Integration of PK-PD-ADA data for assessment of immunogenicity impact

Robert Nelson

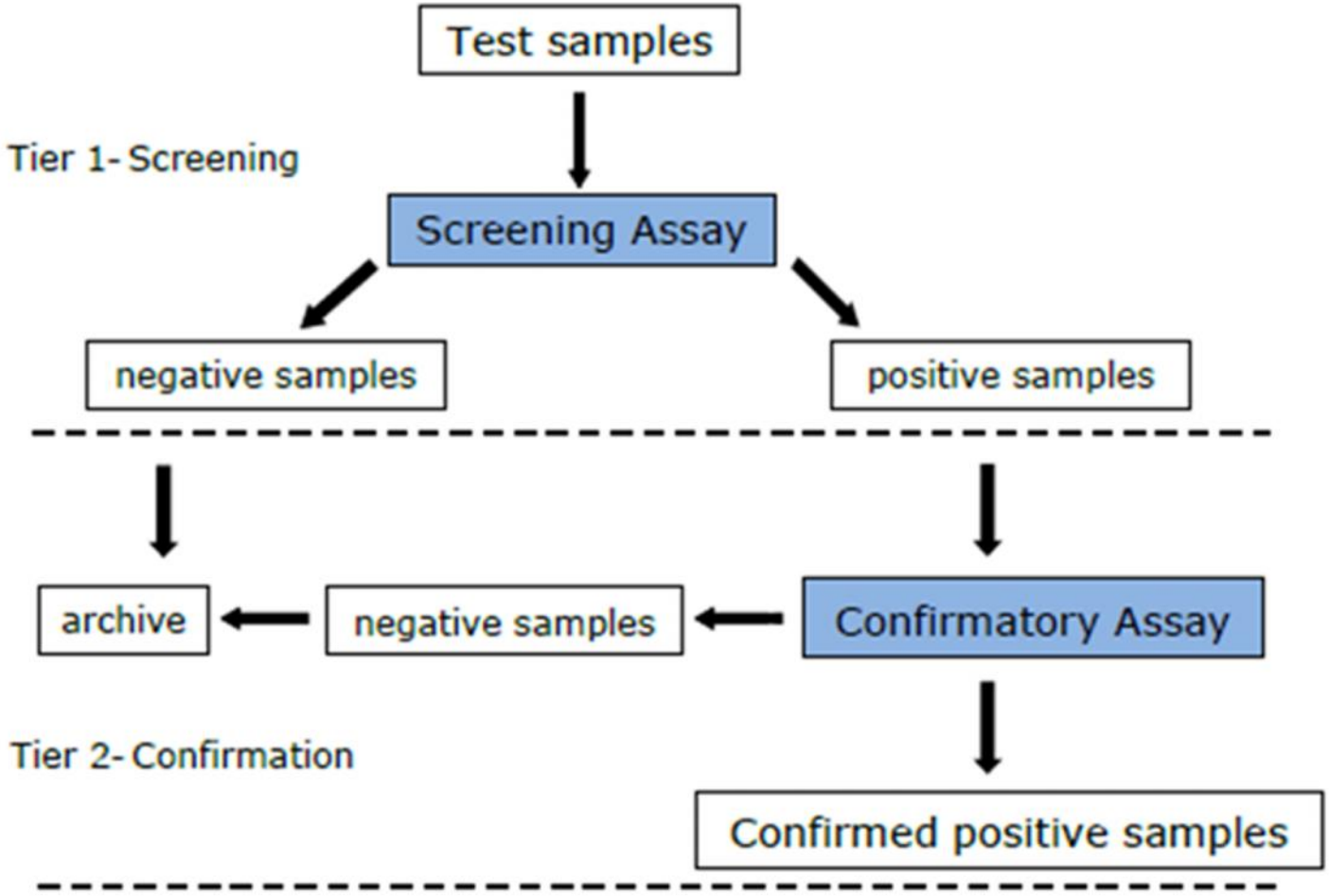
Head of Bioanalytical Sciences, Novimmune SA

