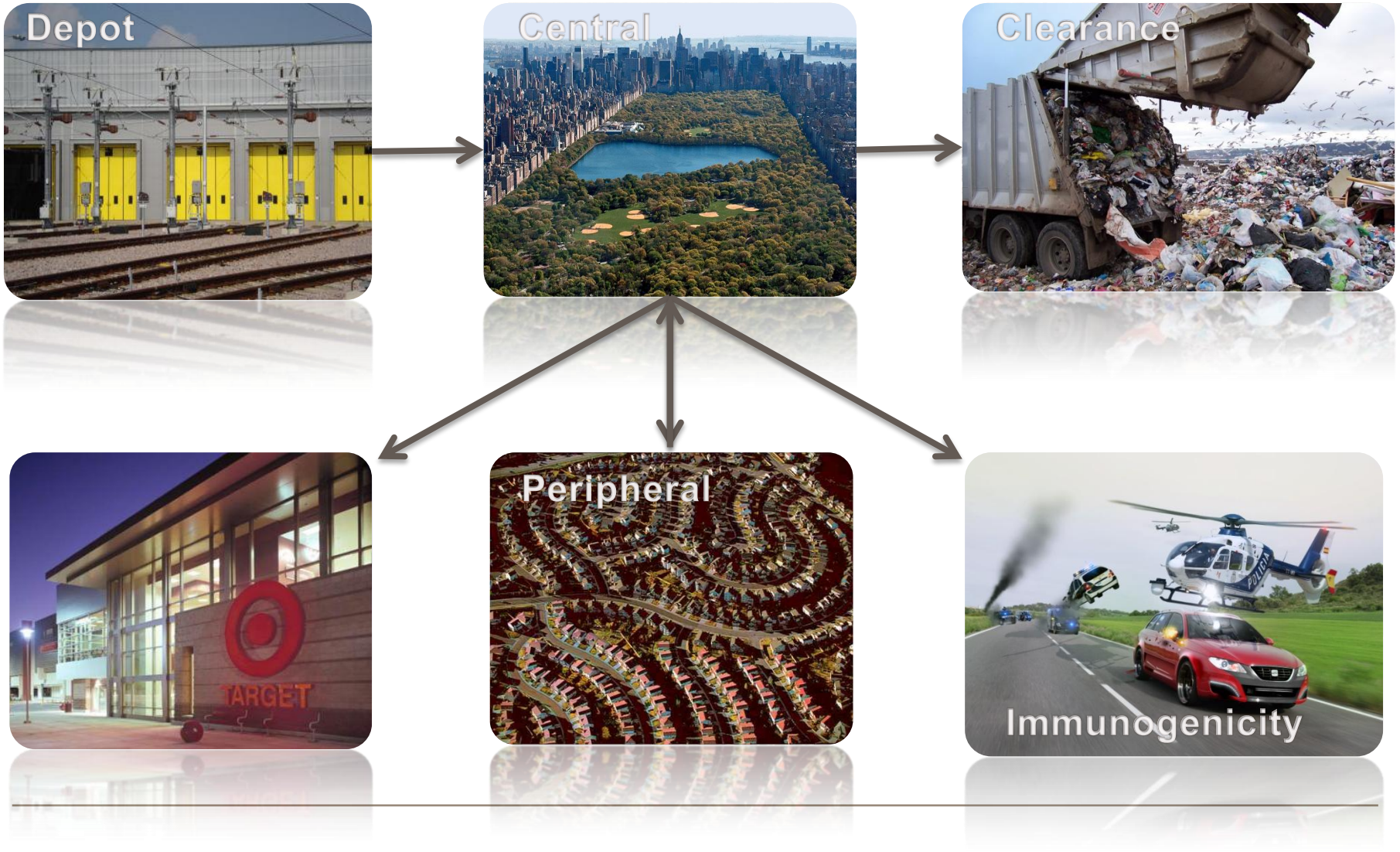
Target-mediated Clearance and Immunogenicity – two sides, one coin

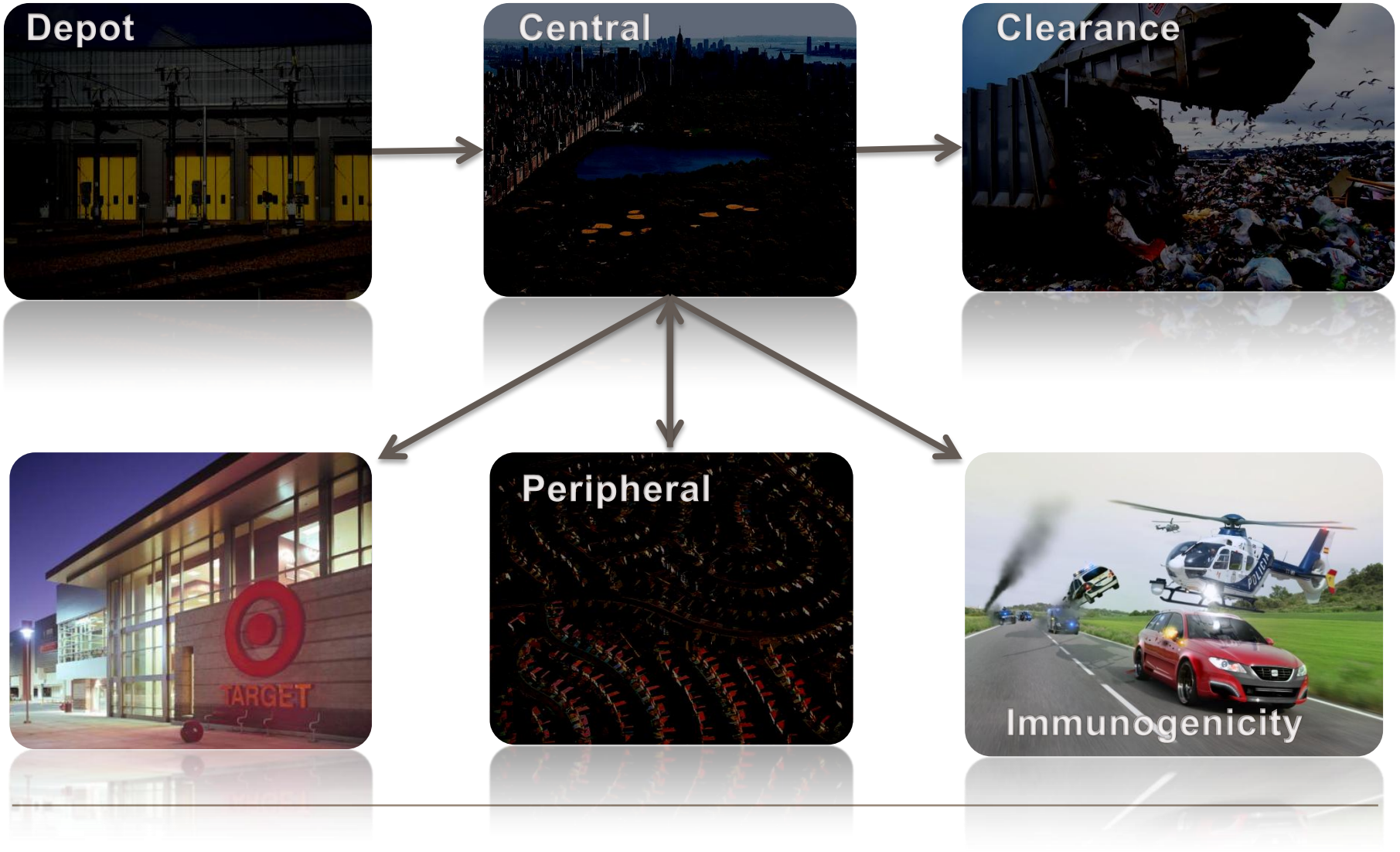
Daren Austin, PhD
Senior Director and Head
Biopharm Clinical Pharmacology

gsk
do more
feel better
live longer

Pharmacokinetic determinants of therapeutic proteins



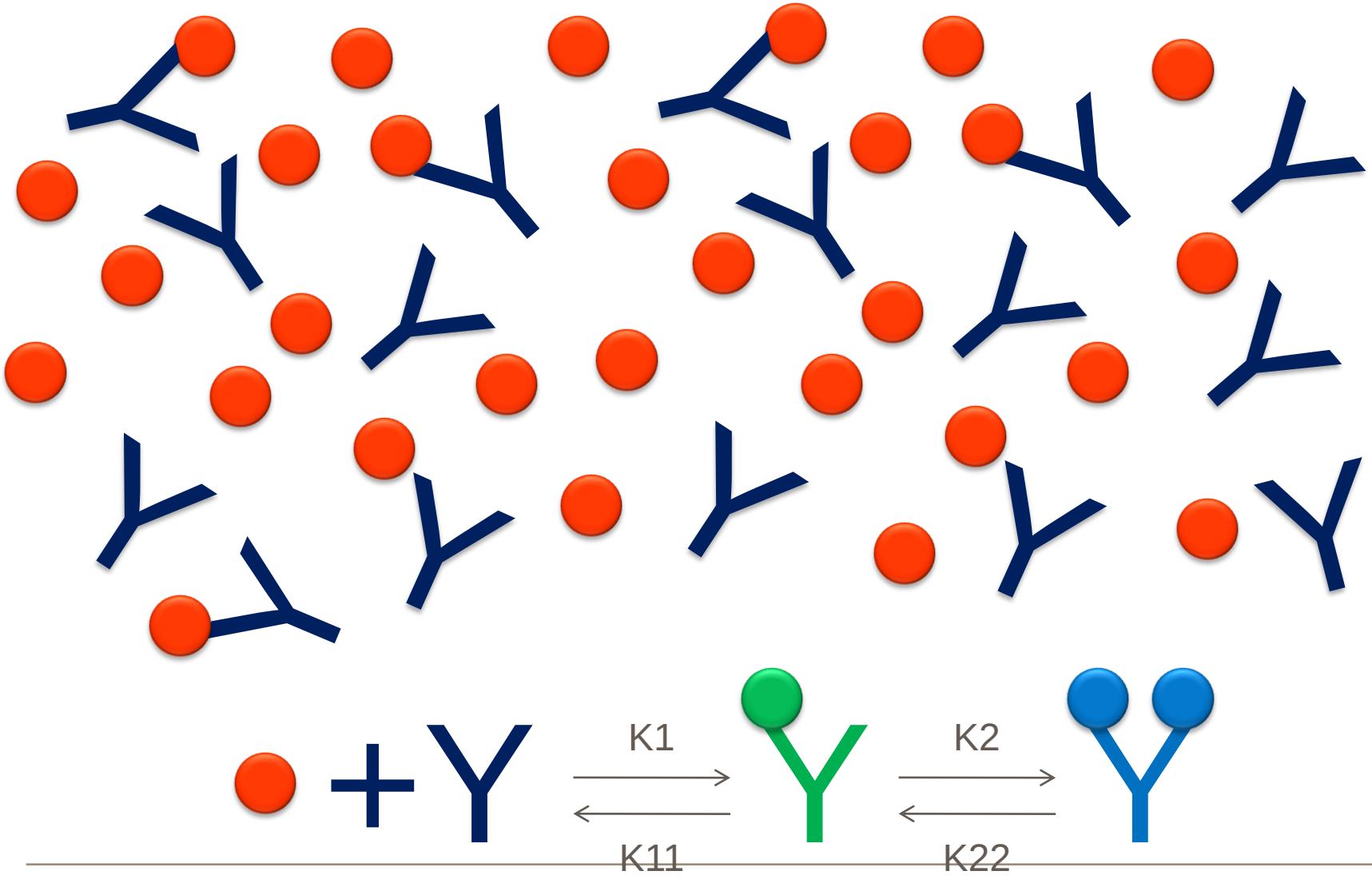
Pharmacokinetic determinants of therapeutic proteins



Antibodies are underdosed c.f. small molecules!

