

Immunogenicity of biotherapeutics; an introduction

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Inspired by **patients.**
Driven by **science.**

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- The immune response

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The importance of understanding anti-drug antibodies (ADA)

In the past two decades, biological therapies, especially anti-tumour necrosis factor agents (anti-TNFs), have revolutionised the management of chronic inflammatory diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis and Crohn's disease (CD).

Despite an acceptable responder rate of 60%–70% across these diseases, **there remains a substantial proportion of patients for whom treatment with anti-TNF agents leads to primary failure** (failure to demonstrate efficacy), **secondary failure** (loss of effectiveness over time despite an initial good response), or induces **significant side effects**.

The generation of **anti-drug abs (ADA)** is increasingly recognised as a mechanism explaining the failure of anti-TNF drugs in chronic inflammatory diseases

What do we mean by 'immunogenicity' of biopharmaceuticals?

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- The term '**immunogenicity**' refers to the ability of a molecule to induce a specific cellular or humoral immune response, which is triggered by **differences between the structures** of foreign molecules and the bodies' natural proteins.¹
- Administering a small dose of a foreign protein is a recognised way of inducing an immune response – (IMMUNISATION/vaccination)
- All Biopharmaceuticals (BPs) are essentially 'foreign'. ²
- The recognition by the immune system of a BP as 'non-self' or foreign which results in an unwanted immune response is described as '*Immunogenicity*'
- A drug (BP) induced immune response results in measurable drug specific antibody production –**anti drug antibodies (ADA)**. ³
- Antibodies are produced and secreted by activated cells of the immune system called B-cells; the target of the antibodies produced is the specific antigen that activates a given B cell.⁴
- The level of measured **ADA (titre) = magnitude of immune response**

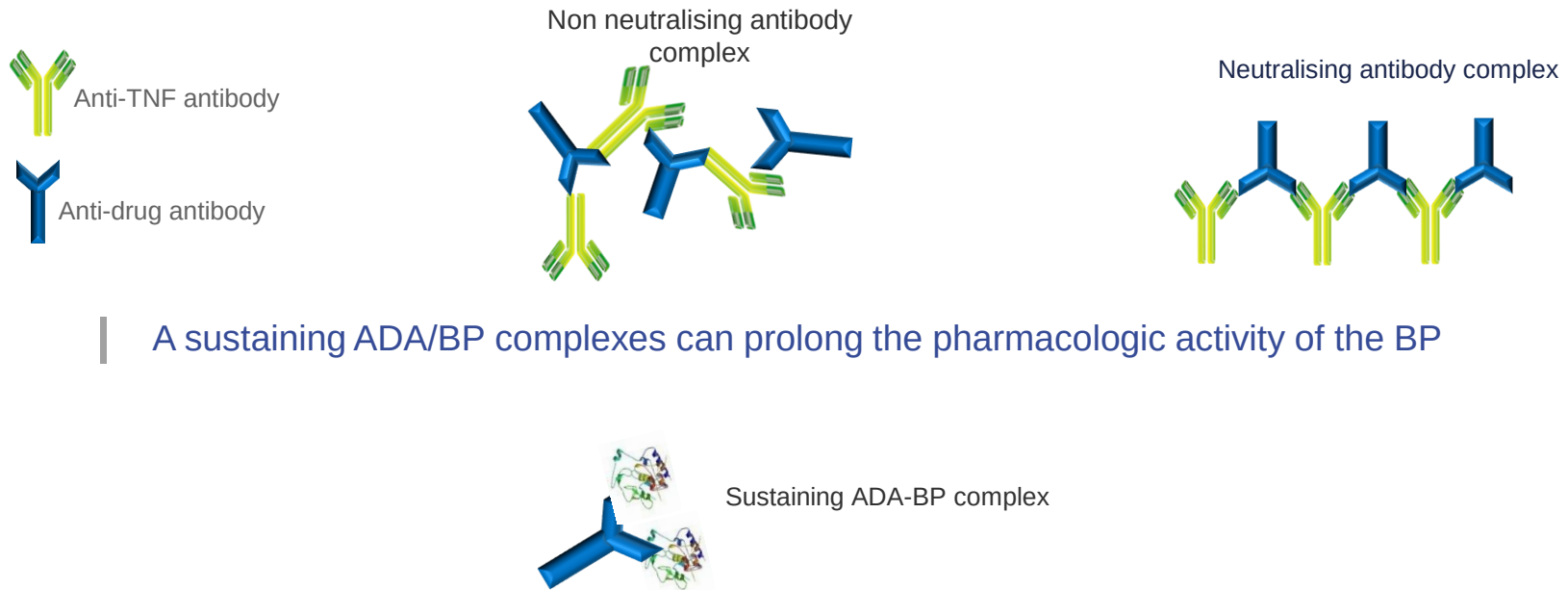
Neutralising , Non Neutralising and sustaining anti drug antibodies; Increased clearance of drug/immune complex

Neutralising ADA block functional activity of the BP

Non neutralising ADA does not affect functional activity of BP

Sustaining antibodies prolongs exposure of the BP

Neutralising or non neutralising ADA form **Ab-BP immune complex** which leads to :
Increased clearance of the immune complex



