An integrated pharmacokinetics-pharmacodynamics-immunogenicity approach for bioanalysis of biological drugs

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Preclinical Safety / Biologics Safety & Disposition

EBF 3rd Open Conference, 2 December 2010

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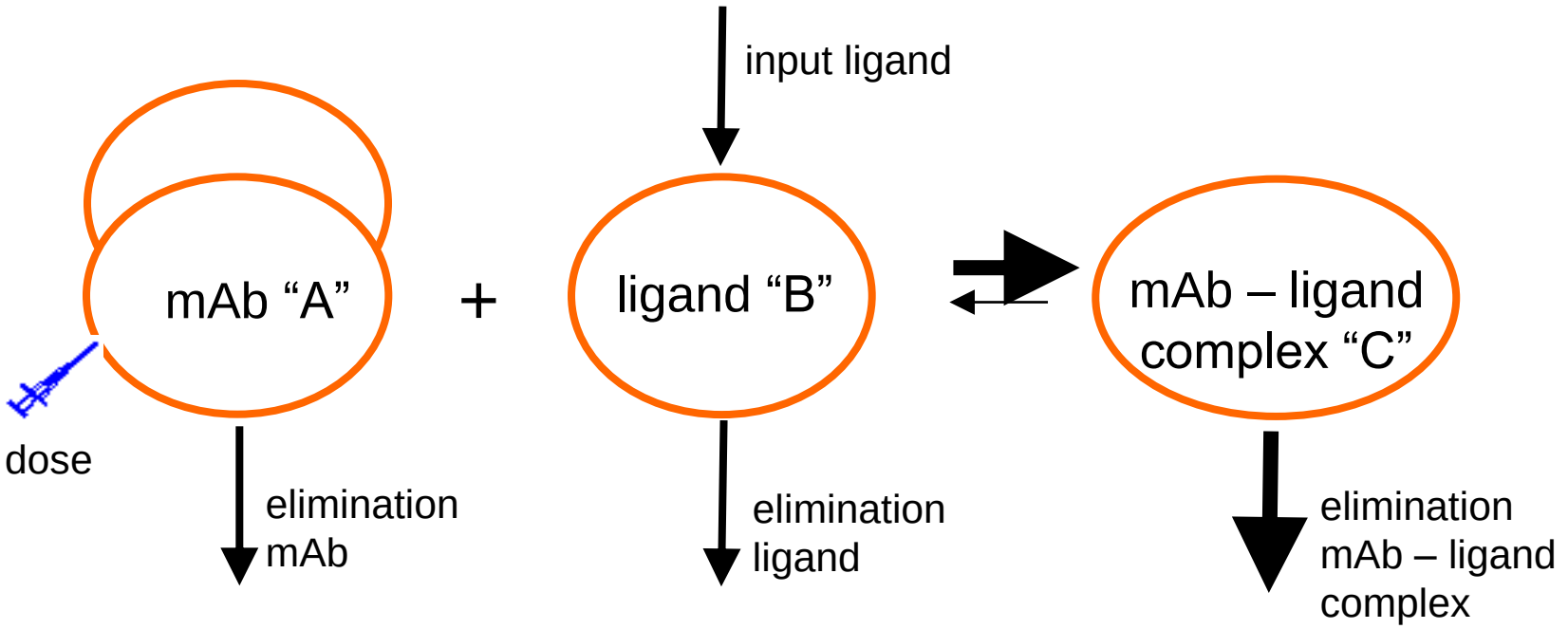
Outline of the presentation

- PK-PD models for monoclonal antibodies
  - ligand binding models for soluble and cell surface targets
  - typical PK-PD behavior
- Integrated bioanalytical strategy: PK-PD and immunogenicity (IG)
  - ELISA formats to characterize PK and PD (soluble and cell surface targets)
  - impact of immunogenicity
- Examples
  - Example 1: soluble target; effect of immunogenicity on PK and PD
  - Example 2: cell surface target; detection of neutralizing immunogenicity from PK assay format
  - Example 3: cell surface target; effect of PK on PD
- Summary

A simple mAb-ligand PK-PD model



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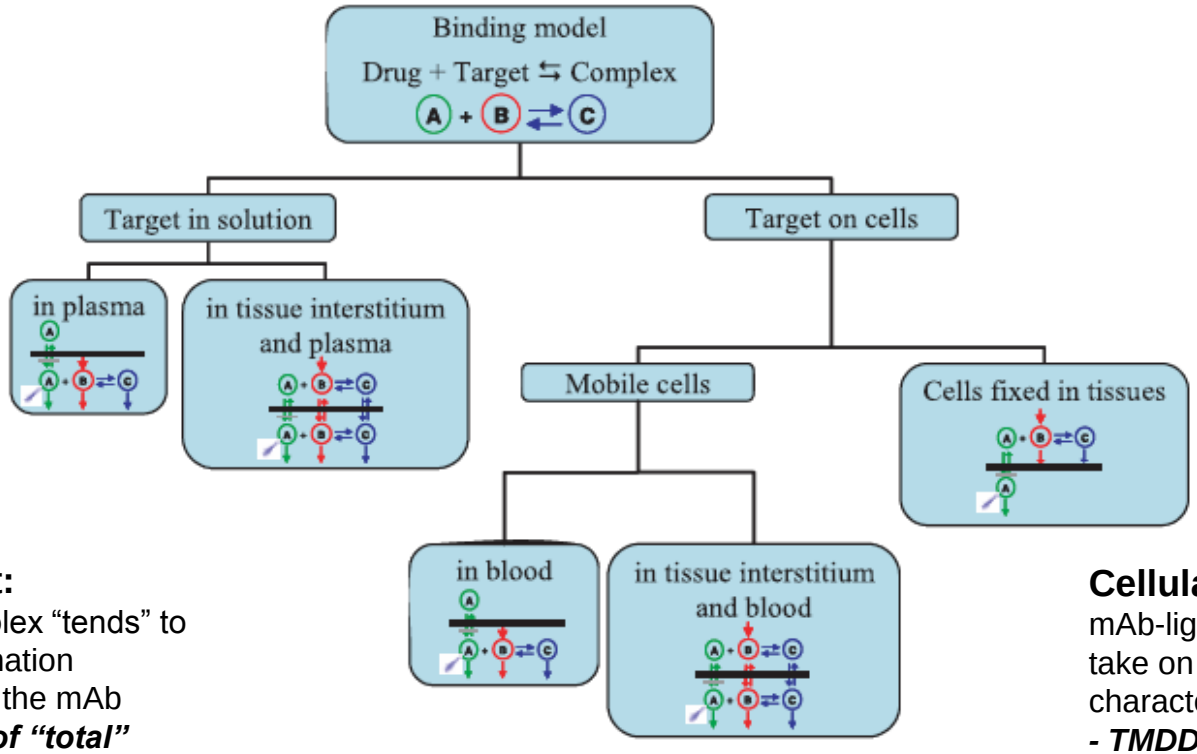
mAb-ligand PK-PD binding model(s)



Soluble target:
mAb-ligand complex "tends" to take on the elimination characteristics of the mAb
- accumulation of "total" (inactive) ligand (PD marker)

Cellular target:
mAb-ligand complex "tends" to take on the elimination characteristics of the ligand
- TMDD apparent (PD marker)

Lowe PJ et al: On setting the first dose in man: Quantitating biotherapeutic drug-target binding through PK and PD models
Basic & Clin Pharmacology & Toxicology 2009; 106: 195-209