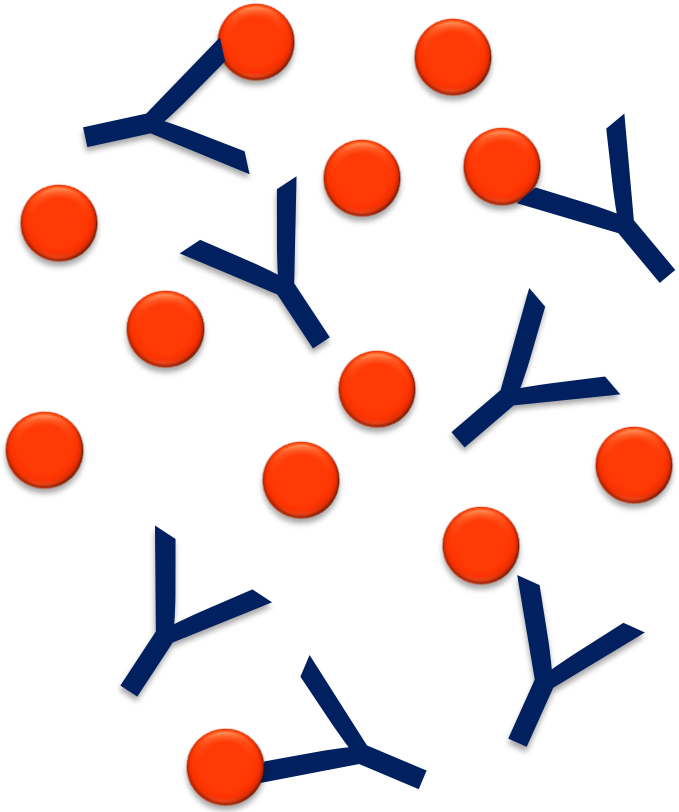
3 mg/kg mAb (MWT 150000), 30 mg NCE (MWT 300)

Some basic theory of antibody binding kinetics



Some basic theory of antibody binding kinetics

Simple mass action equations



Ligand + antibody = complex

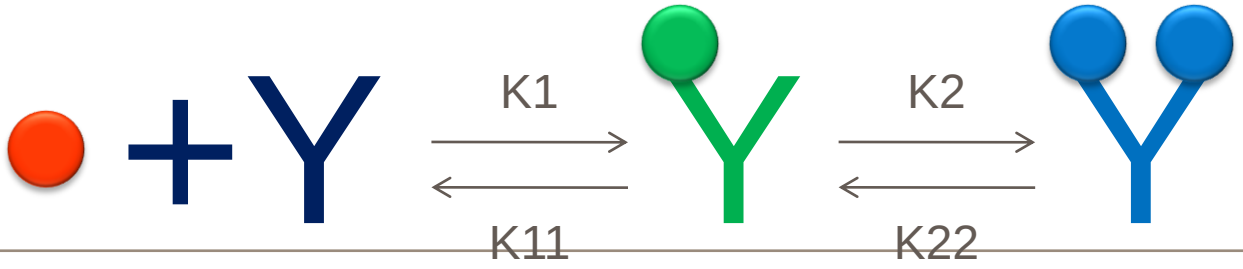
*d/dt (Ab) = -K1*Ag*Ab + K11*AgAb*

*d/dt (Ag) = -K1*Ag*Ab + K11*AgAb - K2*AgAb*Ag + K22*AgAbAg*

*d/dt (AgAb) = K1*Ag*Ab - K11*AgAb - K2*AgAb*Ag + K22*AgAbAg*

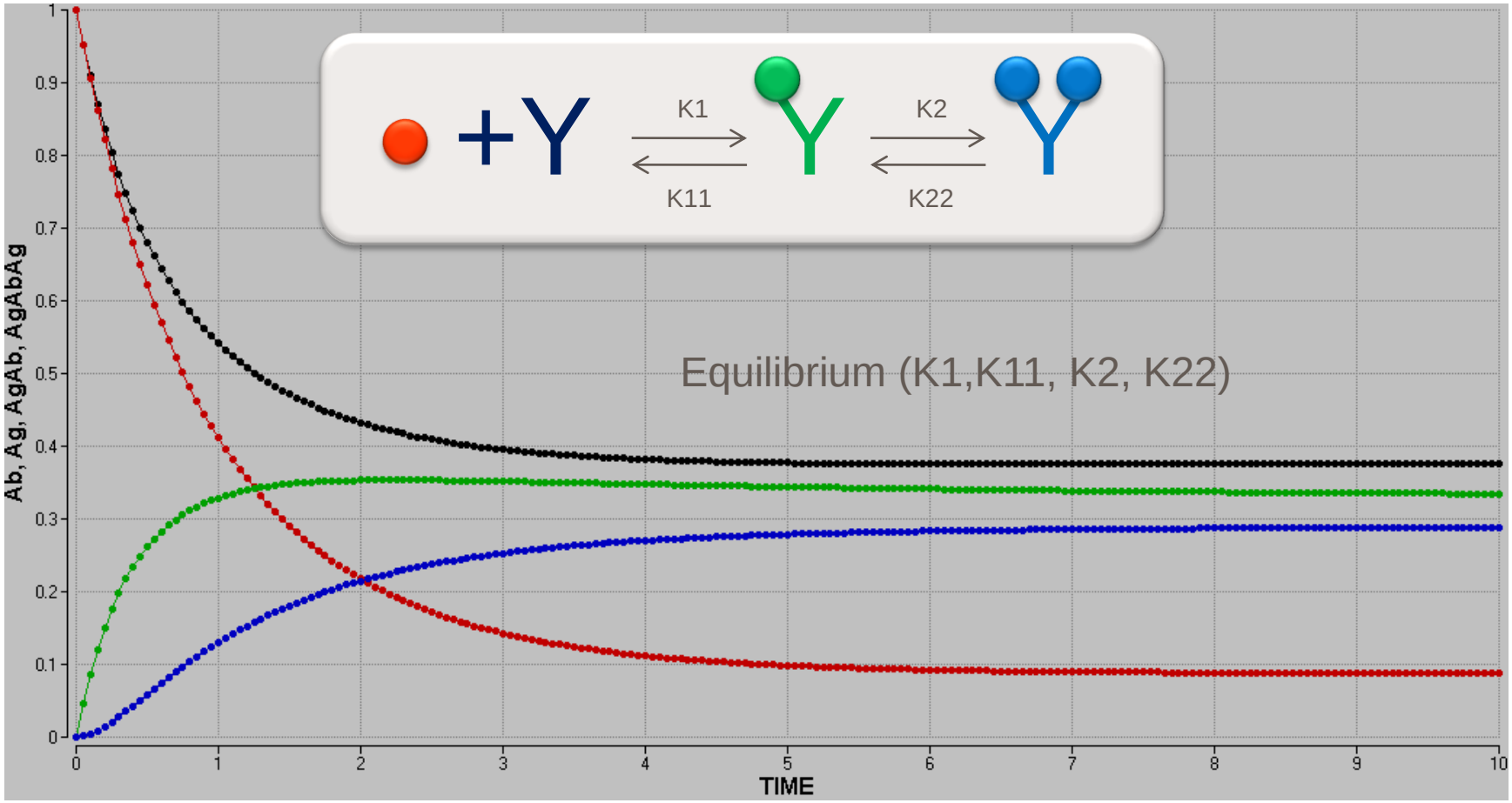
*d/dt (AgAbAg) = K2*AgAb*Ag - K22*AgAbAg*