A sustaining ADA/BP complexes can prolong the pharmacologic activity of the BP

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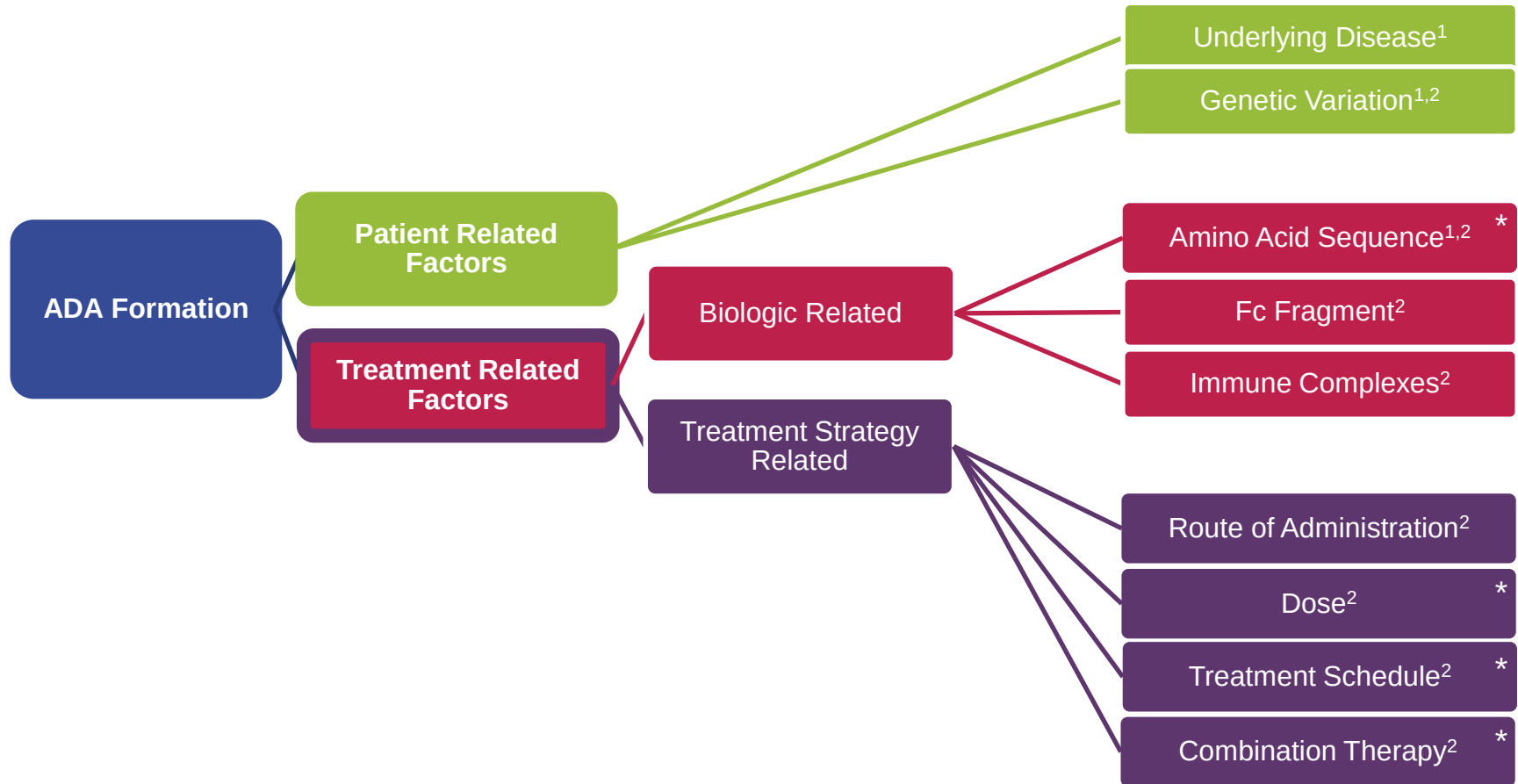
Consequences of unwanted immunogenicity

Measuring anti drug antibodies

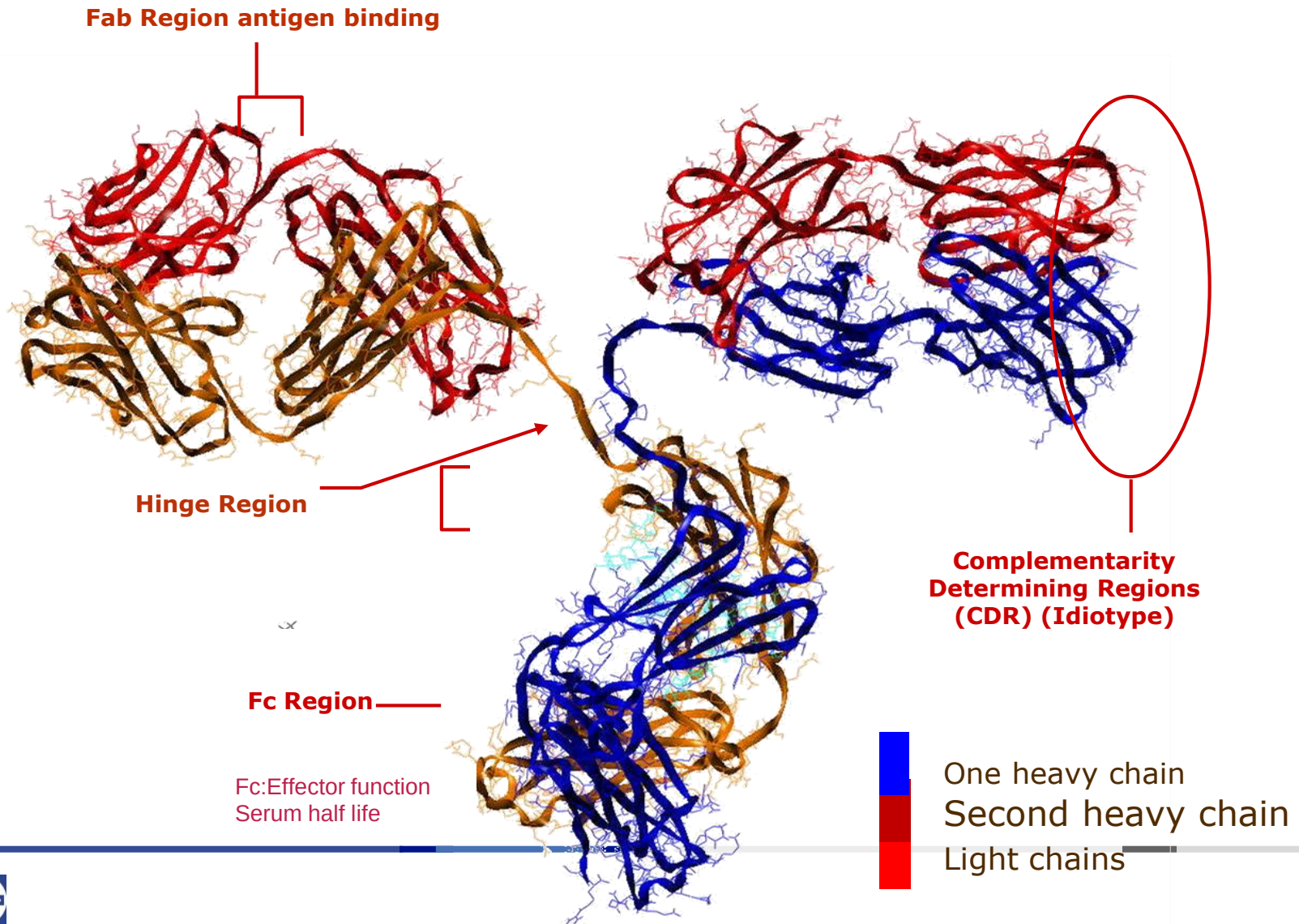
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Factors That May Influence ADA Formation