rnelson@novimmune.com

Presentation outline

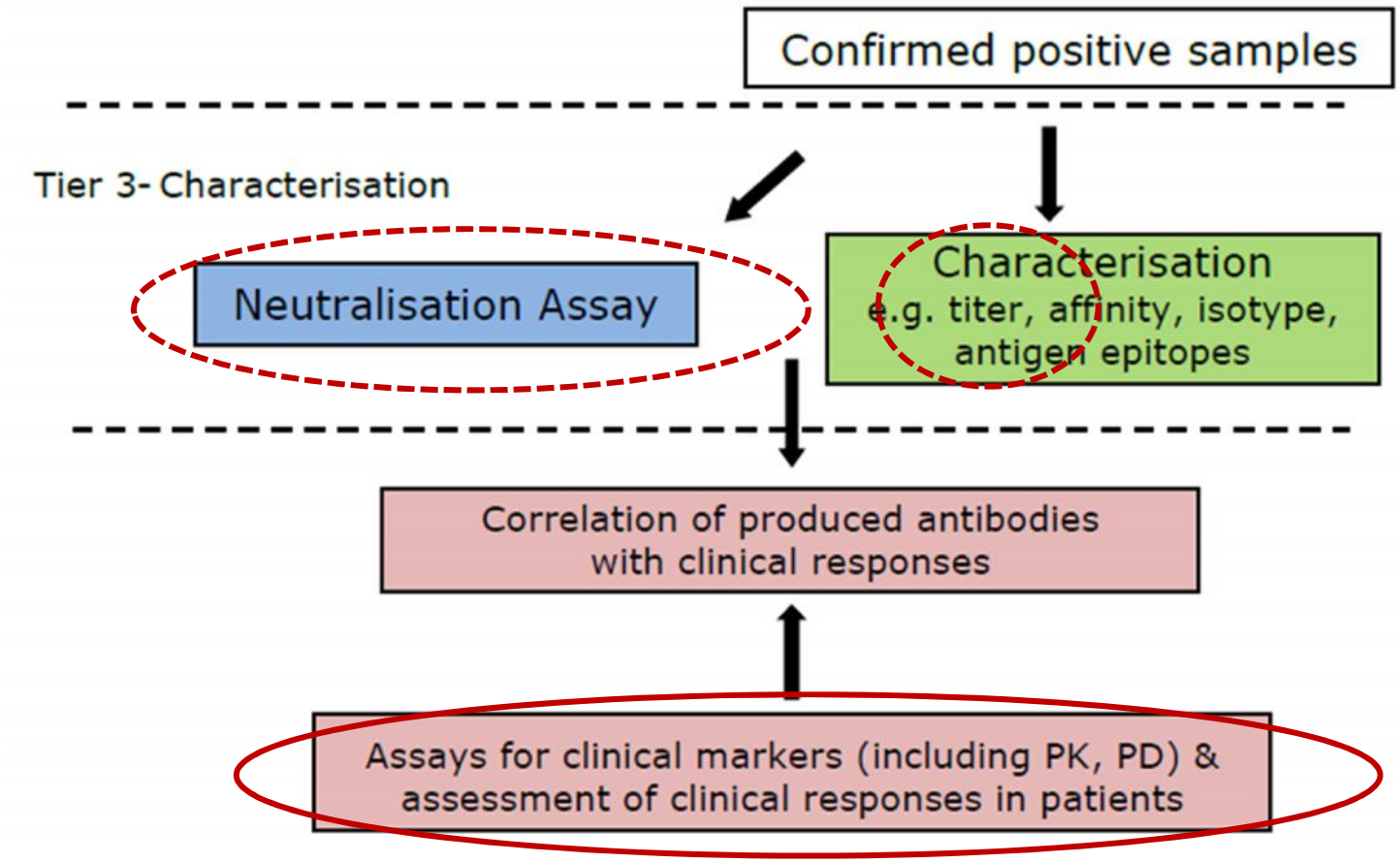
- Strategy for assessment and reporting of immunogenicity
- Integration of PK-PD into immunogenicity assessment
- Case study