Ab(total) = Ab + Ag + AgAbAg
Ag(total) = Ag + AgAb + 2 AgAbAg



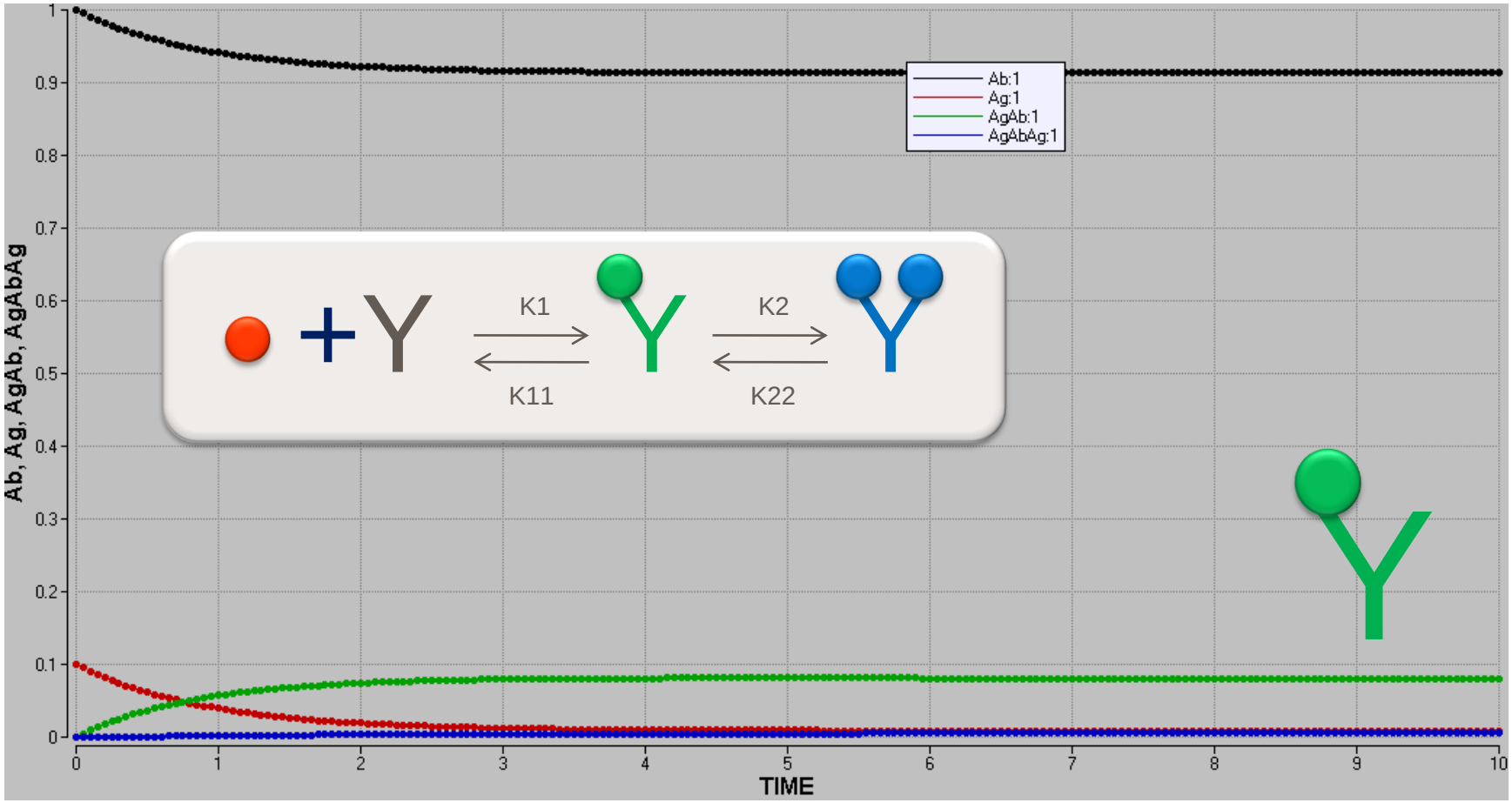
Antibody, antigen and complex

Total antibody and antigen are fixed to unity



Antibody in excess of antigen

Antibody excess means that antigen exists almost entirely as AgAb



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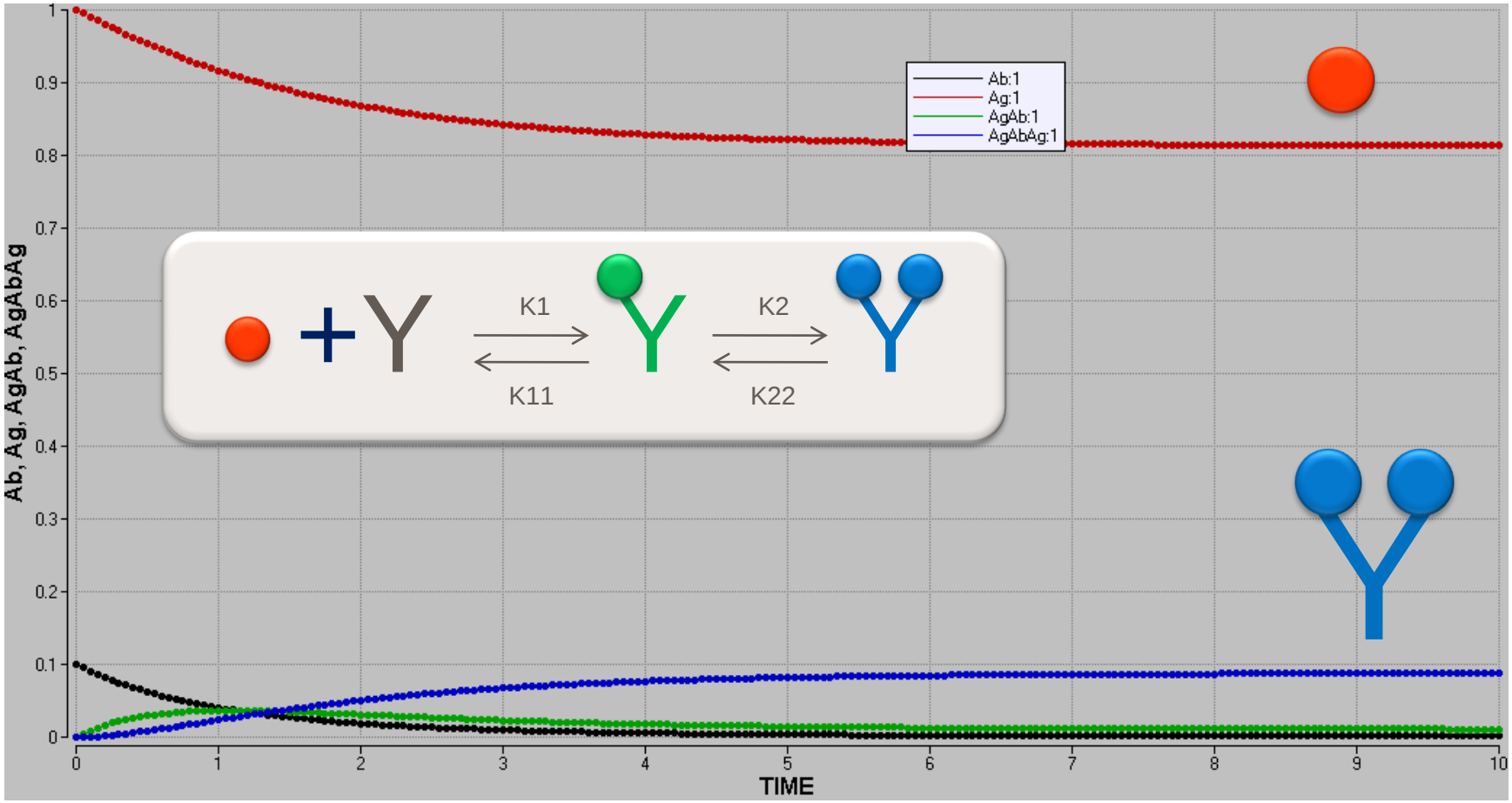
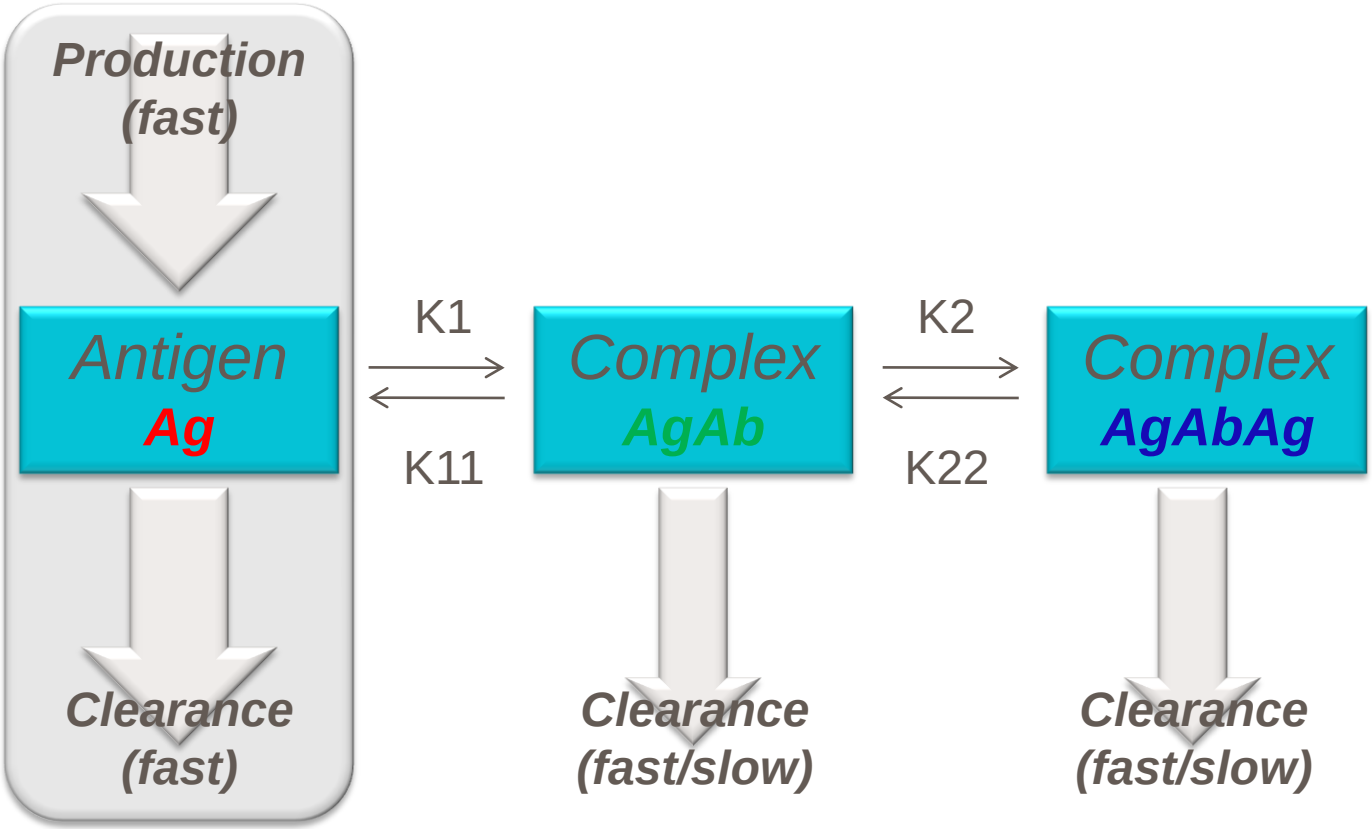


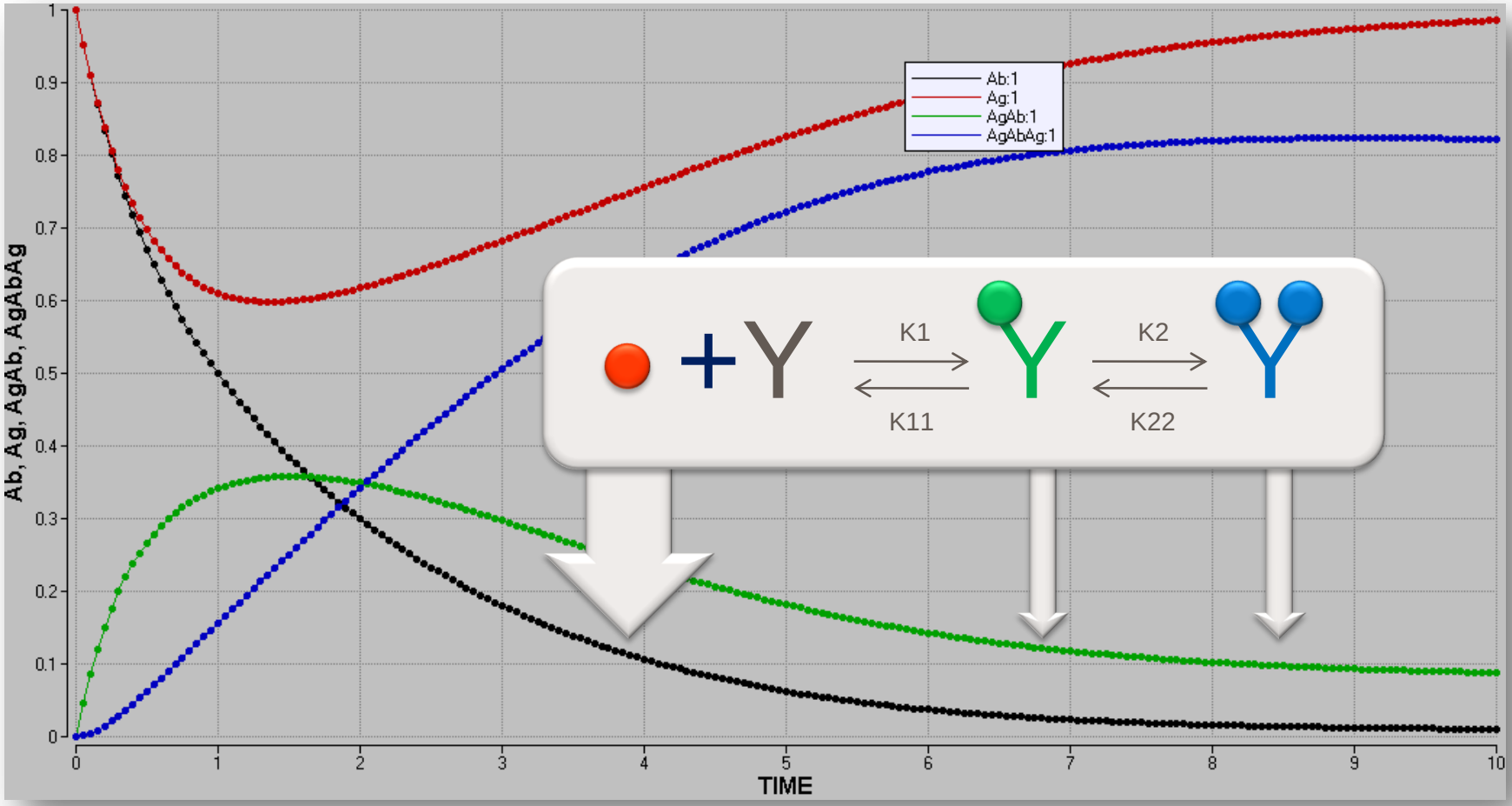
A simple model of antigen turnover with binding