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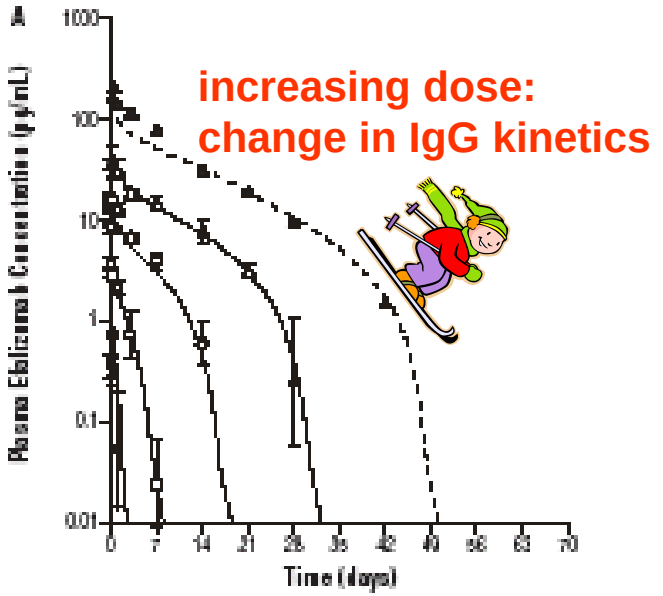
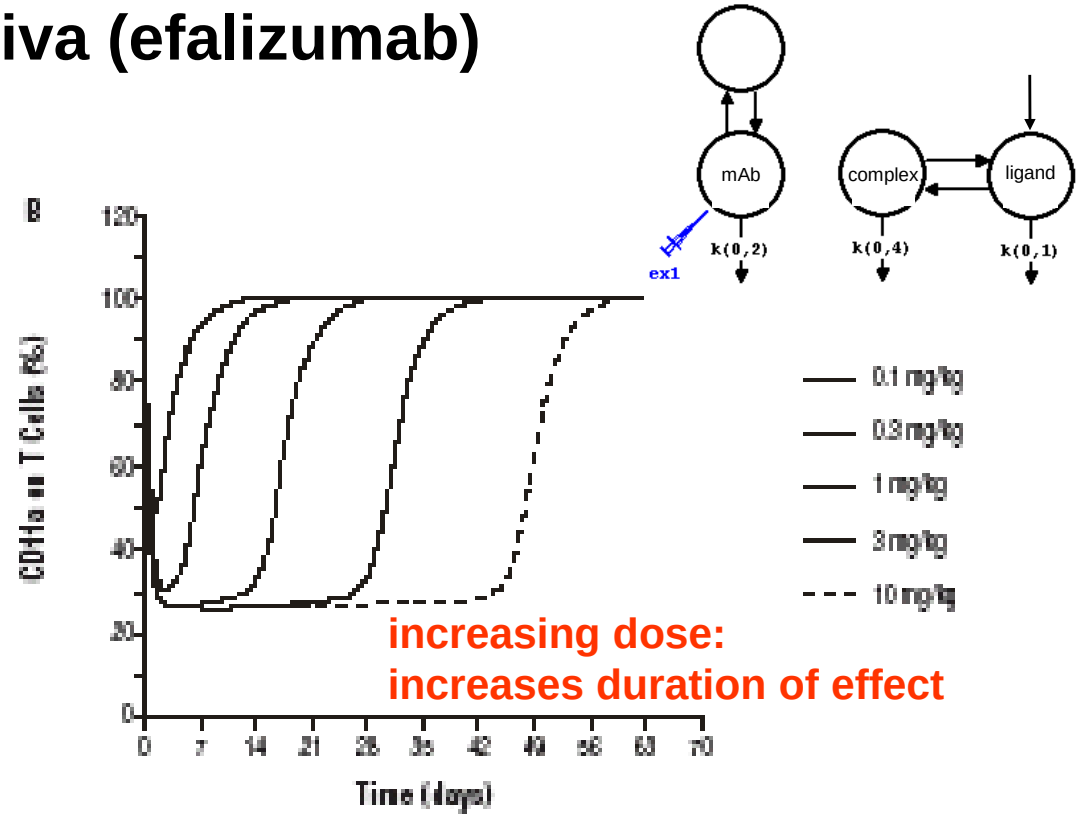
“Typical” PK-PD behavior – cellular target

anti-CD11a mAb – Raptiva (efalizumab)





Joshi et al An overview of the pharmacokinetics and pharmacodynamics of efalizumab: a monoclonal antibody approved for use in psoriasis J Clin Pharmacol 2006; 46: 10-20

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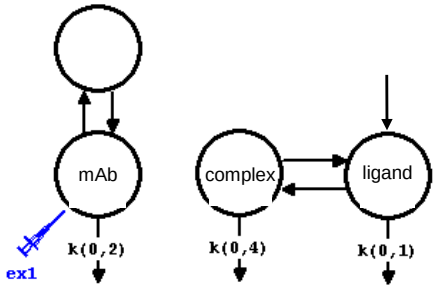
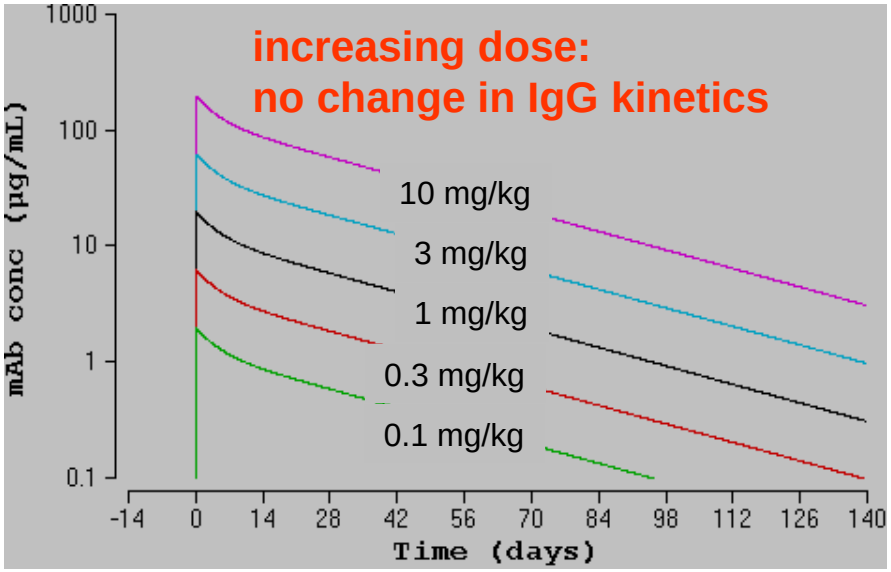
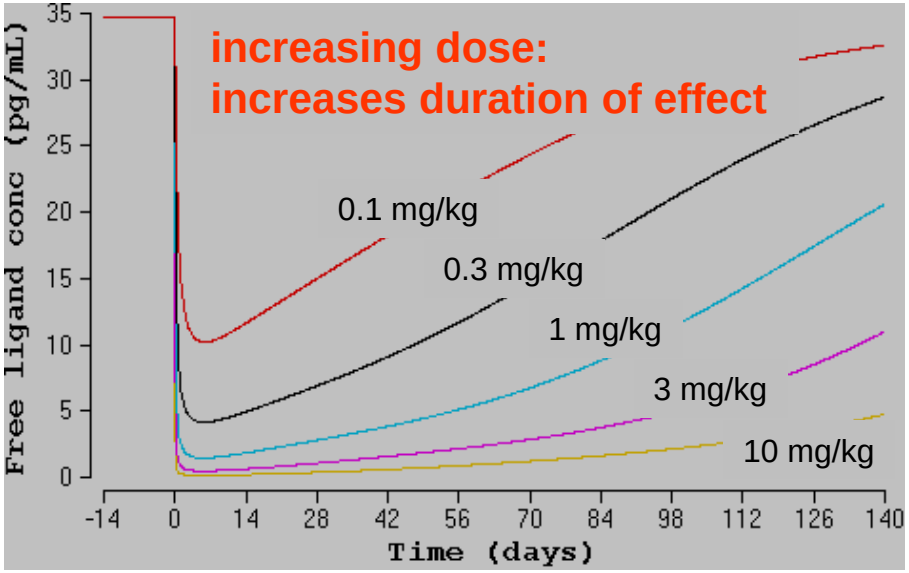
“Typical” PK-PD behavior – soluble target