Strategy for immunogenicity evaluation



EMA Guideline on Immunogenicity assessment of therapeutic proteins
Annex 1: An example of a strategy for immunogenicity assessment

Strategy for immunogenicity evaluation



EMA Guideline on Immunogenicity assessment of therapeutic proteins
Annex 1: An example of a strategy for immunogenicity assessment

Assessing and reporting immunogenicity

The AAPS Journal, Vol. 16, No. 4, July 2014 (© 2014)
DOI: 10.1208/s12248-014-9599-2

White Paper

Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations

G. Shankar,[1,14] S. Arkin,[2] L. Cocea,[3] V. Devanarayan,[4] S. Kirshner,[5] A. Kromminga,[6] V. Quarmby,[7] S. Richards,[8] C. K. Schneider,[9,10] M. Subramanyam,[11] S. Swanson,[12] D. Verthelyi,[5] and S. Yim[13]

Assessing and reporting immunogenicity

- Determining the characteristics of the ADA response
  - ADA-positive
  - ADA-negative
  - ADA-inconclusive: drug is present at a level that can interfere with ADA detection
  - Unevaluable: no reportable result after drug administration

Assessing and reporting immunogenicity

- Pre-existing ADA
  - Baseline ADA-positive subjects
  - Titer range

- ADA incidence and titer
  - Overall ADA incidence
  - Treatment-induced ADA incidence
  - Treatment-boosted ADA

Assessing and reporting immunogenicity

- Kinetics of ADA
  - Onset
  - Duration
    - Transient response
    - Persistent response
- Neutralizing ADA
  - Neutralizing or non-neutralizing
  - Incidence and kinetics
- Cross-reactivity
  - When a biologic is identical or nearly identical to an endogenous protein

Is it neutralizing?