Soluble ligands have fast endogenous clearance

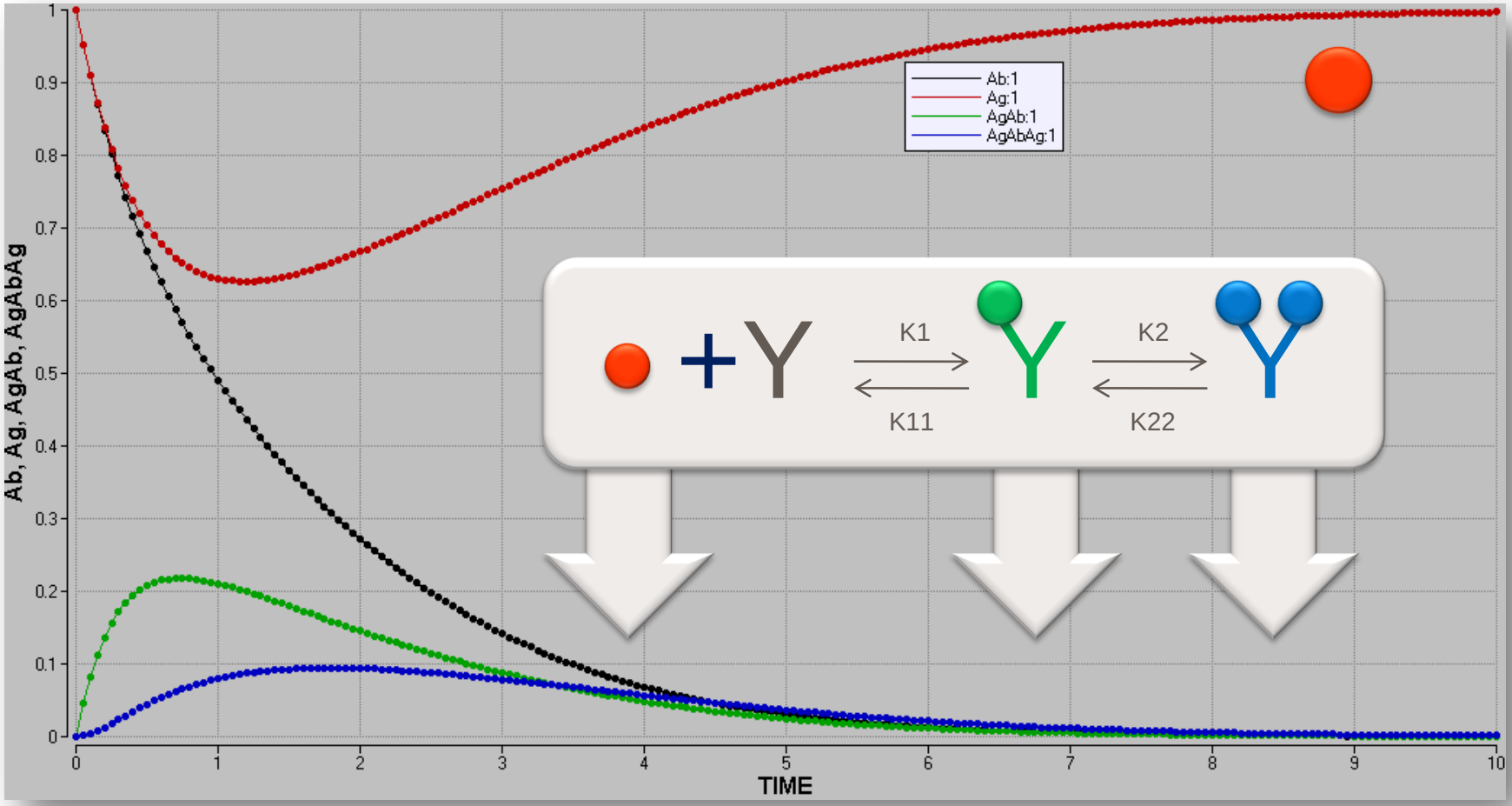


In vivo antigen concentration is a balance of production and clearance rates

Now add turnover of Antigen and SLOW complex clearance

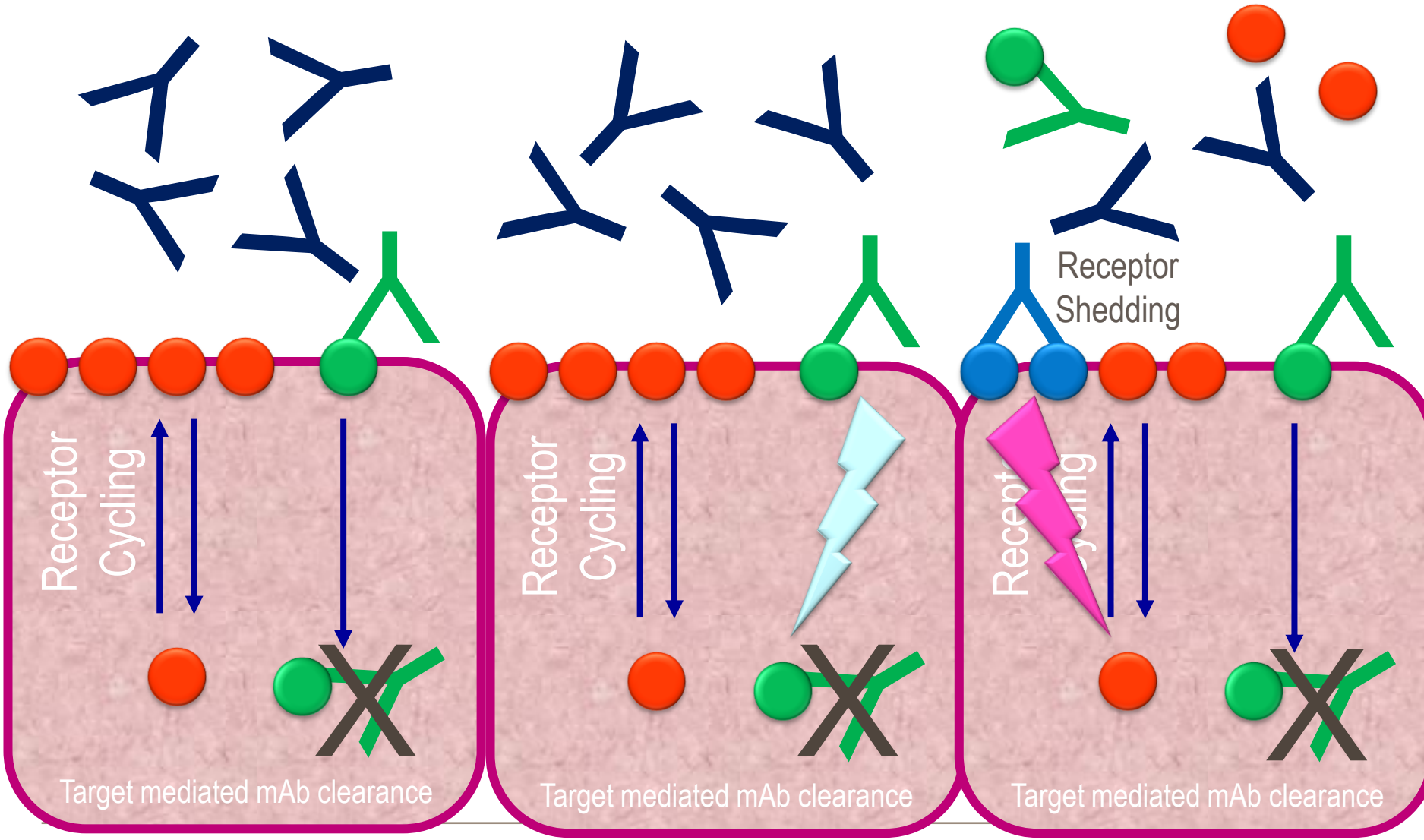


Now add turnover of Antigen and FAST complex clearance

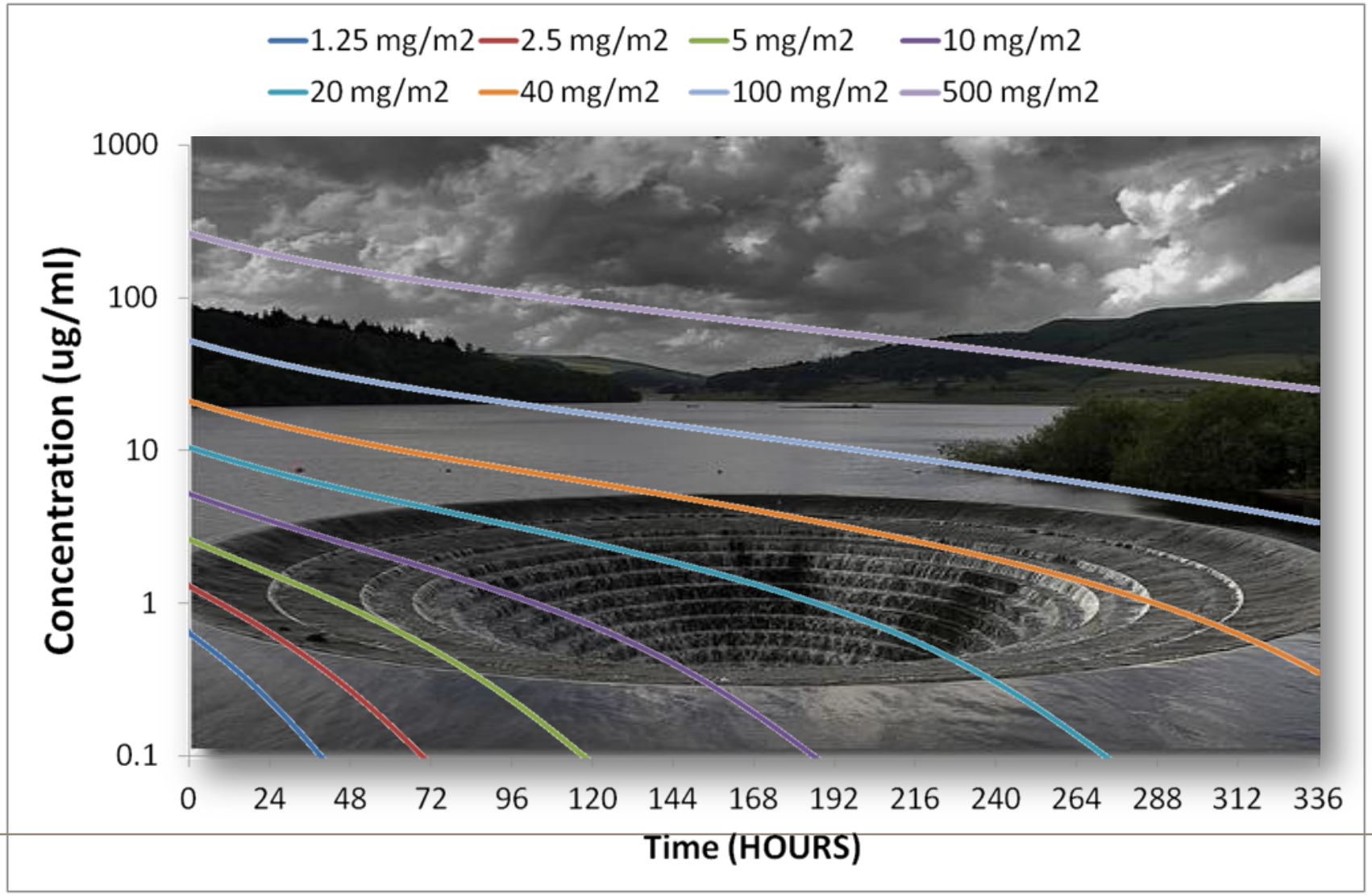


Receptor antibody interactions

Exactly the same principles as the soluble case

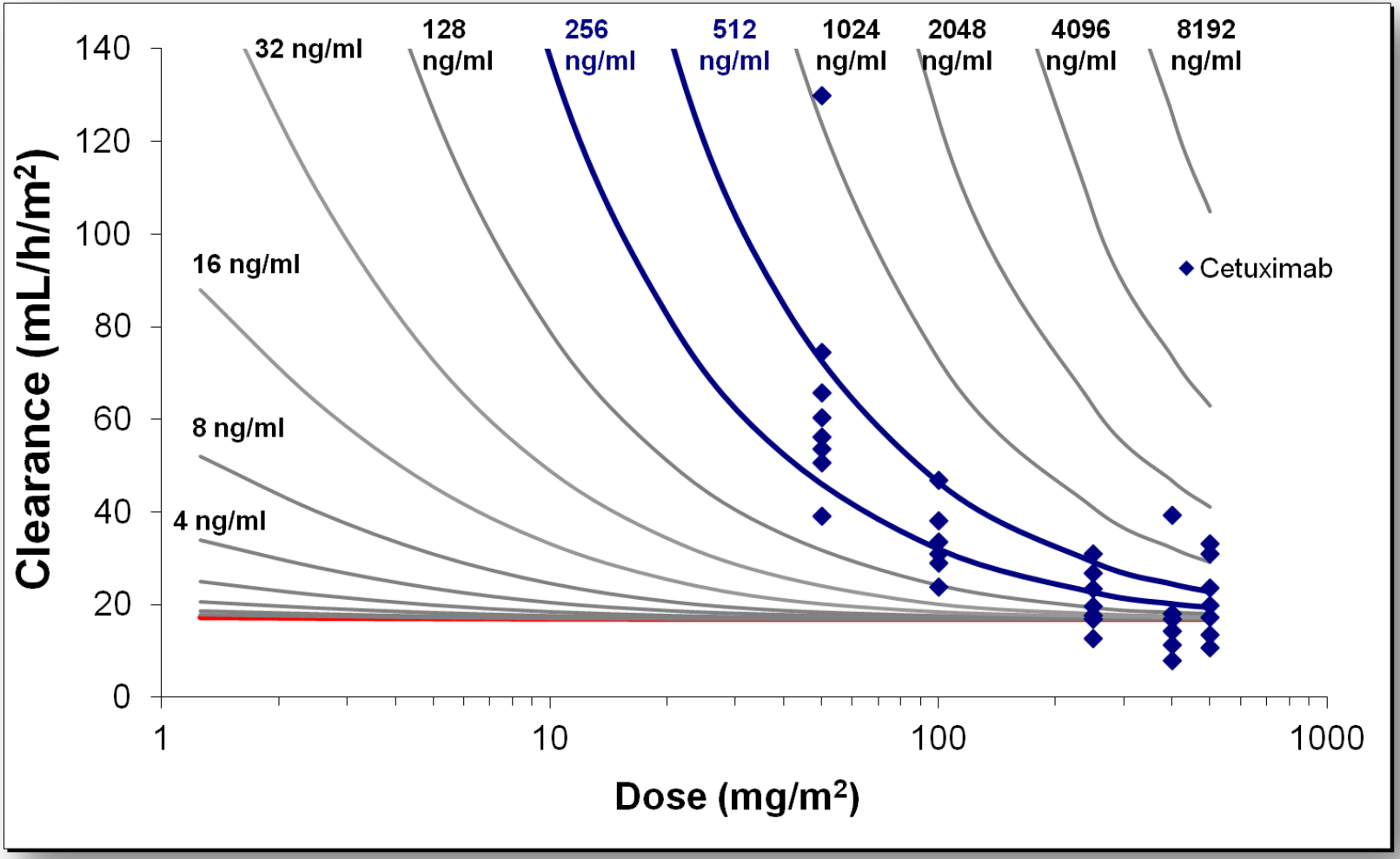


Cetuximab Pharmacokinetics in humans shows characteristic target-mediated clearance at 3 ug/ml



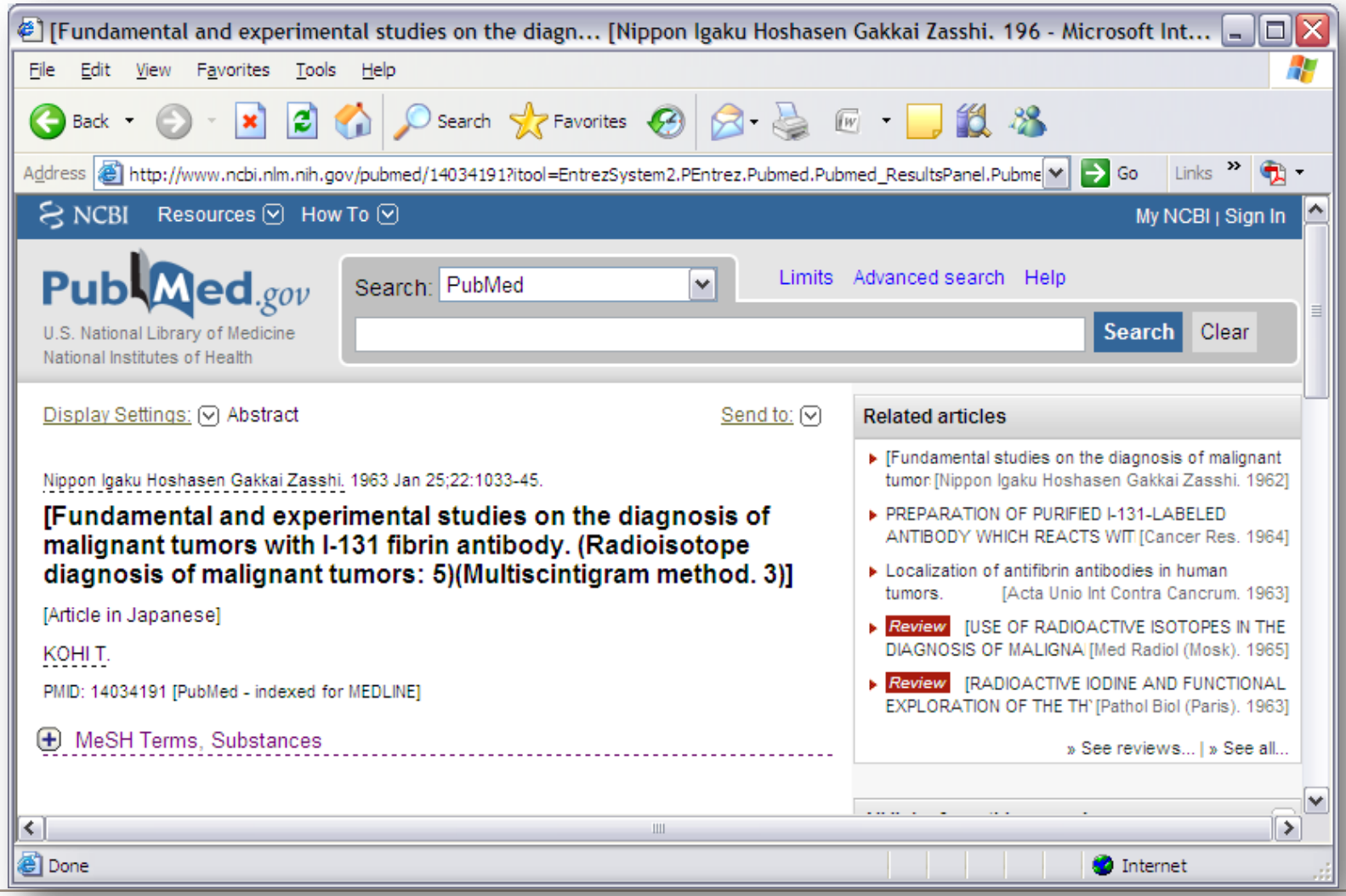
Can we solve the inverse problem?

Clearance = *f*(Target) ...Target = f^{-1}(Clearance)



Fracasso et al. Clin Cancer Res 2007; 13(3) 986-93

PubMed “isotope antibody tumour diagnosis”



An old methodology…brought up to date

Studies for the diagnosis of malignant tumours (1963)

"The most beautiful car ever made" Enzo Ferrari

Therapeutic utility of antibodies in multiple diseases (2011)

Immunogenicity…in the news since 1801