anti-IL1β mAb – Ilaris (canakinumab)

simulation 0.1, 0.3, 1, 3 and 10 mg/kg







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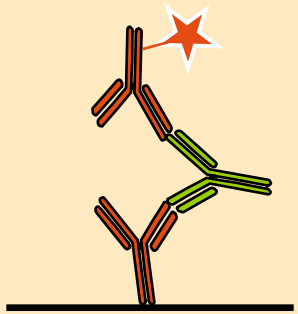
Bioanalytical strategy – Immunogenicity (IG)

Plate based

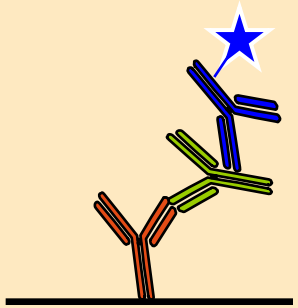


labelled drug

Anti-drug antibody

drug

Bridging format



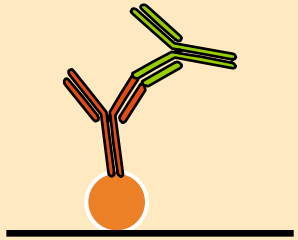
labelled secondary antibody

Anti-drug antibody

drug

Sandwich format

BIAcore

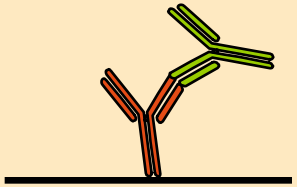


Anti-drug antibody

drug

Protein G

Protein G format



Anti-drug antibody

drug

Direct format

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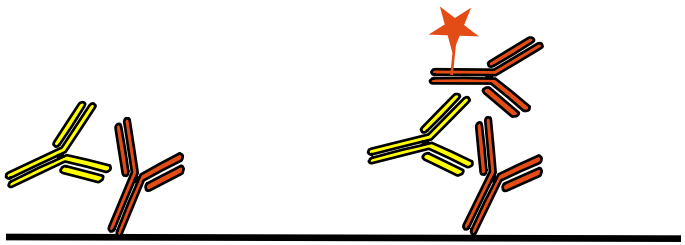
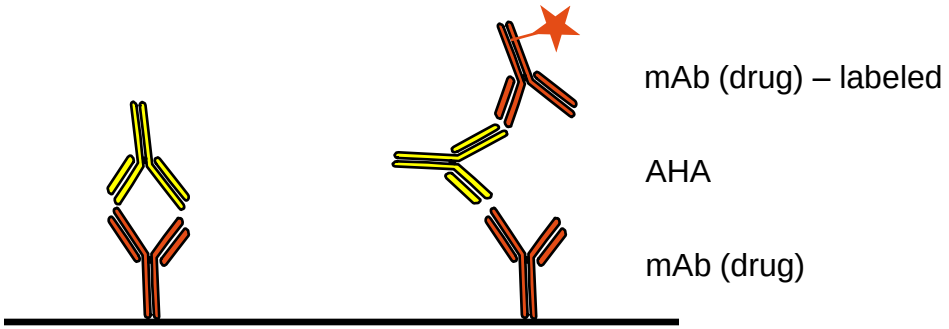
Bioanalytical strategy – immunogenicity (IG)

Initial screening assays for immunogenicity do not differentiate non-neutralizing vs neutralizing immunogenicity

Immunogenicity to Fc region



Neutralising immunogenicity



increase in clearance of mAb
no effect on target binding

increase in clearance of mAb
decrease in capacity for target binding

influence on PK and/or PD assays?

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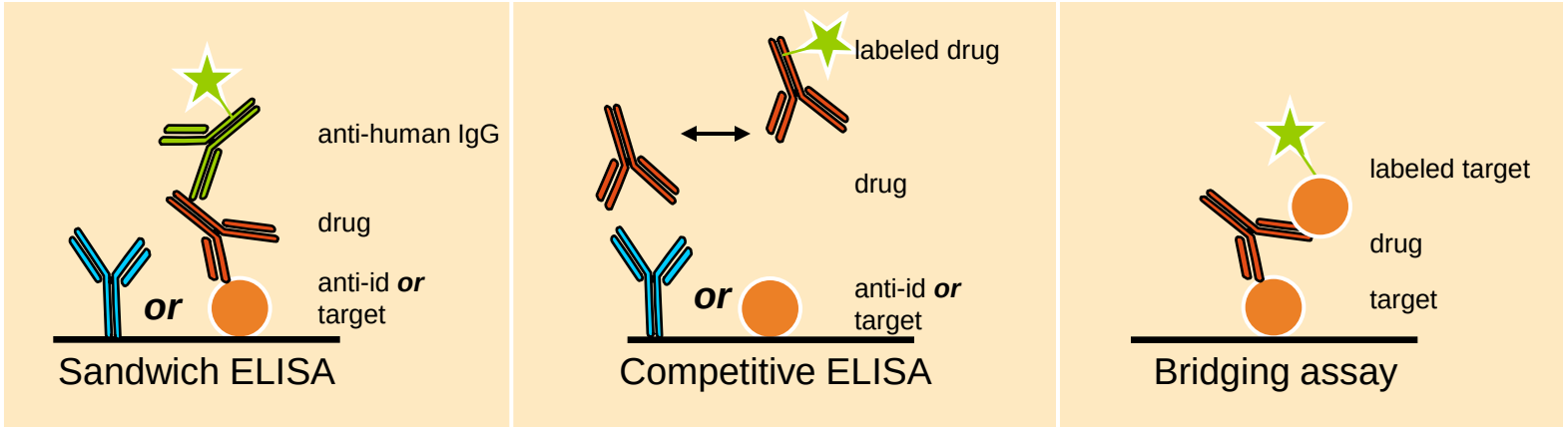
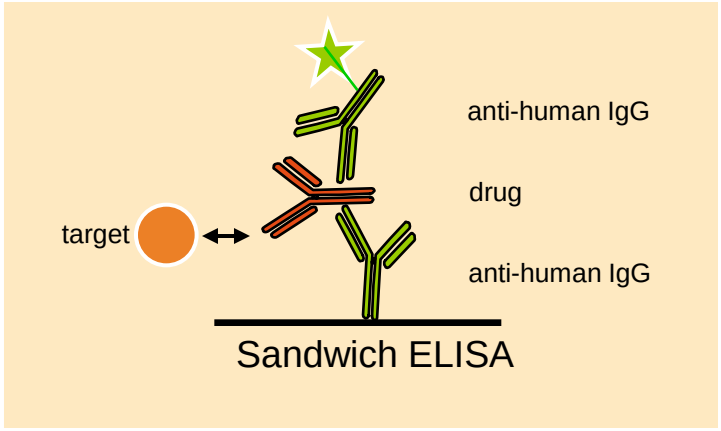
Bioanalytical strategy – pharmacokinetics (PK)