Determining the relationship of ADA with clinical efficacy and safety

- Efficacy
  - Primary non-response
  - Loss of response

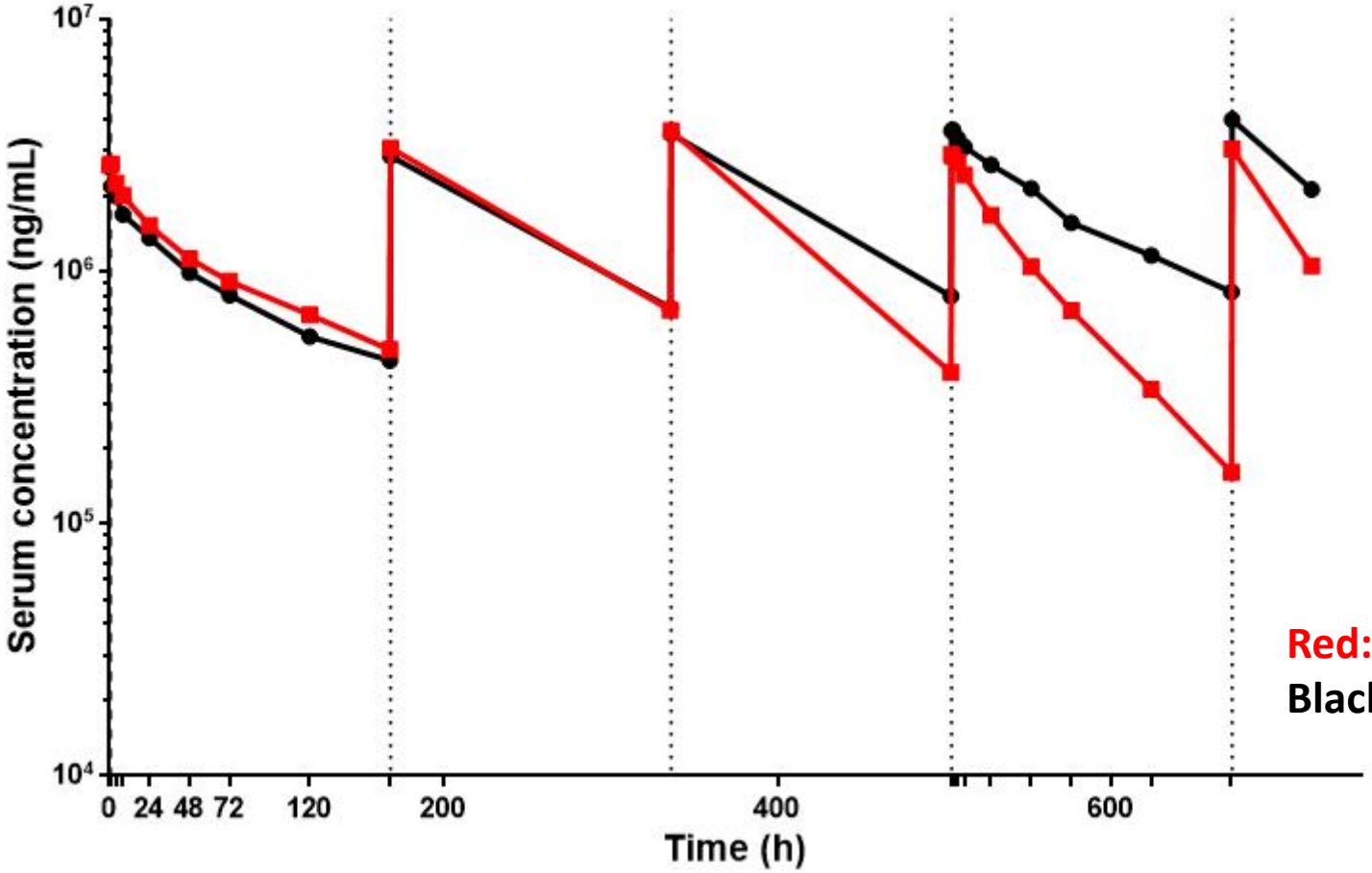
- Safety
  - Acute Adverse Events (AEs)
    - e.g. anaphylaxis
    - investigation of drug-specific IgE
  - Non-acute AEs
    - Delayed hypersensitivity
    - Responses secondary to immune complex and complement-mediated reactions

Determining the impact of ADA on PK & PD

- ADA formation may impact the **pharmacokinetics** (PK) of the therapeutic, i.e., the relationship between dose and the obtained concentrations in e.g. serum
- Can impact the PK of therapeutic in diverse ways
  - Clearing ADA response
  - Drug sustaining ADA response