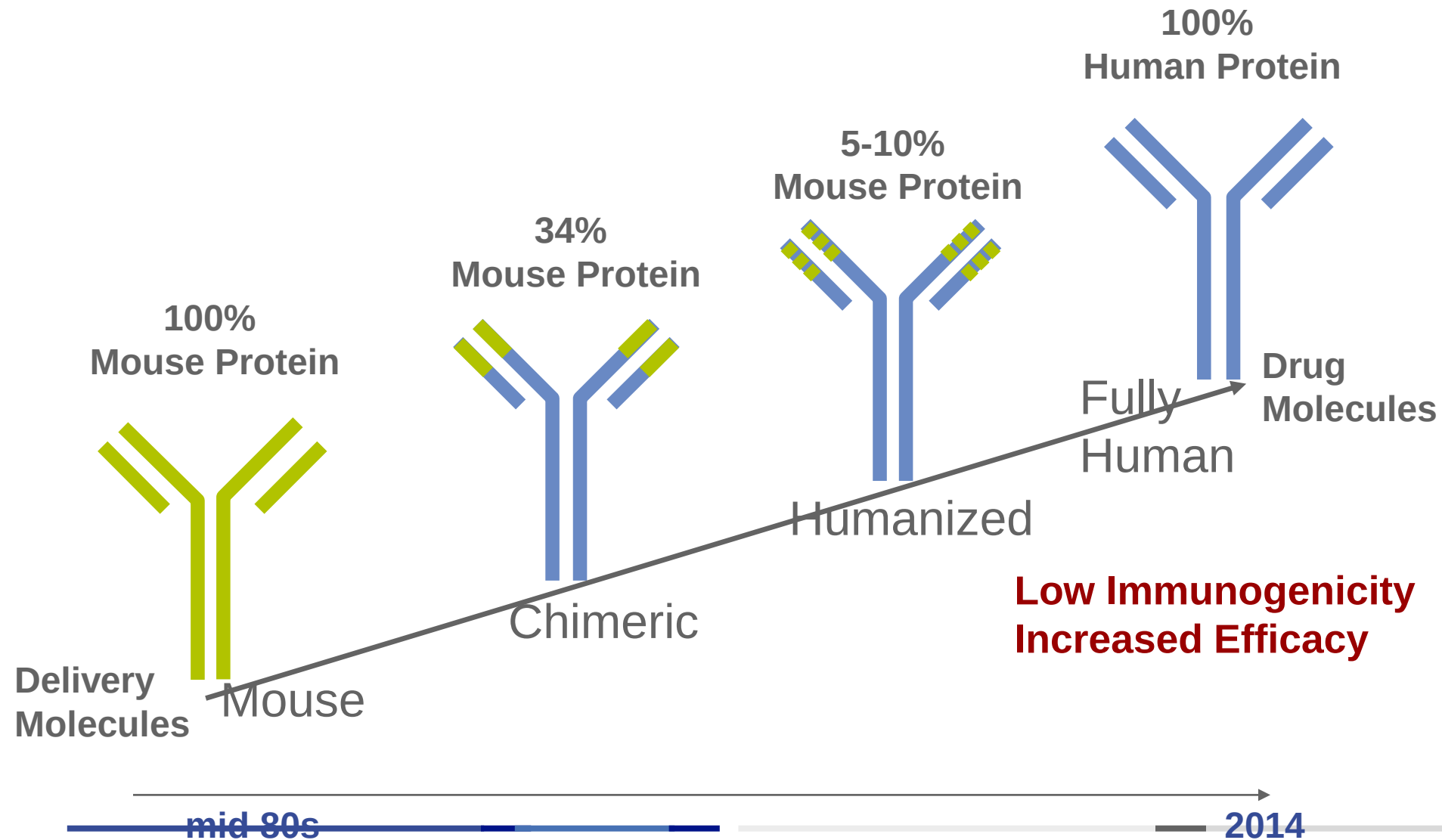


The IgG Molecule: Key Features



Molecular design: Evolution of mAb Technologies has Driven Success

– reduced immunogenicity



Treatment strategy can influence ADA formation

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Study	CDP870-011*	CDP870-014*	CDP870-027(lyo) (52 weeks)			CDP870-050*(liq)		
Dose group	400mg E4W Monotherapy	400mg E4W + MTX	200mg E2W+ MTX	400mg E2W+M TX		200mg E2W+MTX	400mg E2W+MTX	
Excluding safety F/U	25/111 (22.5%)	5/124 (4.0%)	42/392 (10.7%)	8/389 (2.1%)		21/248 (8.5%)	4/246 (1.6%)	
Including safety F/U	N/A	6/124 (4.8%)	47/392 (12%)	10/389 (2.6%)		24/248 (9.7%)	5/246 (2.0%)	
N/A = data not available * Studies CDP870-011, -014 and -050 were 24 week duration.								