Edward Jenner 1796 vaccination (varriolation dates from much earlier)

http://dspace.jorum.ac.uk/xmlui/bitstream/handle/10949/946/Items/S320_1_section3.html

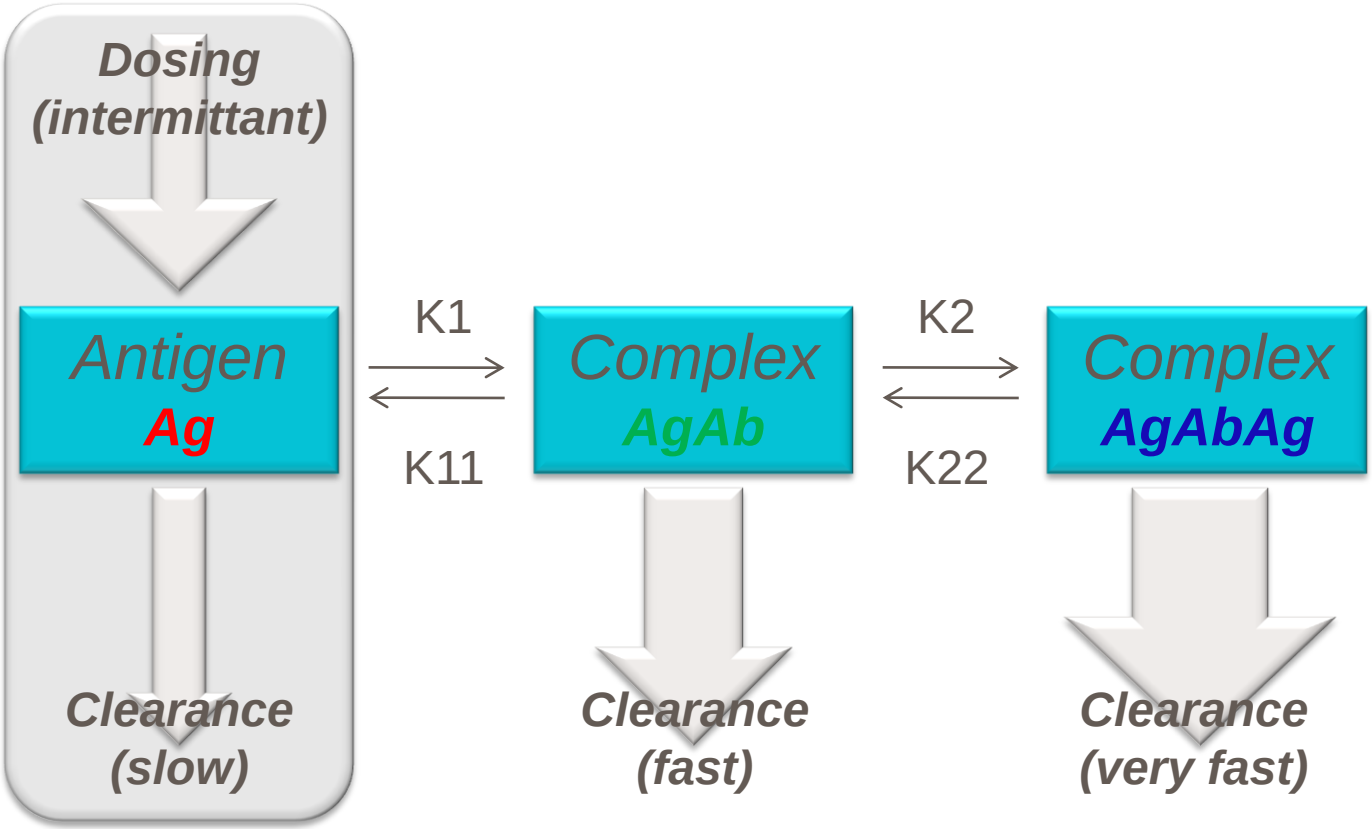
Unwanted immunogenicity

Factors of potential influence

- **Product characteristics**; structure, amino acid sequence, novel epitopes, aggregates, degradation products, oxidation and deamidation
- **Process characteristics**; host cell proteins, other contaminants
- Formulation
- Biological properties; immuno-stimulatory or immuno-suppressive
- Dosing; single or multiple injections, high or low dose, duration
- Route of administration
- Genetic factors (HLA class II and gene deficiencies)
- Immune status: competent or immuno-compromised
- Patient age
- Any concomitant medications
- Disease state: acute or chronic, inflammatory or oncology
- Target: endogenous counterpart, redundant or unique

A simple model of antigen turnover with binding

For immunogenicity, we just “flip” the notion of “target” to the mAb



Onset of appearance of ***Ab*** is stochastic and hence unpredictable at eth subject-level