Determining the impact of ADA on PK & PD

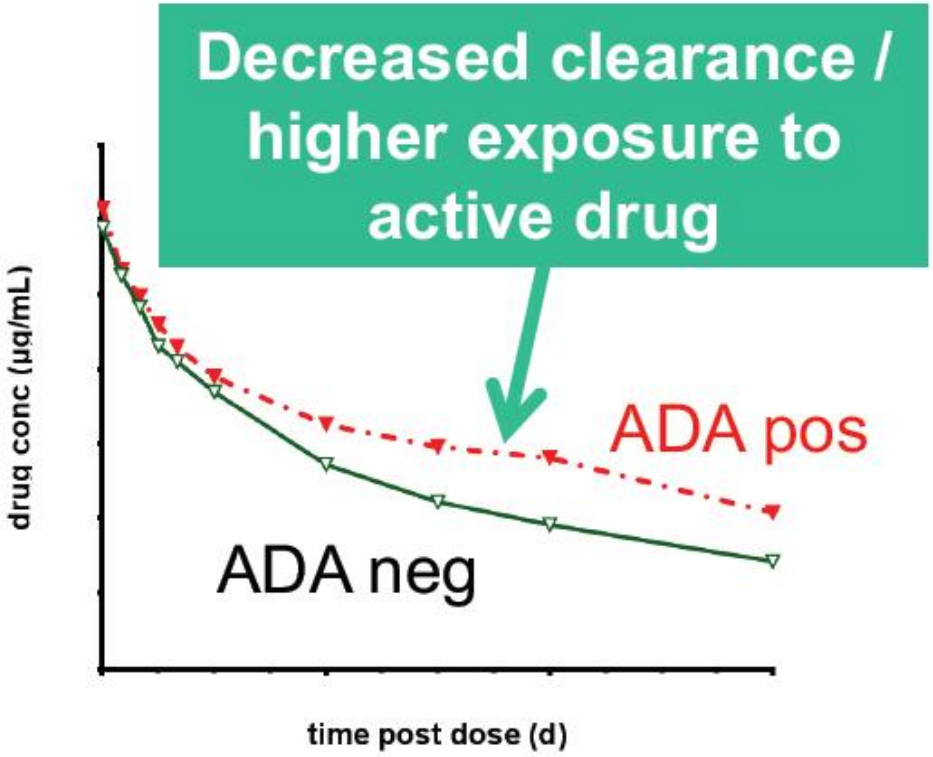
- Clearing ADA response



Red: ADA-positive
Black: ADA-negative

Determining the impact of ADA on PK & PD

- Drug sustaining ADA response



Daniela Stoellner, on behalf of EBF TT-63: Handling of PK data from ADA positive animals
EBF Open Symposium 2016

Determining the impact of ADA on PK & PD

- ADA formation may impact the **pharmacokinetics** (PK) of the therapeutic, i.e., the relationship between dose and the obtained concentrations in e.g. serum
- Can impact the PK of therapeutic in diverse ways
  - Clearing ADA response
  - Drug-sustaining ADA response
- Both neutralizing and non-neutralizing ADA can impact the clearance
- Often the first bioanalytical data which gives an indication of immunogenicity

Determining the impact of ADA on PK & PD

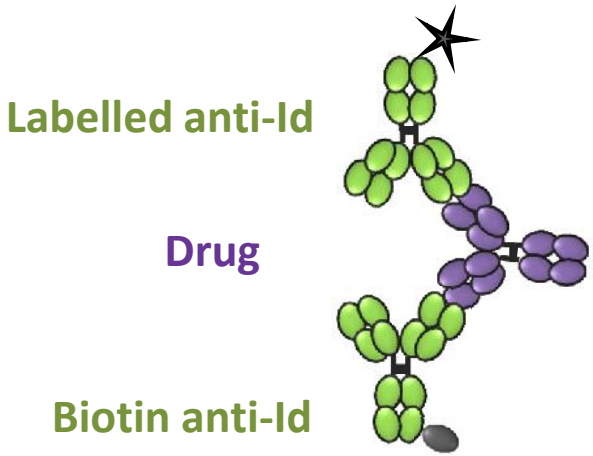
- ADA formation may impact the **pharmacodynamics** (PD) of the therapeutic, which describes the relationship between systemic concentrations (exposure) and therapeutic effects
  - May ultimately affect the efficacy and/or toxicity profile