- Co-medication – immunosuppressant (MTX) can reduce ADA formation ⁴
- Higher dose (high dose tolerance) can reduce ADA formation ^{1,2}
- Dosing frequency – large dosing interval leads to immune boosting and increased ADA³
- Formulations – liq vs lyo

Phase 3 RA placebo controlled studies



¹van-Schouwenburg P et al. Nat Rev Rheumatol. 2013;9(3):164-172

²Maini R et al. Arthritis Rheum. 2006;54(9):2817-2829

³Takeuchi T et al. ACR 2013; Poster 2322

⁴Garcés S et al. Ann Rheum Dis. 2013;72(12):1947-1955

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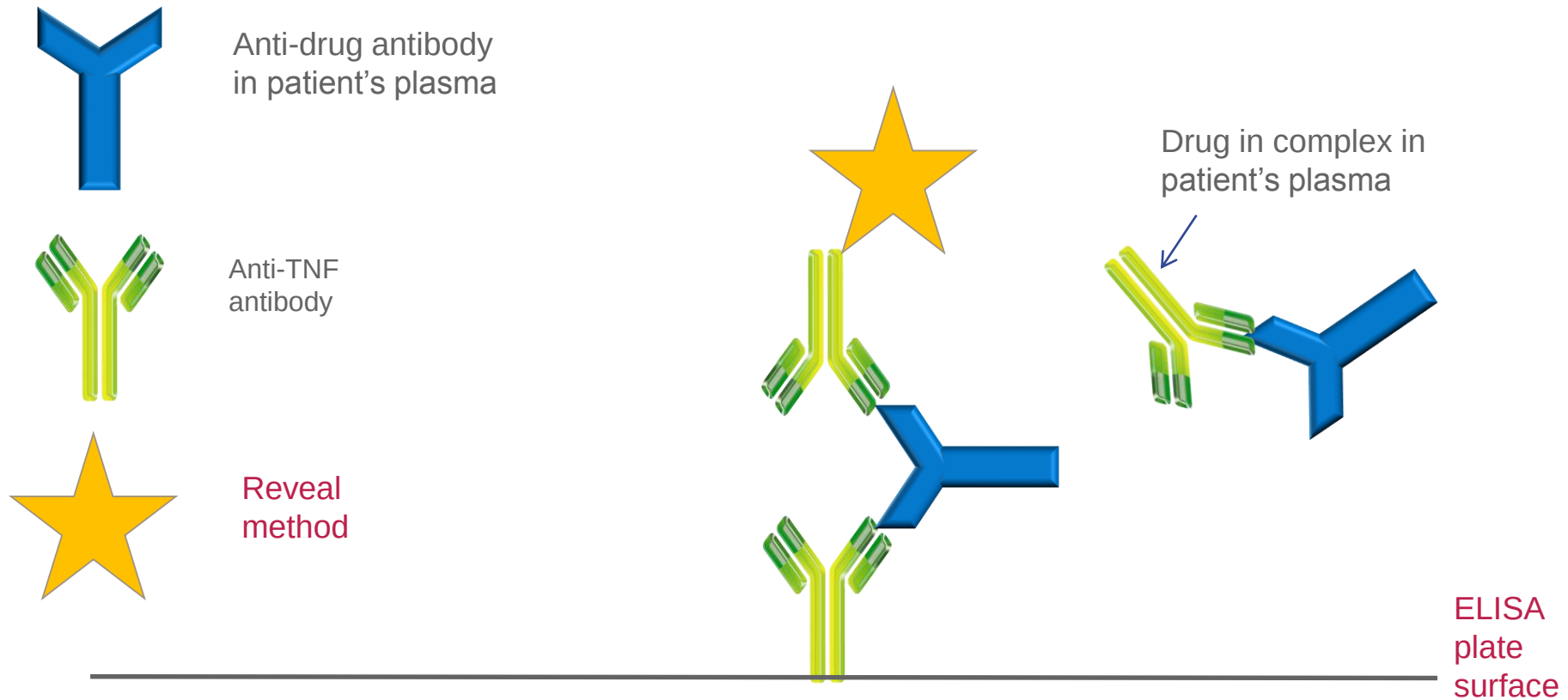
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Conventional Anti-Drug Antibody Response Bridging ELISA: Sensitive to the presence of free drug in the patient plasma



- This assay format measure free anti drug antibodies only
- ADA assays are semi quantitative because they are designed with a rabbit calibrator
- MAGNITUDE of immune response = titre or AU/mL
- No universal standards; ADA data cannot be compared between different assays or products

Drug Tolerance: false negative ADA in the presence of drug

What is drug tolerance?

- Free drug present in the blood will bind anti drug antibodies if present
- Drug/anti drug antibody complexes cannot be measured in the ADA assay
 - a false negative ADA status will be reported

Drug tolerance describes the highest drug concentration at which a ADA signal above the cut point can be measured.