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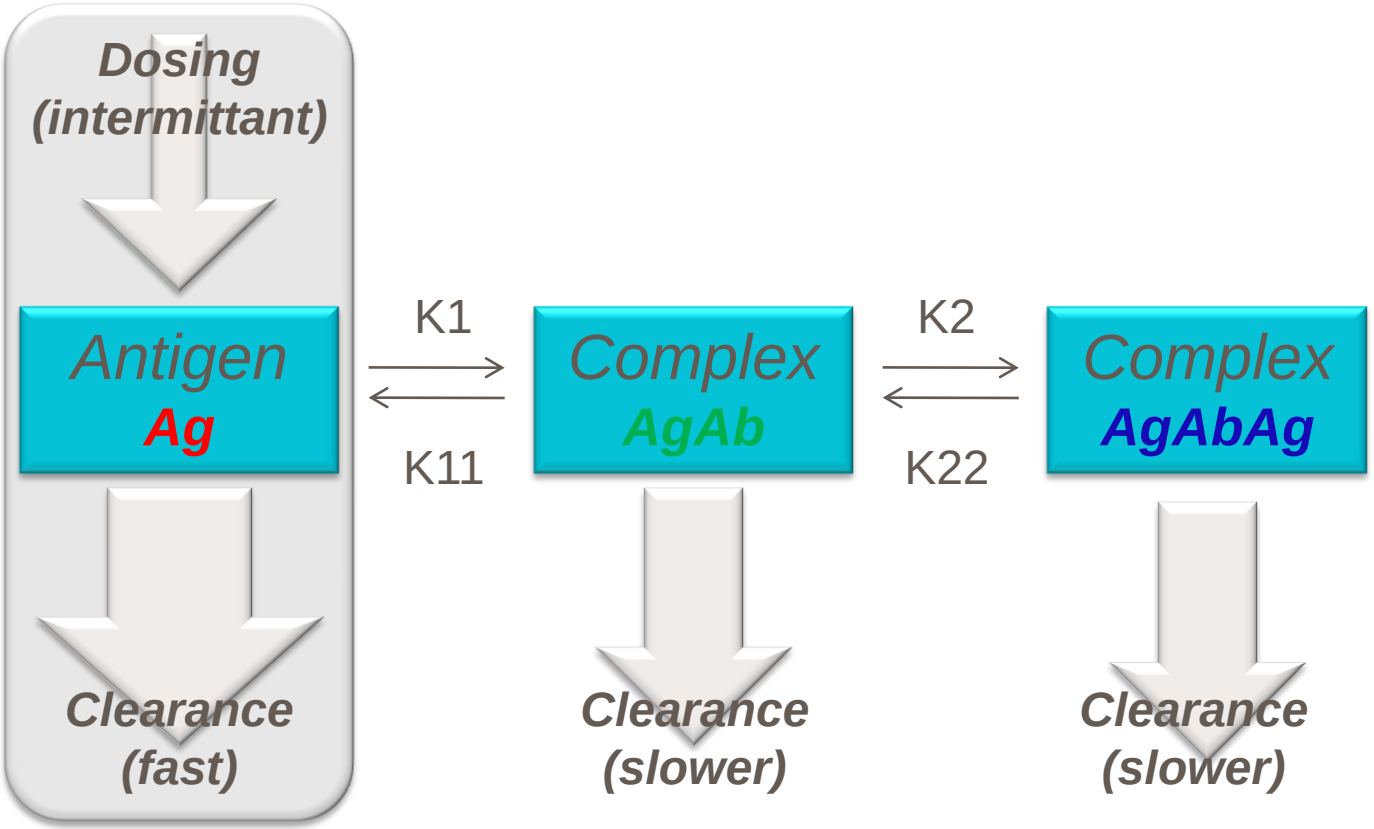

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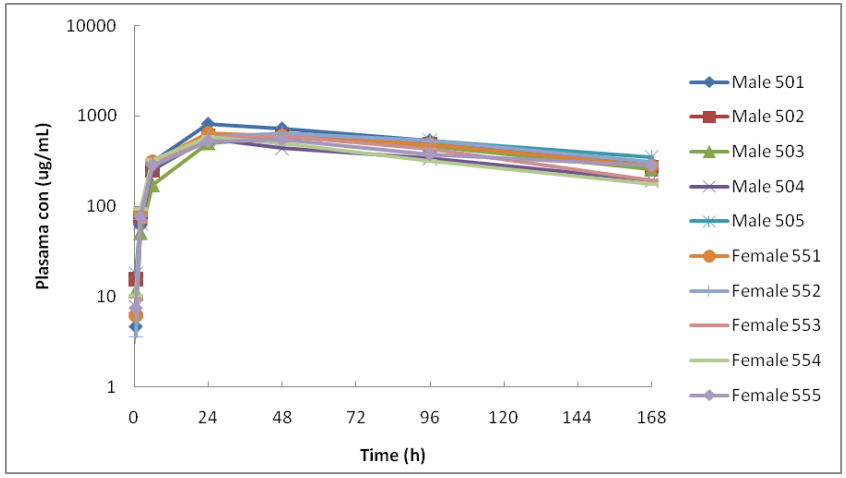
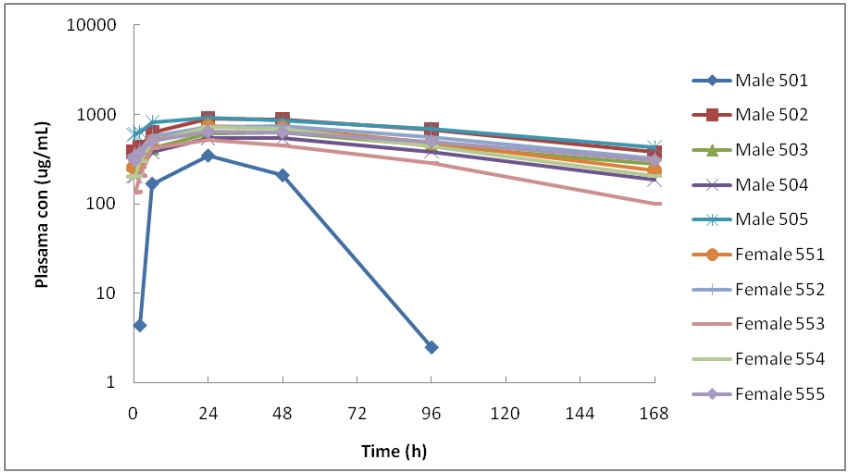
Spot the immunogenic animals (soluble target)

Immunogenic animals show “target-mediated” clearance

Week 4

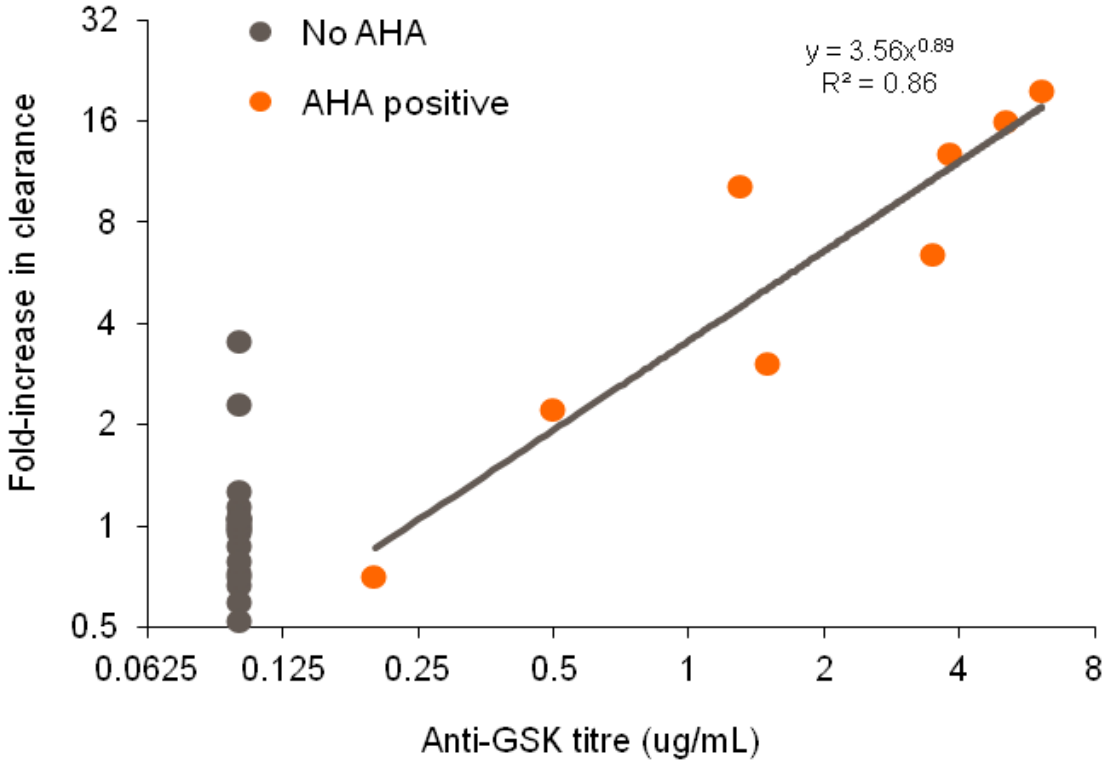


Week 8



Spot the immunogenic animals (soluble target)

Immunogenic animals show “target-mediated” clearance

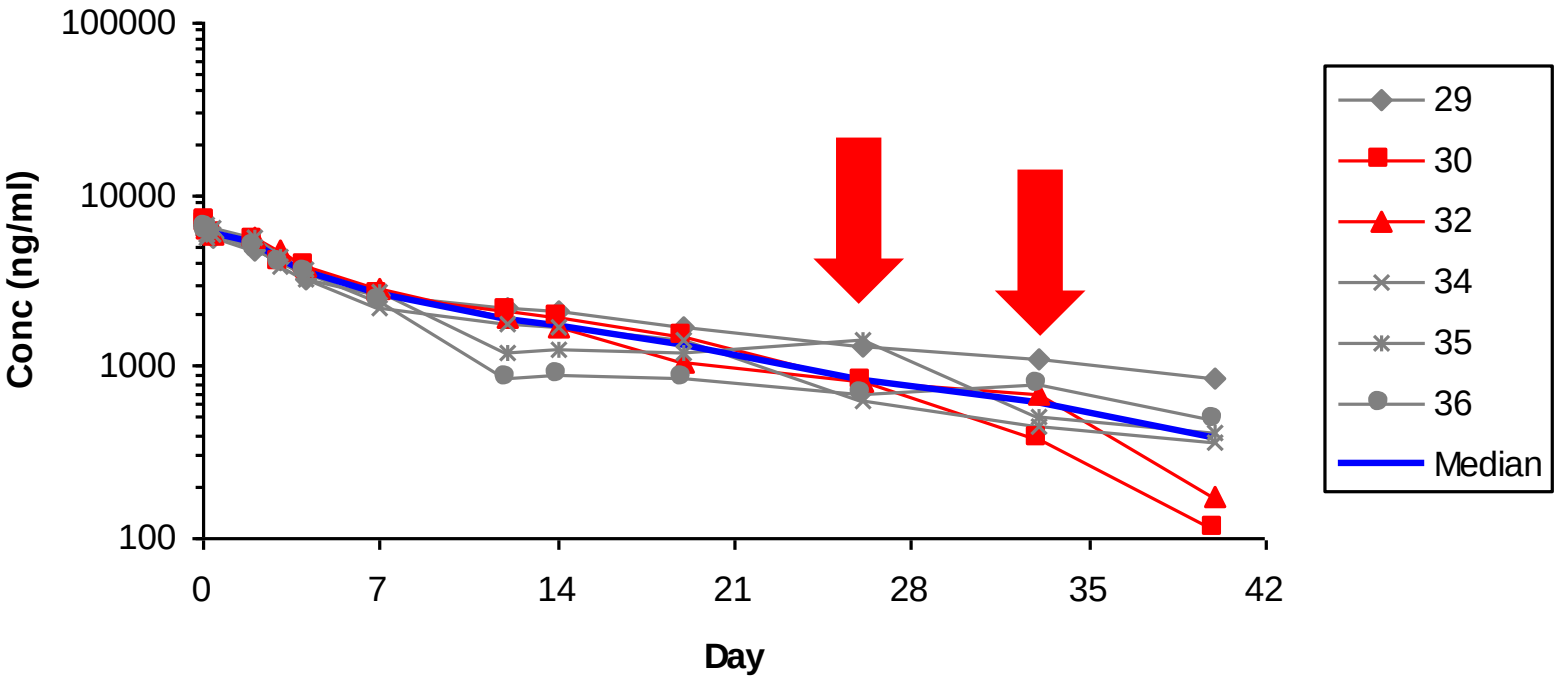


Clearance doubles with anti-human antibody titre

GSK data on file

Spot the immunogenic humans (soluble target)