Free-"bioactive" mAb



Total mAb



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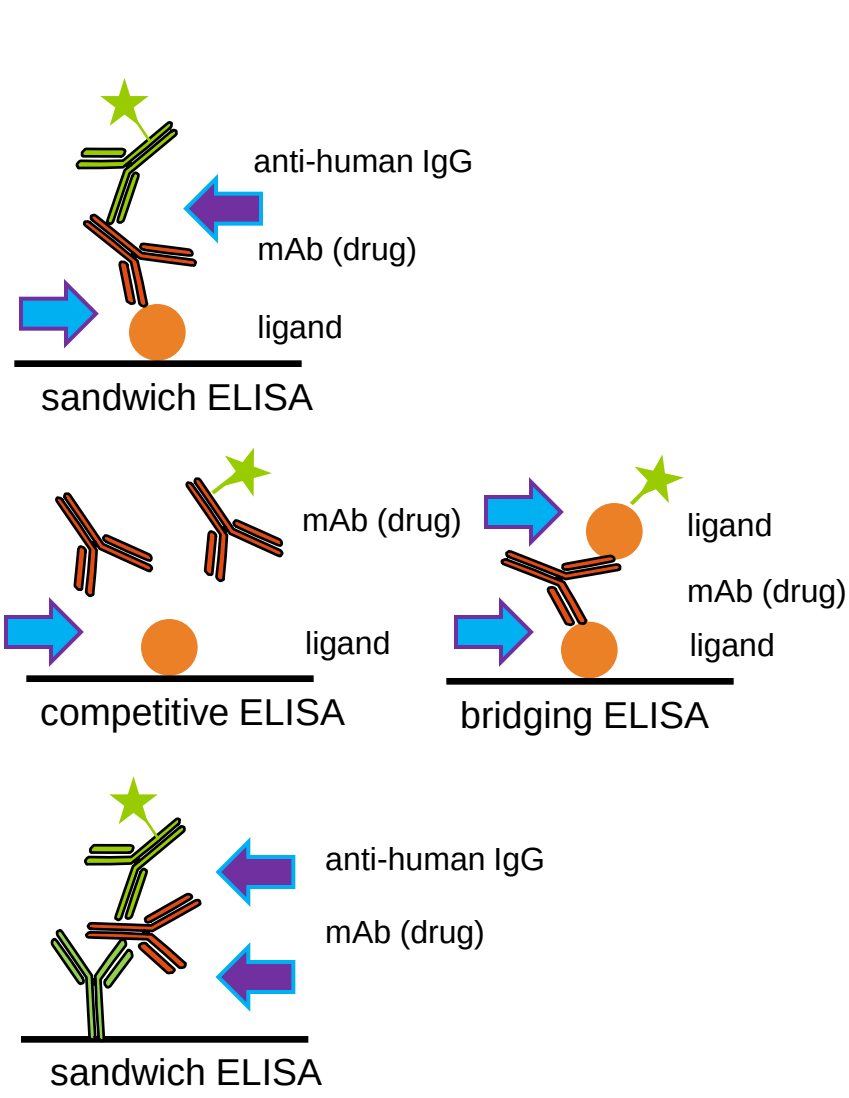
Bioanalytical strategy – PK

Impact of ***neutralizing*** **(nIG)** and ***non-neutralizing*** **(non-nIG)** immunogenicity



nIG and non-nIG may interfere in the PK assay; detected as decrease in exposure (short PK t½)

nIG may intefere in the PK assay; detected as either an increase or decrease in exposure (see example later)

non-nIG may interfere in the total PK assay (pre-clinical); although nIG should not interfere in this assay

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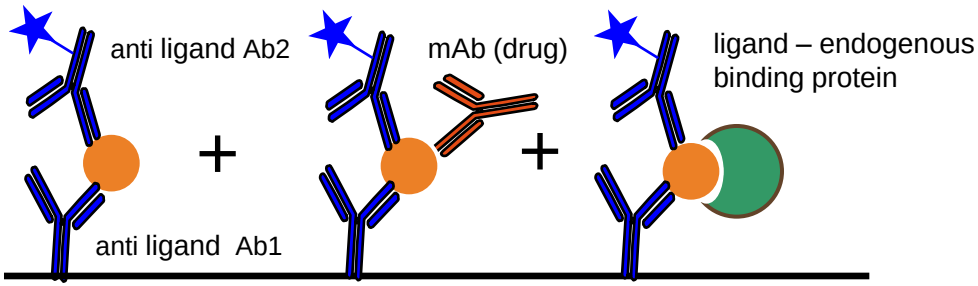
Bioanalytical strategy – PD (soluble ligand)

total ligand (target capture)

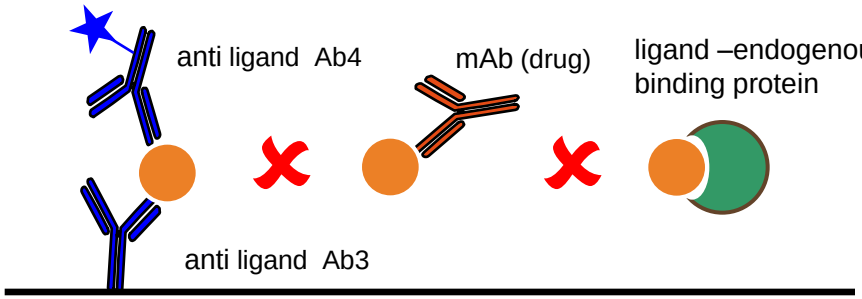


sandwich ELISA

Technically challenging

- capture and detection reagents for ligand are selected which bind in presence of mAb (drug) and endogenous binding protein (if relevant)

free ligand



sandwich ELISA

Technically very challenging

- detection of free ligand (decreasing) in the presence of increasing concentrations of total ligand
- specificity and sensitivity (LLOQ)

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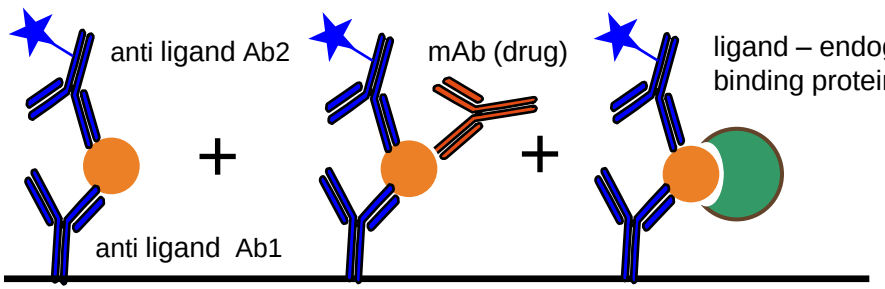
Bioanalytical strategy – PD (soluble ligand)