- Drug tolerance is best assessed with clinical samples where drug levels and ADA levels are known

Factors that influence drug tolerance :

Assay design – homogeneous ECL > heterogeneous ELISA

Drug design - drug interference by monovalent Fab' (CZP) is much lower than for bivalent IgG (IFX, Adali. Golim)

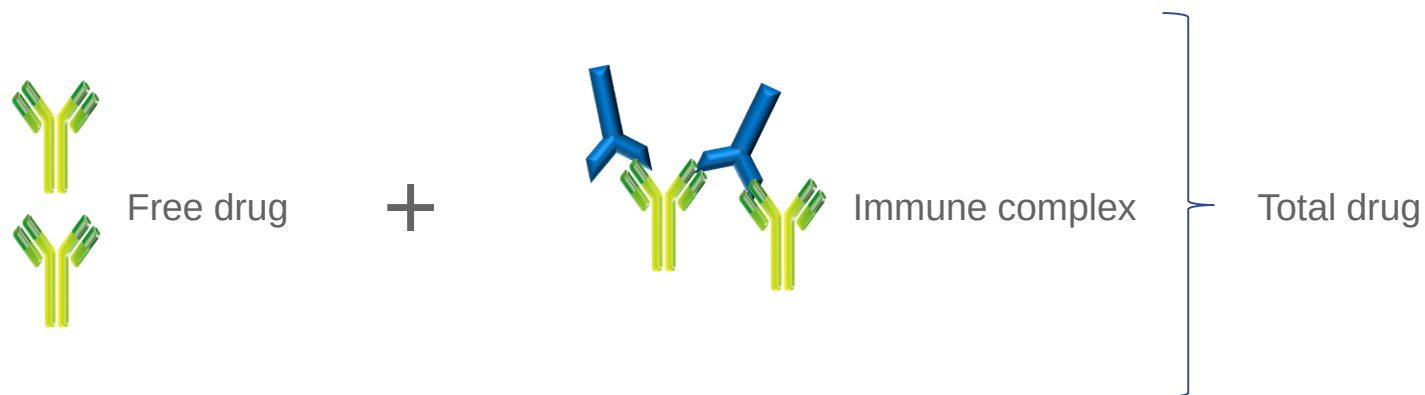
What does this mean?

A negative ADA result in the presence of drug could be misleading

N.B. Collect samples for ADA measurement when drug levels are low

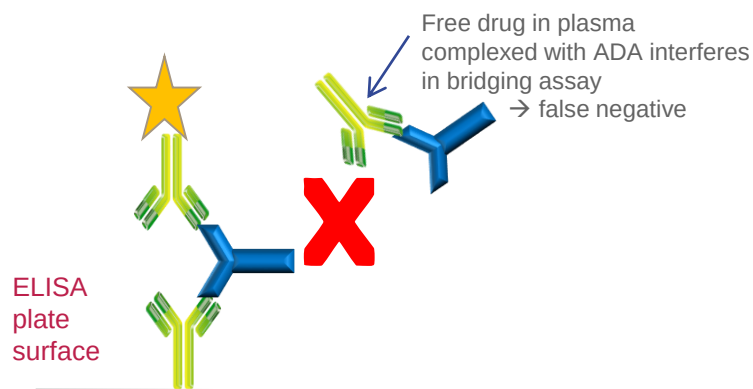
Assays for PK evaluation

- The PK assay can be designed to measure uncomplexed, complexed or total forms depending on assay format
- Typically a measure of the uncomplexed 'free' (bioactive) drug is required for PK/PD, TK/PD analyses
- It is important to understand what form of the drug is being detected in order to reliably interpret PK data for pharmacological effect, Tox NOAEL calculations or FiH prediction
- The inability to detect anti drug antibodies does not mean that ADAs are not impacting PK measurement.

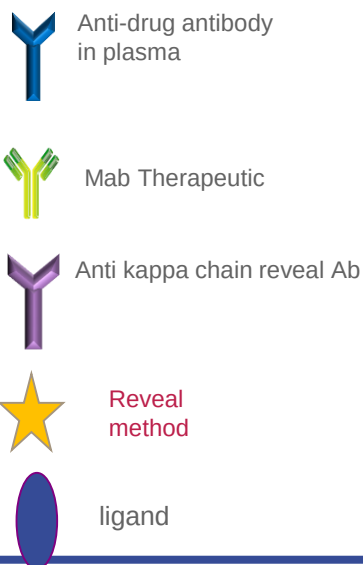
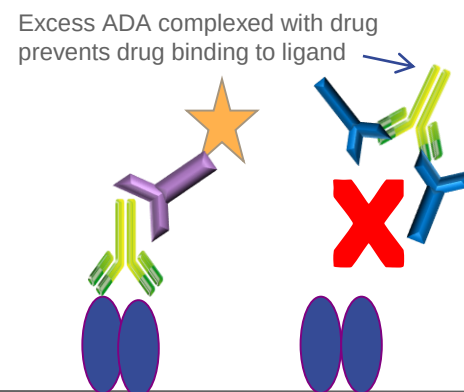


Data interpretation: interference in assays and increased clearance of immune complexes leads to reduced exposure