Onset of appearance of immunogenicity is dose-dependent



Immunogenicity and target-mediated clearance will be confounded

GSK data on file

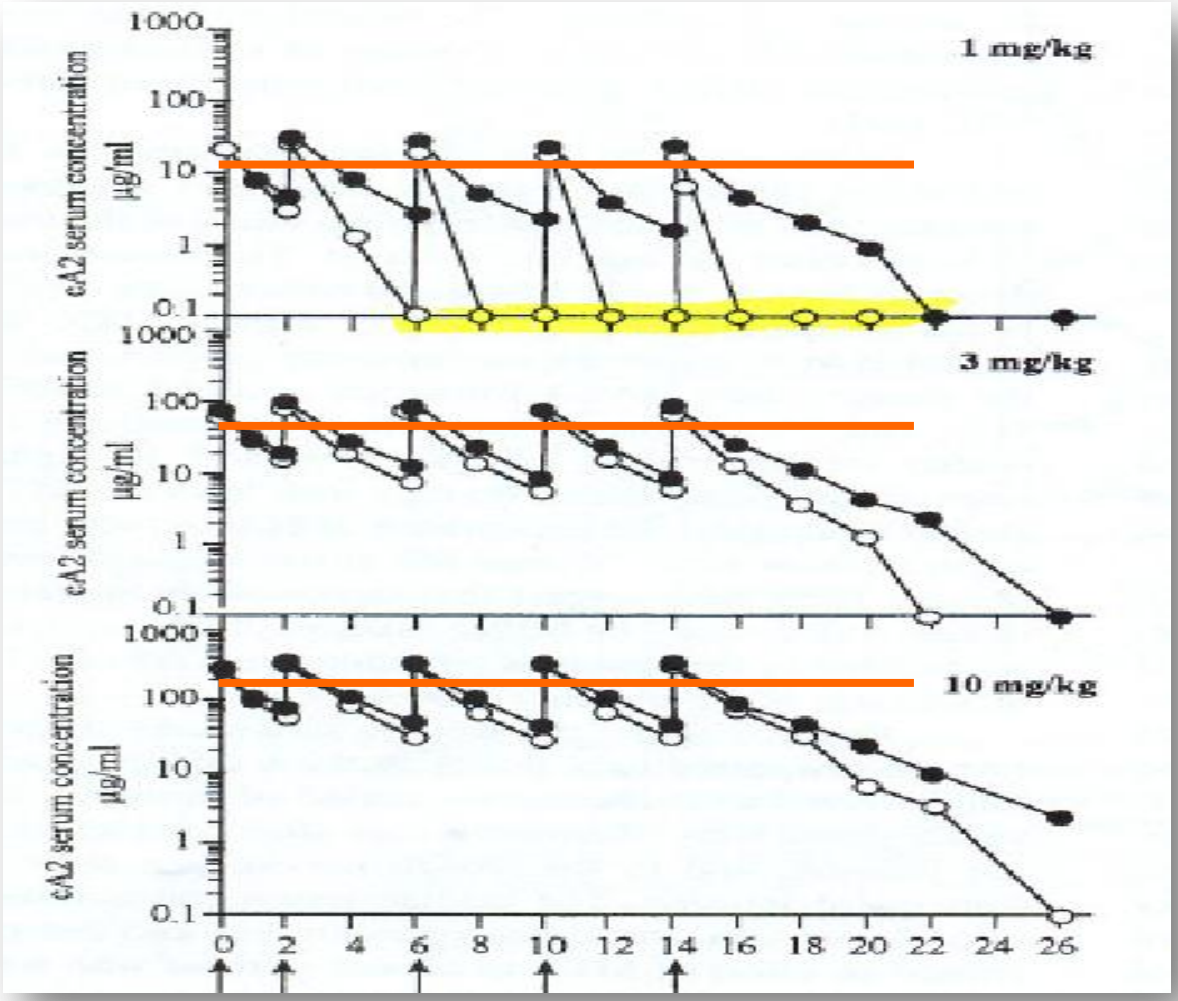
Clinical consequences of immunogenicity

Of varying target-dependent significance

- Increased clearance (Pharmacokinetics)
  - Seen at low doses
  - May be capacity limited
  - Saturated at high doses
  - Route dependent?
- Reduced clinical effect (Pharmacodynamics)
- Onset time may be up to two weeks
- Long-term safety
  - Neutralizing of endogenous analogue
- Effect of rechallenge/repeat dosing
  - Immediate hypersensitivity

Pharmacokinetic consequences of immunogenicity

Infliximab aTNF in RA. Maini et al (1998) Arthritis Rheum. 41; 1552-63



Css = Dose/CL.28d

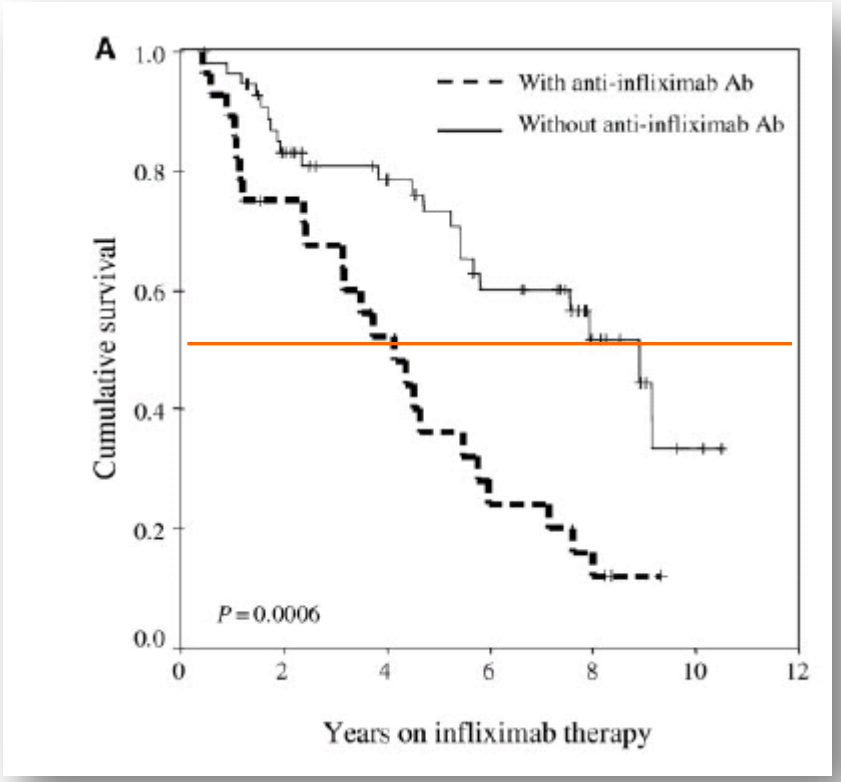
Css = 15/45/150 µg/mL

Faster clearance at low doses due to immunogenic reaction

Relationships between Ctau and efficacy in several diseases

Clinical consequences of immunogenicity?

Pascual-Salcedo et al, (2011). Rheumatology; 50:1445–1452

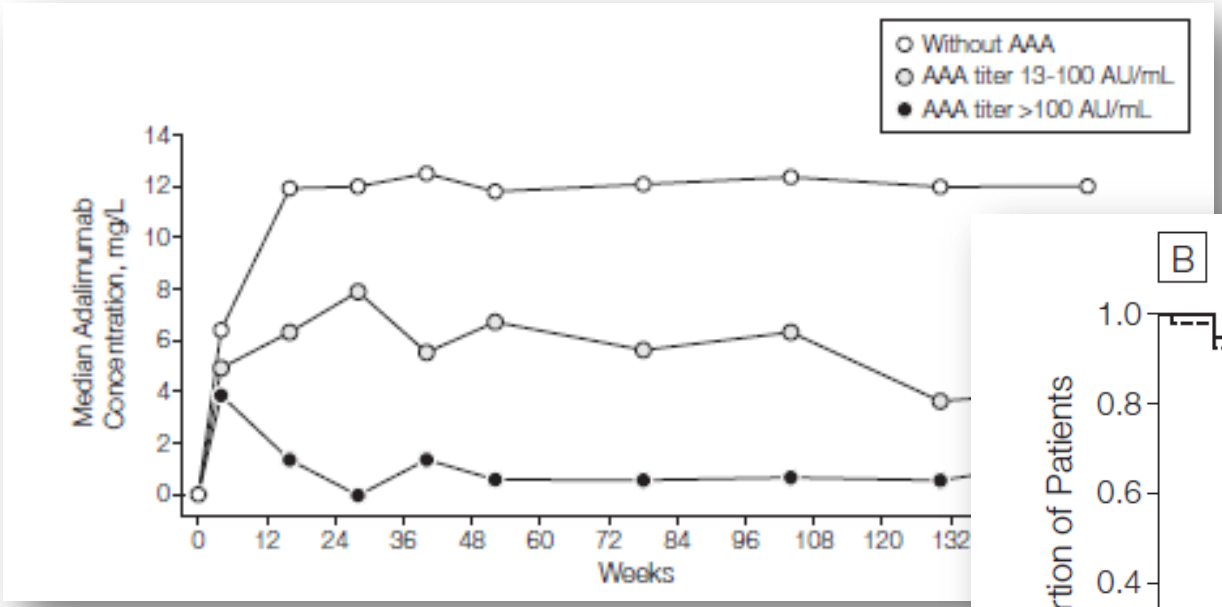


Median time duration of treatment is shortened by **four years**

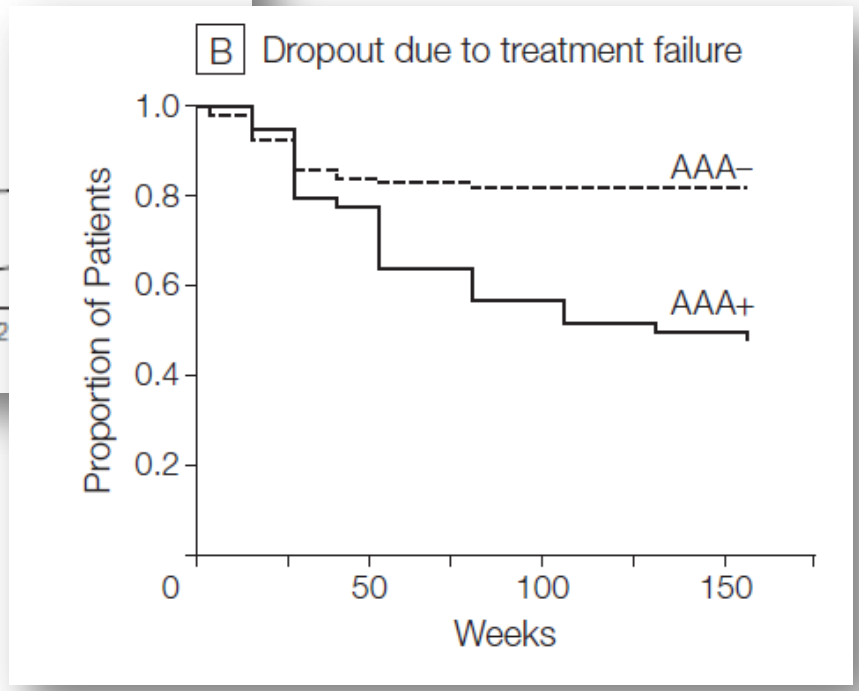
Conclusions unchanged for another aTNFa, adalimumab