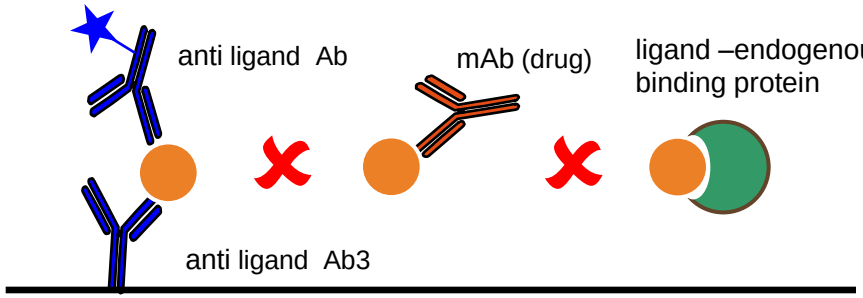
Impact of ***neutralizing* (nIG)** and **non-neutralizing (non-nIG)** immunogenicity

total ligand (target capture)



sandwich ELISA

free ligand



sandwich ELISA

Immunogenicity to mAb (drug) should not directly interfere with PD assay format for either total or free ligand per se if appropriate reagents can be identified (i.e. different binding epitope(s) to drug)

However:

nIG may lead to decreased ligand capture and therefore a decrease in total ligand but also directly interfere with the PD assay if the drug is used for detection (see example)

more rapid clearance of mAb (drug) from nIG and/or non-nIG will also lead to decreased ligand capture and a more rapid return to baseline free ligand

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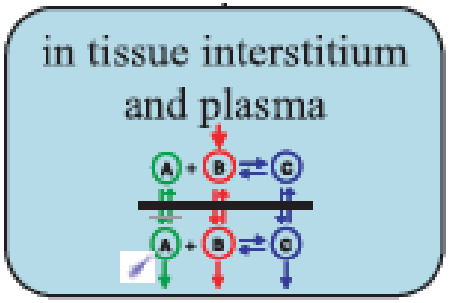
Example 1: background



- fully human IgG1 mAb; high affinity against soluble target
- target ligand can be measured in the systemic circulation at baseline
  - high expression, high turnover?
- mAb acts as a “capture system”

  increase in mAb-ligand complex (detected in serum) is a “biomarker” for suppression of free ligand in interstitial space via a PK/PD model

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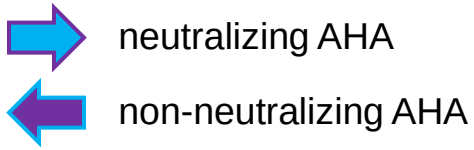
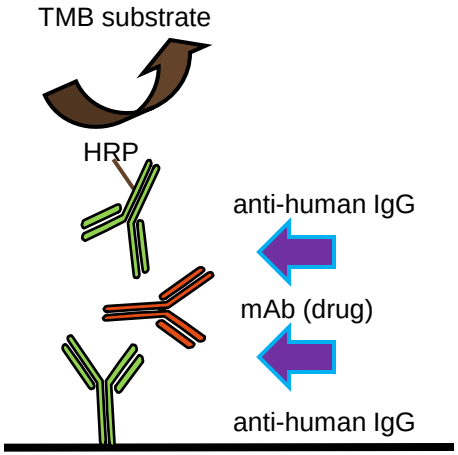
Example 1: pre-clinical bioanalytical strategy

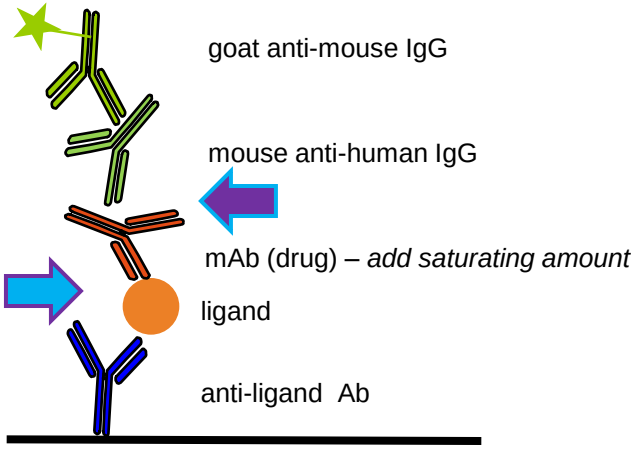


PK assay: total mAb



sandwich ELISA

PD assay: total target (target capture)



sandwich ELISA

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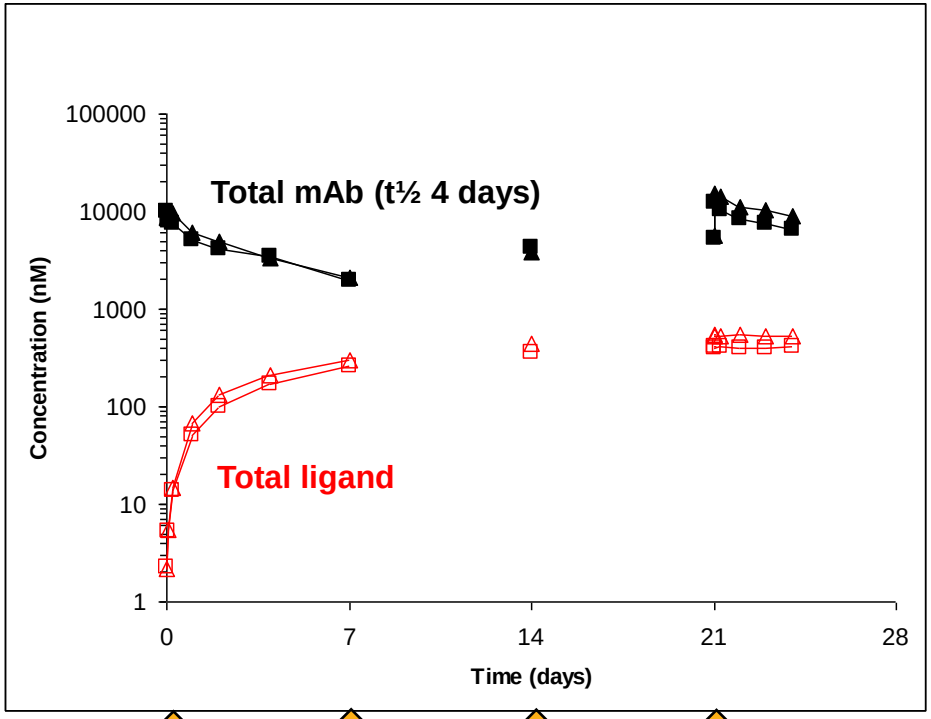
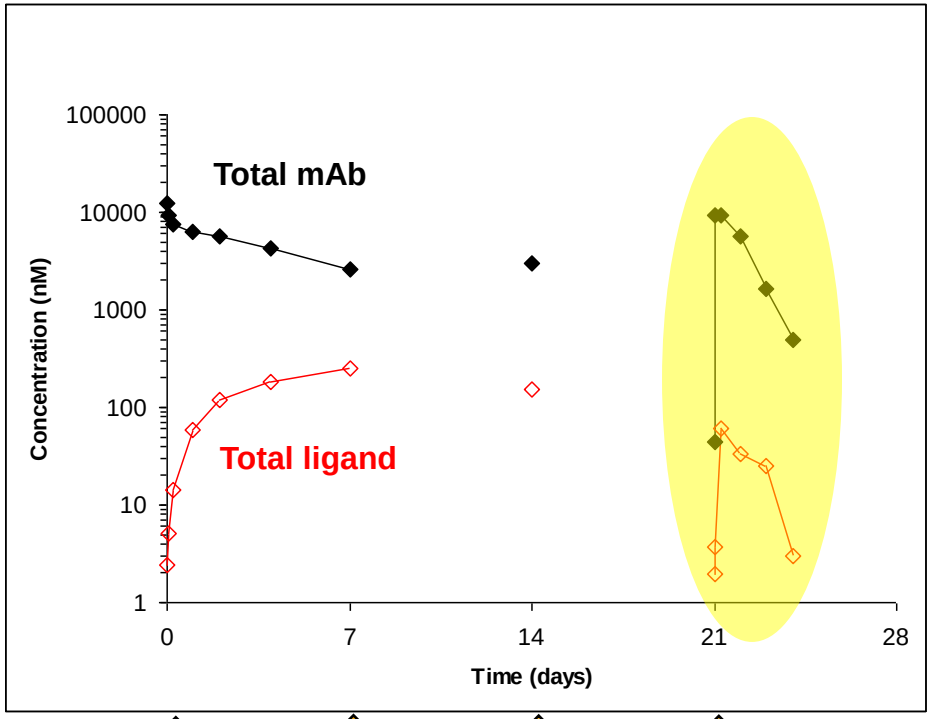
Example 1: PK-PD data (4wk DRF study cynomolgus monkey)

50 mg/kg mAb - days 0, 7, 14, 21



NB One animal excluded from plot ...