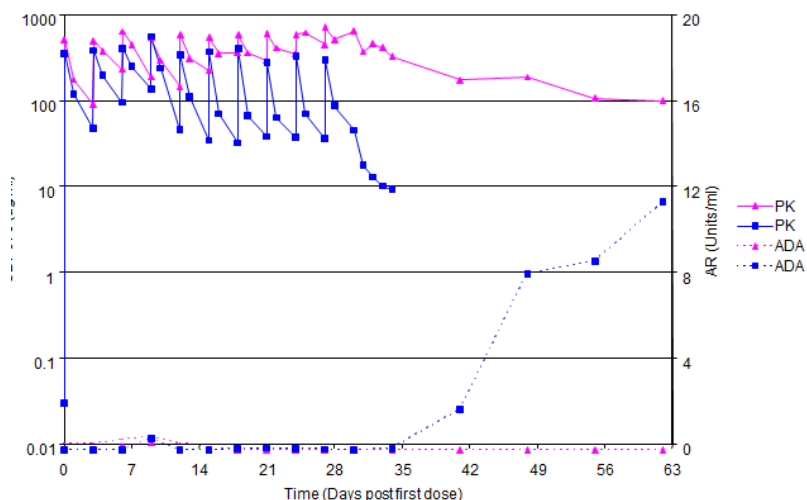
ADA bridging ELISA



PK ligand binding ELISA

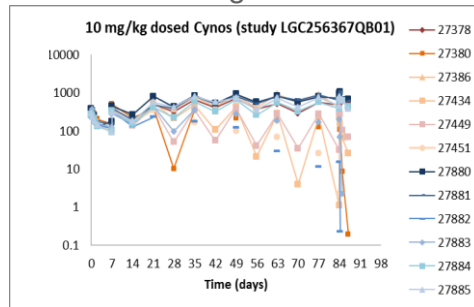


Therapeutic Mab $\mu\text{g/mL}$

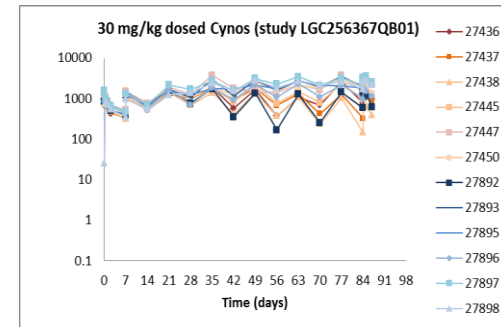


Data Interpretation: impact of ADAs on PK and PD

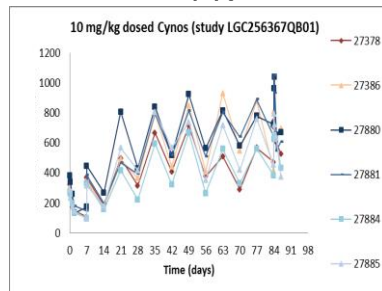
PK 10mg/mL dose



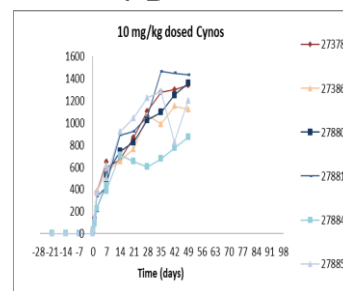
PK 30mg/mL



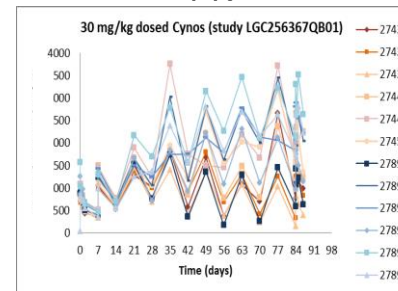
PK



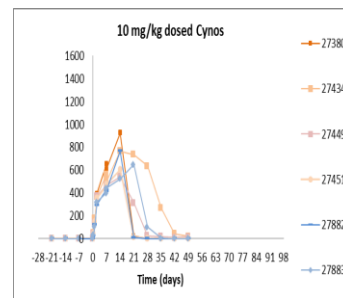
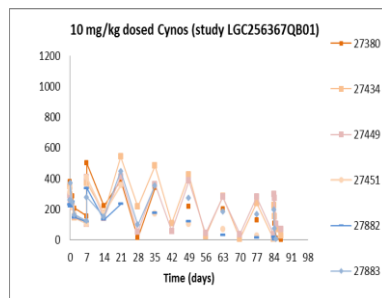
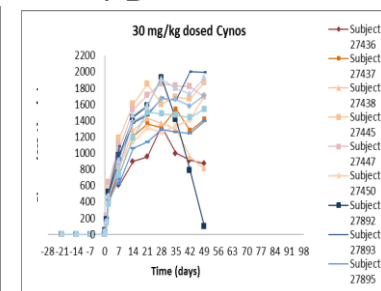
PD



PK



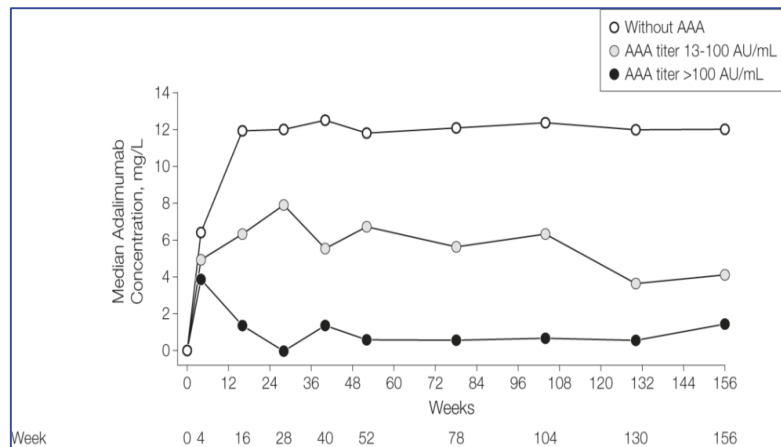
PD



- 13 week repeat dose tox study
- ADA not measured
- Integrating PK and PD data infers an immune response
- Data suggests a minimal effective trough level of drug for positive PD response in both dose groups