Bartelds et al (2011). JAMA 305(14): 1460-1468

Pharmacokinetics



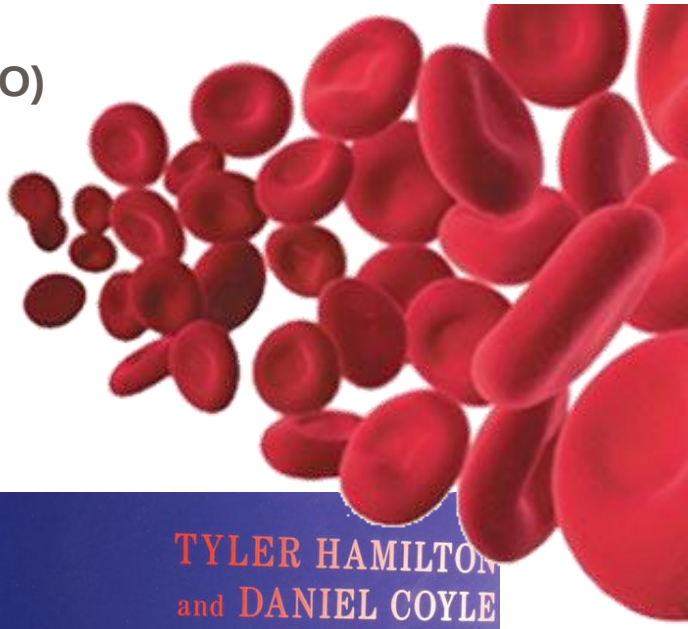
Treatment failure

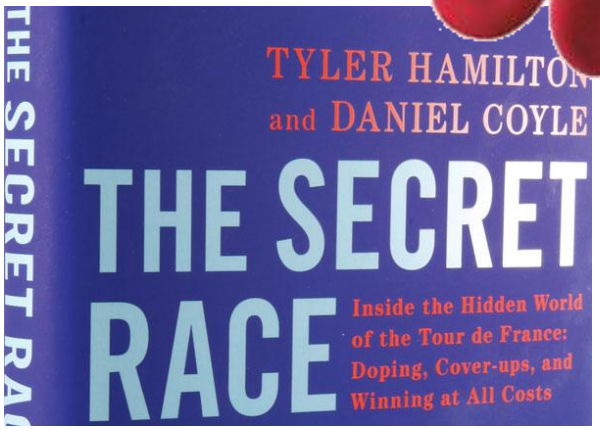


Antibody-mediated pure red blood cell aplasia

The immunogenicity “poster child”

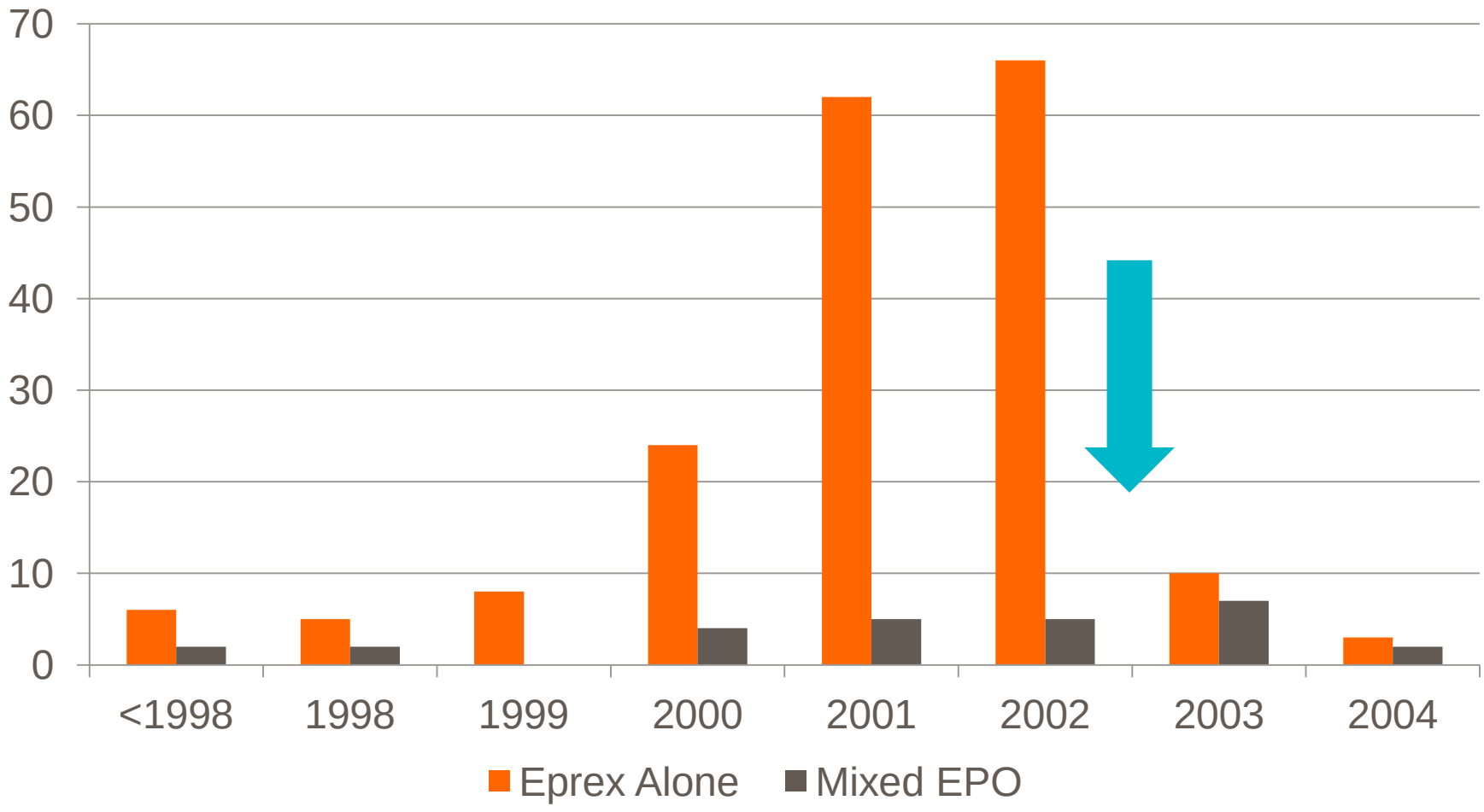
- Erythropoeitin is the stimulating growth factor that promotes red blood cell growth
- Antibodies against EPO can neutralize endogenous signal leading to a decline in RBCs
- Could be an auto-immune disease but…
- **Very rare prior to 1998 (10 years after launch of rHuEPO)**
- **Large increase seen from 1999-2002**
- Patients with anaemia associated with kidney disease





Incidence of PRCA following launch of subcutaneous Eprex

217 cases anti-EPO +ve, 206 received Eprex, 192 (SC), nine IV and SC



Temporal association with subcut release and uncoated stoppers

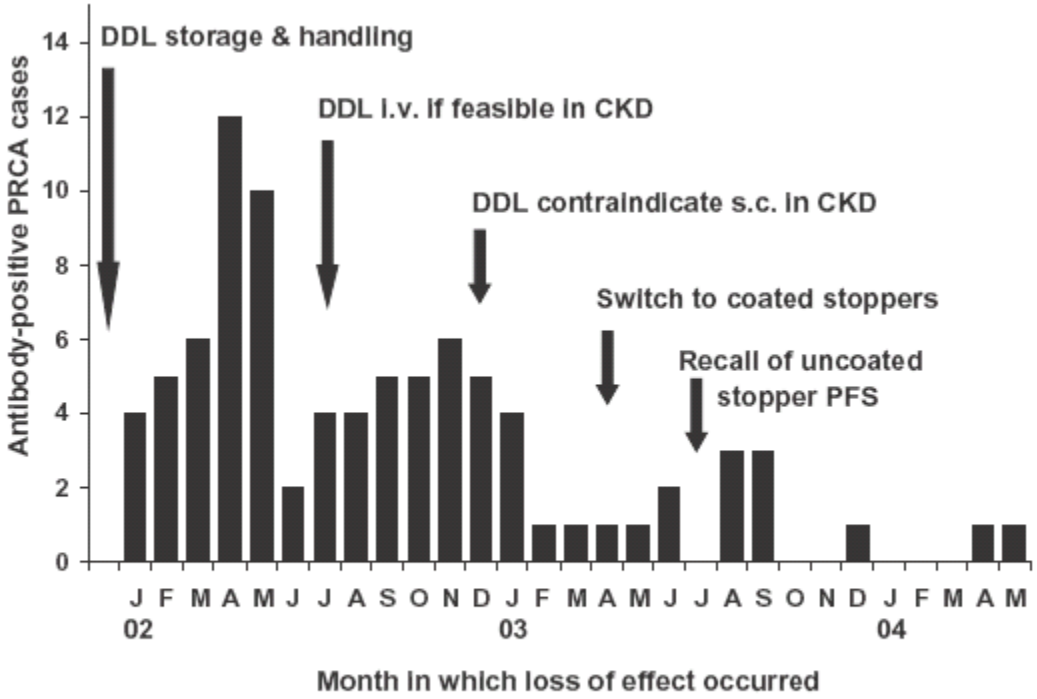


Fig. 3. Temporal correlation of the s.c. contraindication and replacement of uncoated with coated rubber stoppers and incidence of EPREX®-associated pure red cell aplasia. CKD = chronic kidney disease; DDL = 'Dear Doctor' letter; PFS = prefilled syringe.

Hypersensitivity consequences of immunogenicity

Ticks and red meat – an unlikely association

Lone Star Tick

Red meat

http://www.nydailynews.com/news/national/tick-bite-n-woman-meat-allergy-article-1.1858811

http://aedrops.com/tick-bite-allergy-to-red-meat-allergic-reaction-on-the-rise/

Hypersensitivity consequences of immunogenicity

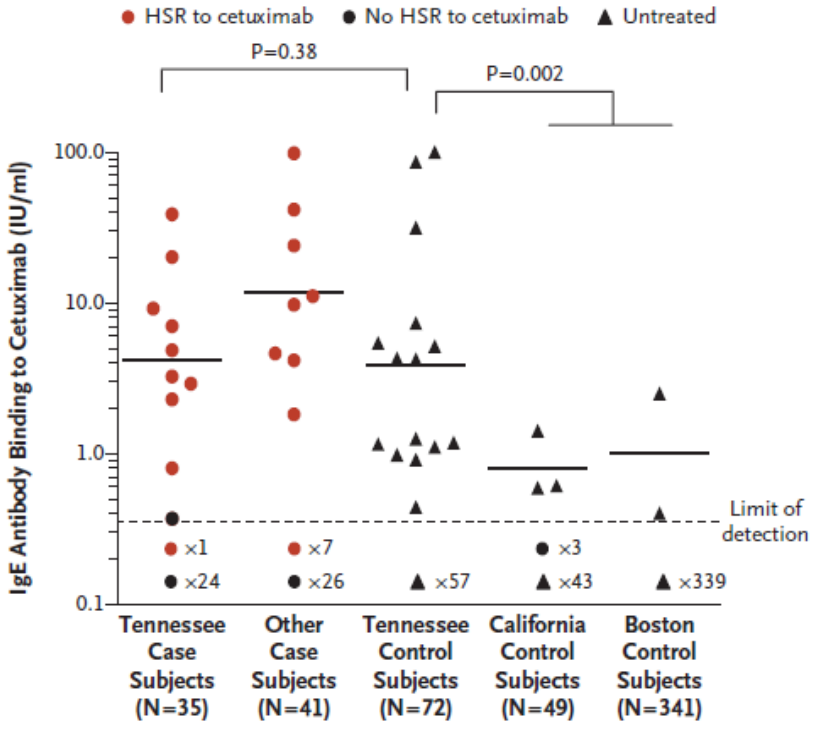
And the consequences for **cetuximab hypersensitivity**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cetuximab-Induced Anaphylaxis and IgE Specific for Galactose-α-1,3-Galactose

Christine H. Chung, M.D., Beloo Mirakhur, M.D., Ph.D., Emily Chan, M.D., Ph.D., Quynh-Thu Le, M.D., Jordan Berlin, M.D., Michael Morse, M.D., Barbara A. Murphy, M.D., Shama M. Satinover, M.S., Jacob Hosen, B.S., David Mauro, M.D., Ph.D., Robbert J. Slebos, Ph.D., Qinwei Zhou, Ph.D., Diane Gold, M.D., Tina Hatley, M.D., Daniel J. Hicklin, Ph.D., and Thomas A.E. Platts-Mills, M.D., Ph.D.



Conclusions

- Target-mediated clearance is nothing new and has been recognized since the advent of antibodies and other peptides as ***clinical*** agents
- Since antibodies and other therapeutic proteins tend to be (relatively) under-dosed, and degraded by naturally, interplay with target must be understood
- For receptor targets, expression and turnover determines dose and frequency
- Receptor targets do however have a better track record for efficacy than soluble ligand binding
- Target levels determines PK determines target levels – the inverse problem
- Immunogenicity is also nothing new
- There are many determinants but few established consequences
- Exposure-response, even in the presence of immunogenicity, is important
- Stochasticity means that modelling efforts may only be ***descriptive***
- Sometimes all is not as it seems – in fact often!