50 mg/kg mAb - days 0, 7, 14, 21



evidence of IG from PK and PD data after the third dose; *confirmed on Biacore*

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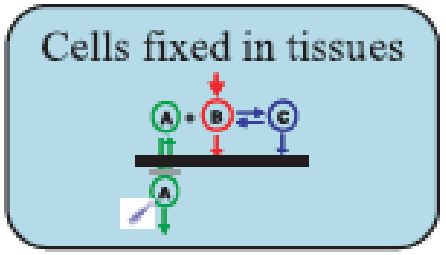
Example 1: Conclusion

- In this example, mAb(drug)-ligand complex appears to be eliminated more rapidly than typical human IgG in cynomolgus monkey
- Immunogenicity apparent in both, PK and PD behavior
- No information about neutralizing capacity of the immune response; although PK-PD suggest that pre-dose on day 14 less target was captured as compared to the other two animals → slight indication for neutralizing anti-drug antibodies at least at the beginning of the response

Example 2: background



- Fully human IgG1 mAb; high affinity against cell surface target
- At low concentrations, mAb (drug) is expected to be cleared by target mediated disposition (TMDD)
- No PD (receptor occupancy) as target cells present only at low level in serum

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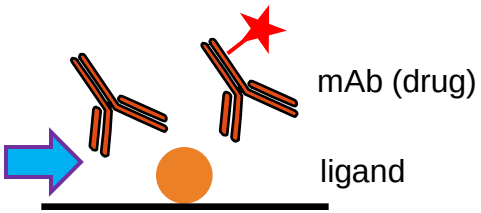
Example 2: pre-clinical bioanalytical strategy

neutralizing AHA

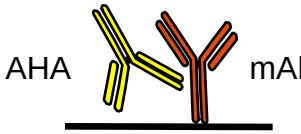
non-neutralizing AHA

PK assay format 1: free “bioactive” mAb



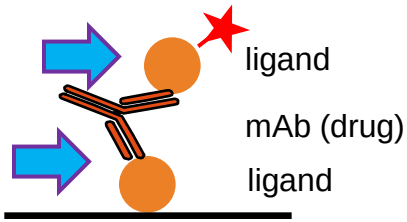
competitive ELISA

Immunogenicity assay:



Biacore

PK assay format 2: free “bioactive” mAb



bridging ELISA

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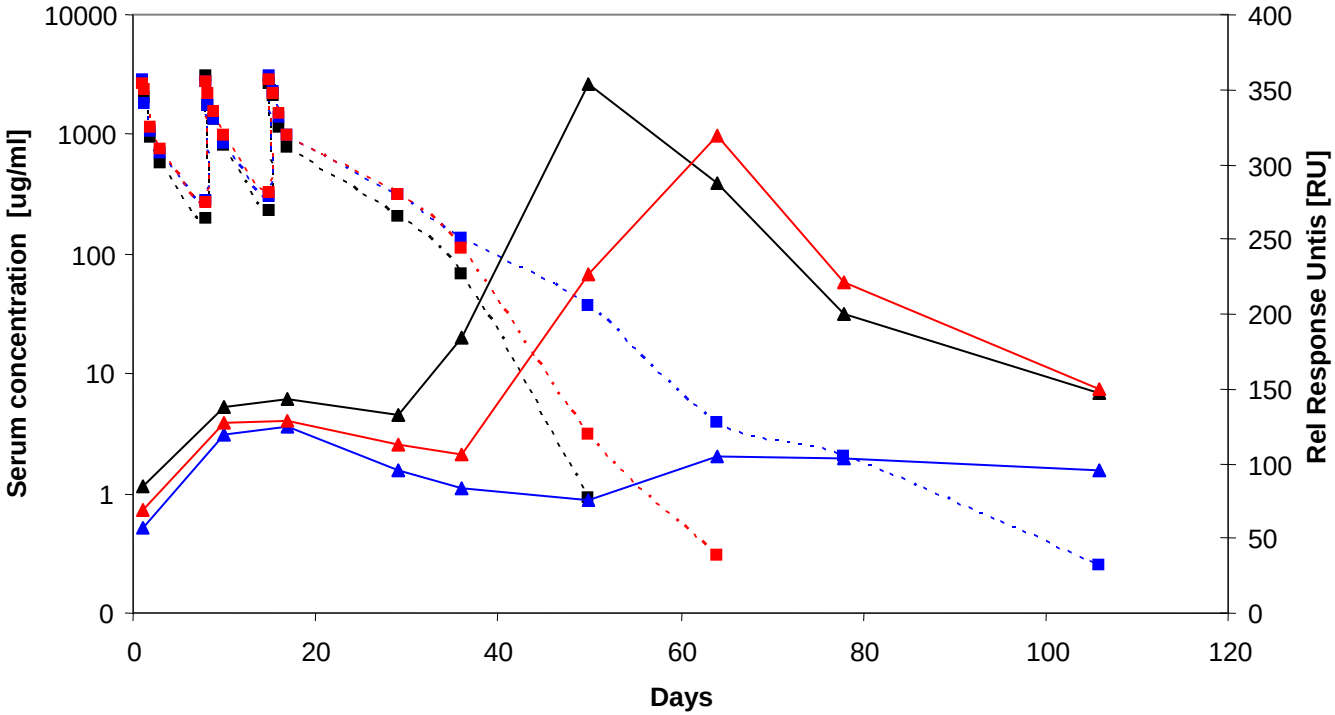
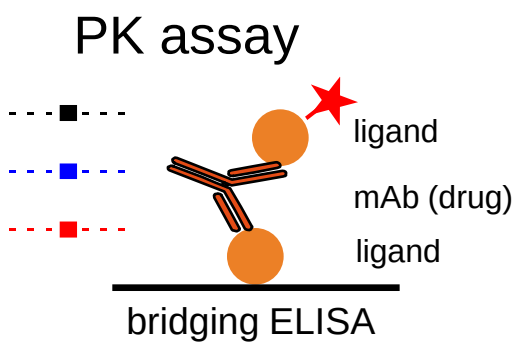
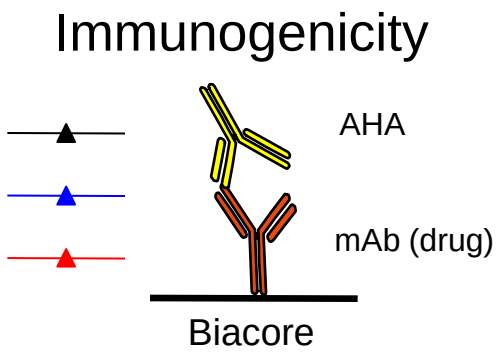
Example 2: PK and IG data (cynomolgus monkey)