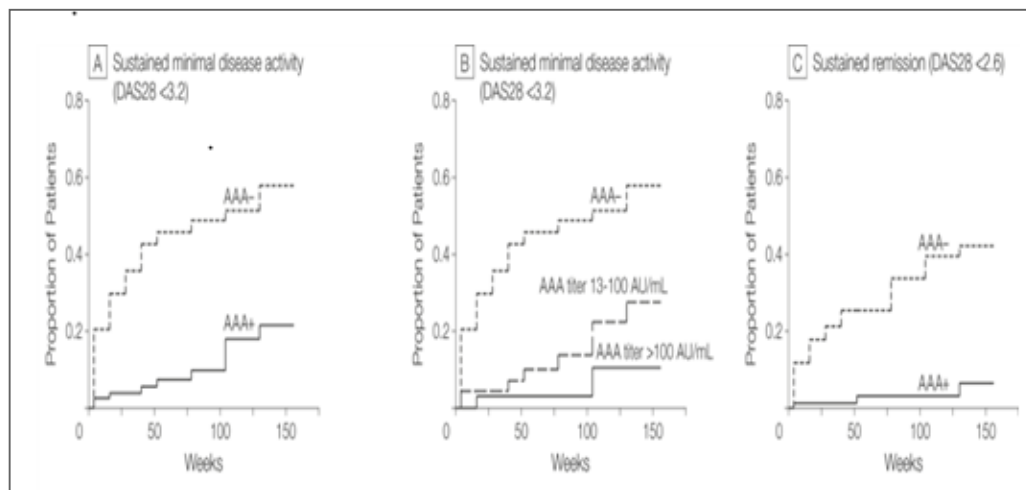
Impact of ADA on PK&Efficacy; From: Development of Antidrug Antibodies Against Adalimumab and Association With Disease Activity and Treatment Failure During Long-term Follow-up

ADA impact on drug exposure



- Median adalimumab concentrations($\mu\text{g/mL}$) per time point
- Patients who were AAA-negative had significantly higher adalimumab concentrations compared with patients with low AAA ($P < .001$) and high antibody titers ($P < .001$).

ADA impact on sustained minimal disease (DAS28<3.2)



- Ninety-five of 196 patients without AAA reached sustained minimal disease activity vs 8 of 45 patients with low AAA titers (13-100 AU/mL), and 2 of 31 patients with high AAA titers (>100 AU/mL).

In Summary - Consequences of immunogenicity

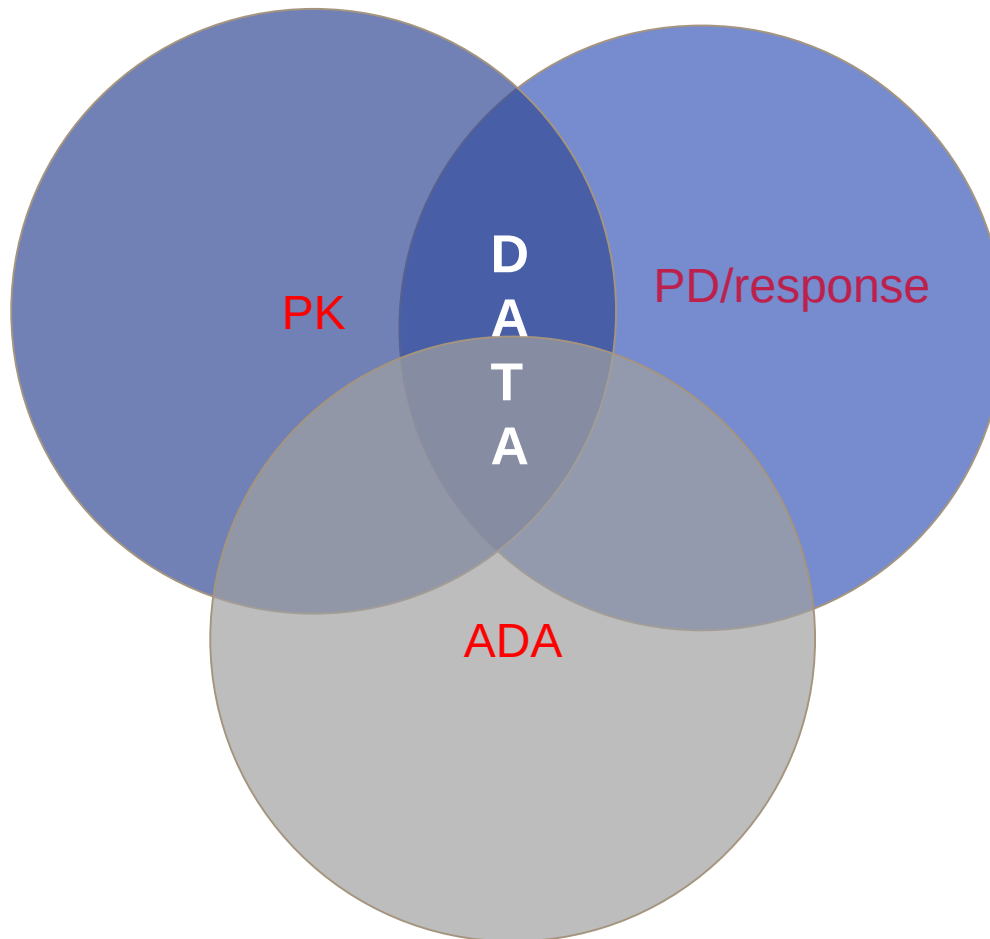


Risk:	Observed:	Confirmed:
Change in exposure	PK profile - sustaining ADA response - clearing ADA response (mAb)	----- Immunogenicity testing strategy ----- ::
Loss of target engagement	target capture (soluble ligand), TMDD (cell surface target) Down stream biomarkers	
Loss of efficacy	clinical endpoint(s)	
Increase in immune related AEs	AE reporting by class anaphylaxis (worst case)	
Cross-reaction to endogenous proteins	recombinant endogenous proteins and protein mimetics loss of non-redundant function(s)	