Three doses 100 mg/kg i.v. days 0, 7, 14 (n=3 animals)







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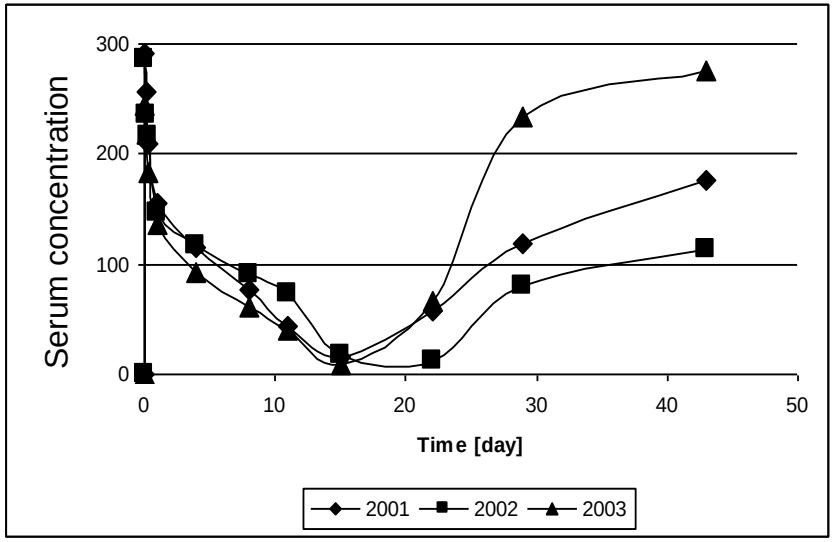
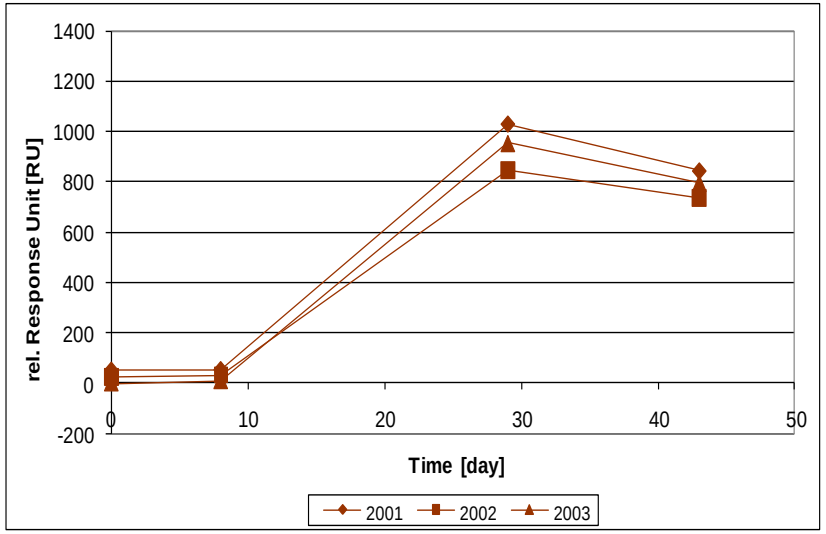
Example 2: PK and IG data (cynomolgus monkey)

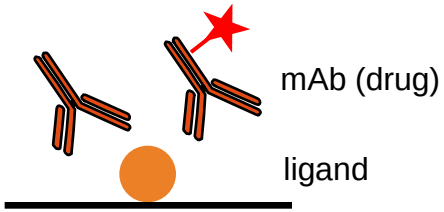
Single dose 10 mg/kg i.v. n=3 animals

PK

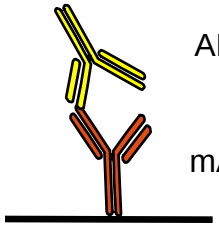


Immunogenicity





competitive ELISA



Biacore

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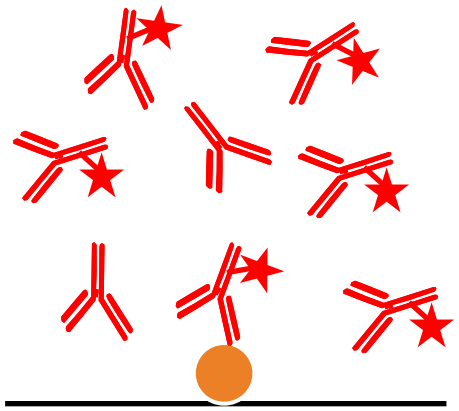
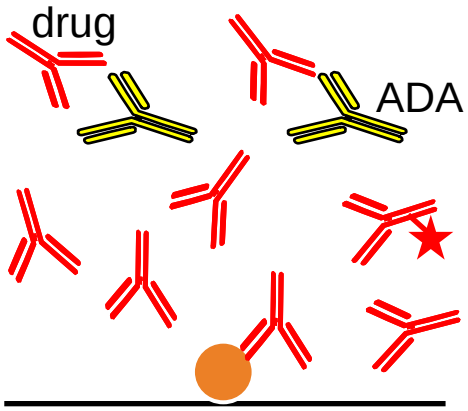
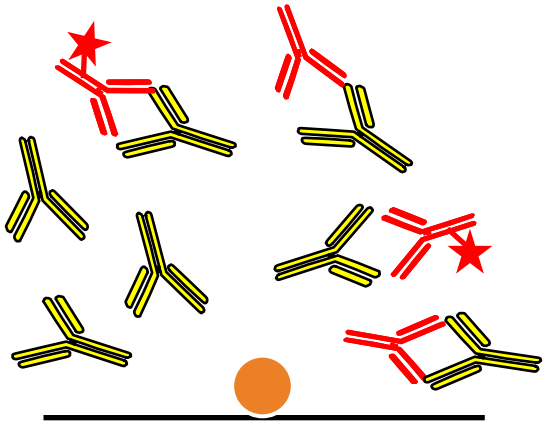
Example 2: influence of IG on competitive ELISA







Low mAb concentration No immunogenicity Preferential binding of labeled mAb to ELISA plate	**High mAb concentration Low AHA response Preferential binding of mAb to ELISA plate**	**Low mAb concentration High AHA response AHA blocks binding of mAb and labelled mAB to ELISA plate**
High signal = low mAb concentration	Low signal = high mAb concentration	Low signal = high mAb concentration
CORRECT	**CORRECT**	**INCORRECT**

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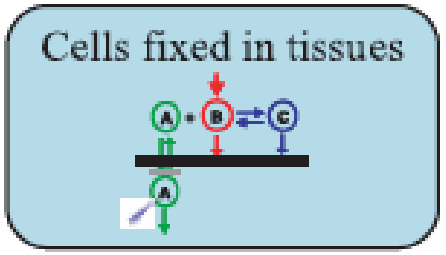
Example 2: Conclusion

- Immunogenicity is apparent in both the competitive and bridging ELISA PK assay formats
  - The bridging ELISA format does not allow to differentiate between TMDD, nIG or increased clearance due to non-nIG
  - The competitive format allows identification of nIG by giving false positive results at low drug concentration in presence of strong immune response

Example 3: background



- Fully human IgG1 mAb; high affinity against cell surface target
- At low concentrations, mAb (drug) is expected to be cleared by target mediated disposition (TMDD)
- No receptor occupancy available as target is expressed in solid tissues
- PD is analyzed by a physiological response readout