- **Additional consideration:** ADA response may re-instate Fc function to an “Fc-silenced” molecule
- **N.B.** The incidence of immune response often too low in Ph III studies to reflect true immunogenicity of TP.
- Post-marketing surveillance necessary

Interplay of data: Pharmacokinetics/Pharmacodynamics/Immunogenicity

Immunogenicity data does not stand alone



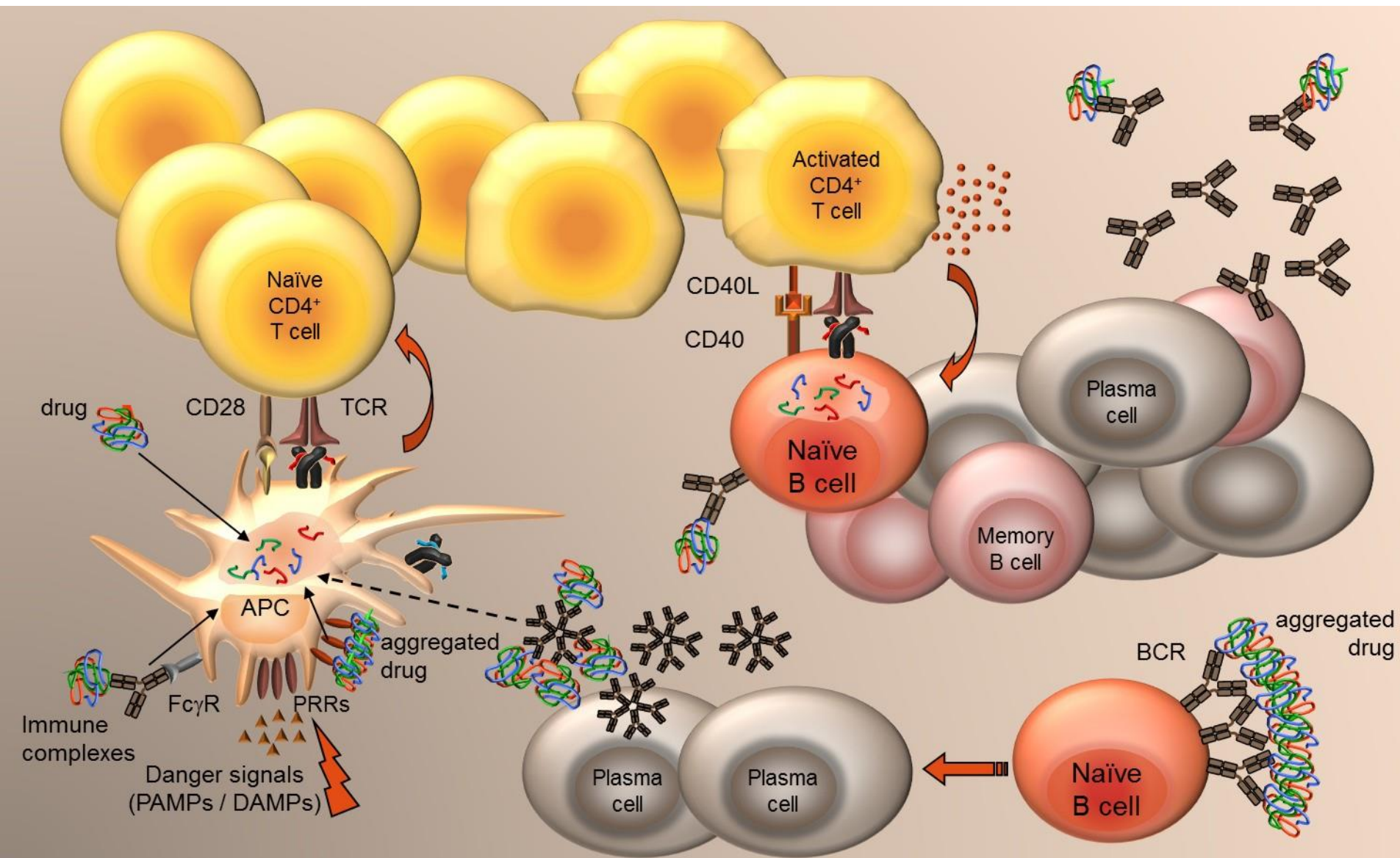
Always consider the data as a whole

In Summary

- All Biotherapeutics are potentially immunogenic in man
- Multiple factors are known to influence the formation of ADAs
- A discrepancy can exist between the amount of ADAs produced by a patient and the level detected
- ADA data should be interpreted and reported in the context of assay design/strategy
- Valid comparisons cannot be made between trials as assays are not standardised even in a drug class such as anti TNFs
- The presence of ADA impact PK assays and PK data interpretation
- Ideally the consequences of a drug's immunogenicity should be assessed in conjunction with impact on drug exposure, PD, efficacy and safety
- Immunogenicity should be reported in a clinically relevant context

Back ups

The Immune response - Pathways Driving Immunogenicity of MAbs/Proteins



The Immune Response to Therapeutic mAbs/Proteins

- Immune responses to proteins characterized by generation of Abs: T cell-dependent or independent.
- T-independent Ab responses: B cells recognize repeated pattern (motif) in therapeutic protein & transiently produce low-affinity IgM Abs.
 - without activated Th cells, naïve B cells do not class switch or fully mature and activated antigen-specific B cells are rendered anergic or undergo apoptosis.
- T-dependent (Td) Ab responses: Abs generated in conjunction with T cell help → involves complex interplay between APCs, T cells, cytokines & B cells
 - importance of genetic factors such as HLA haplotype expression & T cell/B cell repertoire in IRs to proteins.
 - Measurement of ADA IgG responses indicates T cell involvement in IR to a protein