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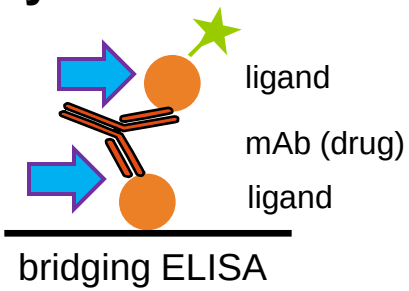
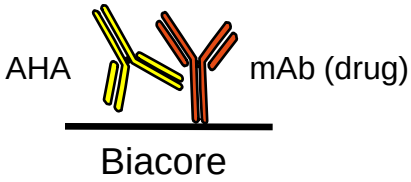
Example 3: pre-clinical bioanalytical strategy

PK assay format 1: free “bioactive” mAb



Blue arrows: interference with neutralizing AHA

Immunogenicity assay:



PD: analysis of physiological response

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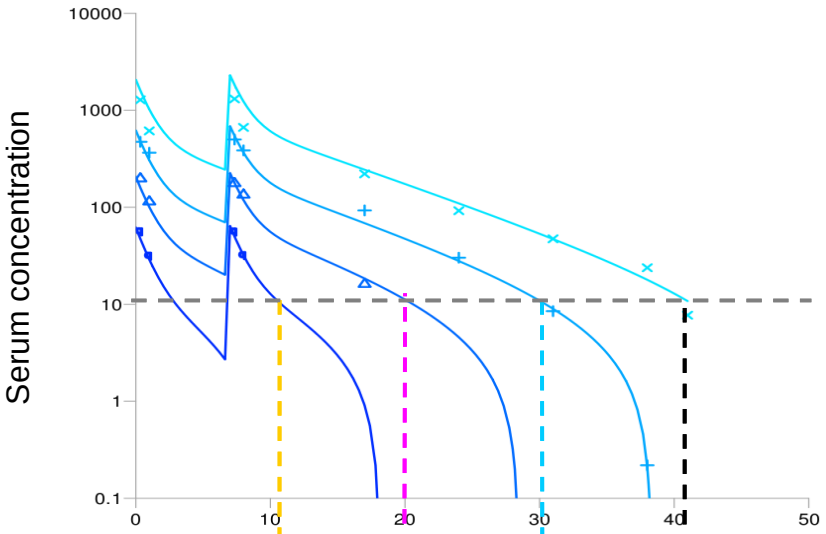
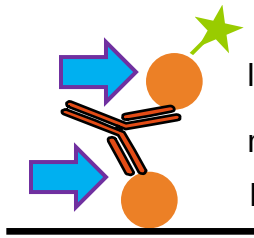
Example 3: PK and PD data (rat)

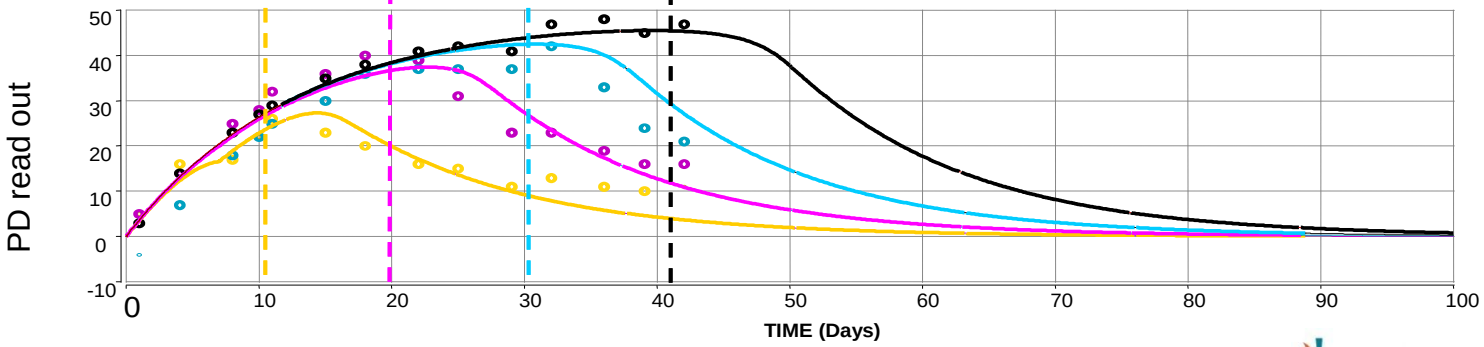
Based on data of a two-dose (day 0 and day 7) DRF study in rat



PK



bridging ELISA



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Example 3: Conclusion

- Immunogenicity cannot explain the typical PK found in all animals showing an infliction point at a serum concentration of 10 µg/mL where clearance increases
  - The increased clearance is most likely due to target-mediated disposition when the concentration in serum drops below that needed to saturate an receptor mediated elimination mechanism
  - The direct connection between the saturation of target mediated disposition and a sustained PD effect likely reflects that (nearly) complete receptor occupancy is required to drive the PD

Outline of the presentation

- PK-PD models for monoclonal antibodies
  - ligand binding models for soluble and cell surface targets
  - typical PK-PD behavior
- Integrated bioanalytical strategy: PK-PD and immunogenicity (IG)
  - ELISA formats to characterize PK and PD (soluble and cell surface targets)
  - impact of immunogenicity
- Examples
  - Example 1: soluble target; effect of immunogenicity on PK and PD
  - Example 2: cell surface target; detection of neutralizing immunogenicity from PK assay format
  - Example 3: cell surface target; effect of PK on PD
- Summary

Draft immunogenicity addendum ICH S6:

Immunogenicity assessments are conducted to assist in the interpretation of the study results and design of subsequent studies. Such analysis in non-clinical animal studies are not relevant in terms of predicting potential immunogenicity in humans. ***Measurement of anti-drug antibodies (ADA) in non-clinical studies is not routinely required if there is evidence of sustained pharmacodynamic activity and no unexpected changes in the pharmaco- / toxicokinetics of the test article during the dosing or recovery phase, and/or no evidence of immune mediated reactions*** (immune complex related, vasculitis, anaphylaxis etc), ADA testing is typically not warranted. However, it is difficult to predict whether such analyses will be needed prior to completion of the in-life phase of the study; therefore it is often useful to obtain appropriate samples during the course of the study, which may be subsequently analysed to aid in interpretation of the study results

Draft immunogenicity addendum ICH S6:

When study results suggest potential for immunogenicity, antibody detection assays should be conducted to evaluate the presence of ADAs. When ADAs are detected it is important to address neutralising activity, but not titre because of the poor correlation with neutralising potential. ***Although assessment of neutralising activity can be addressed using a separate neutralising antibody assay, other approaches can also be valid and may be more robust, such as monitoring of a PD marker, use of an ex-vivo bioactivity assay or the combination of assay formats for PK-PD which address neutralising potential.***

Summary

- An integrated design of bioanalytical assays and interpretation strategy maximizes information about PK, PD and IG interrelationship
- An integrated bioanalytical strategy should take into account:
  - nature of the target; eg cell surface, soluble
  - target expression and target turnover
  - influence of IG on analytical formats for PK and PD assays
- The need for specific neutralizing assays may be obviated by the use of alternative markers of functional activity

THANK YOU for your attention

Acknowledgements:

Sebastian Spindeldreher

Peter Lloyd

Jennifer Sims

Andrew Warren

Annette Zaar

Sherri Dudal

Kerstin Kentsch

Ulf Klein

Phil Lowe

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