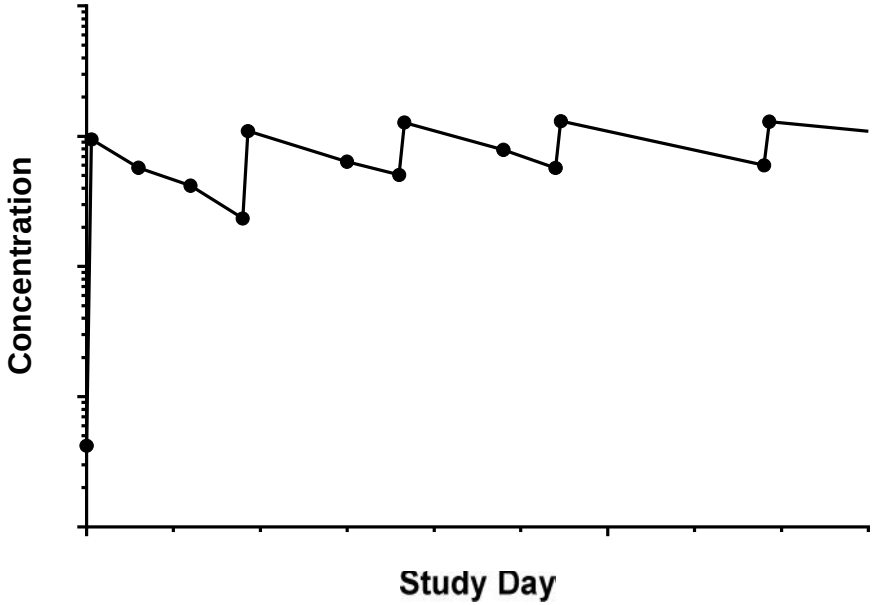
Case study

- **Monoclonal antibody (mAb) therapeutic**
  - Soluble target in inflammatory disease
  - Binds to and neutralizes target

The assays

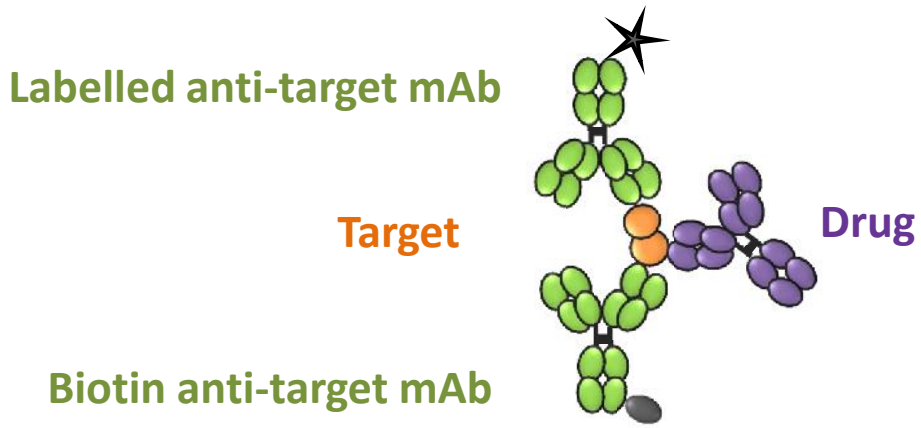
- **'Free' PK**
  - Anti-idiotype sandwich immunoassay
  - Range 100 – 8000 ng/mL
  - Interference of target (and ADA)





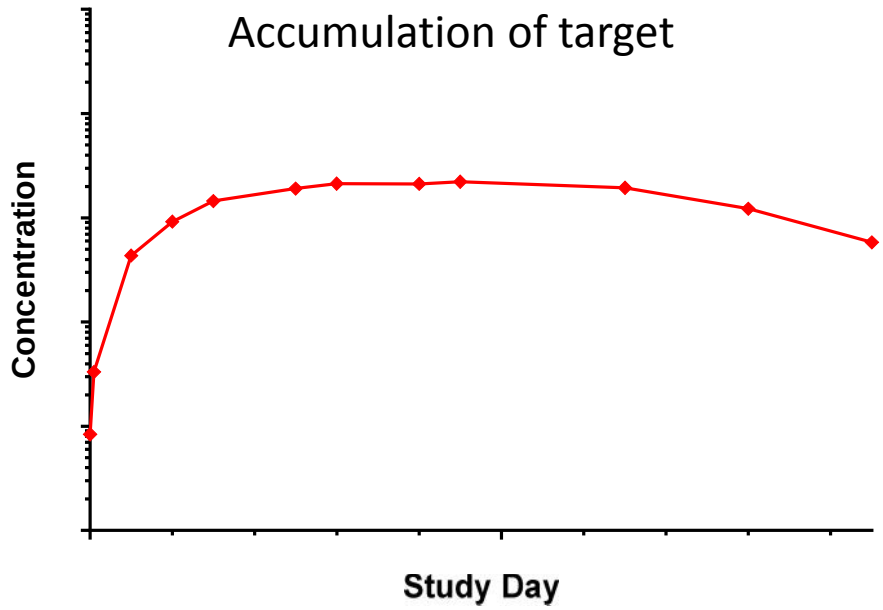
The assays

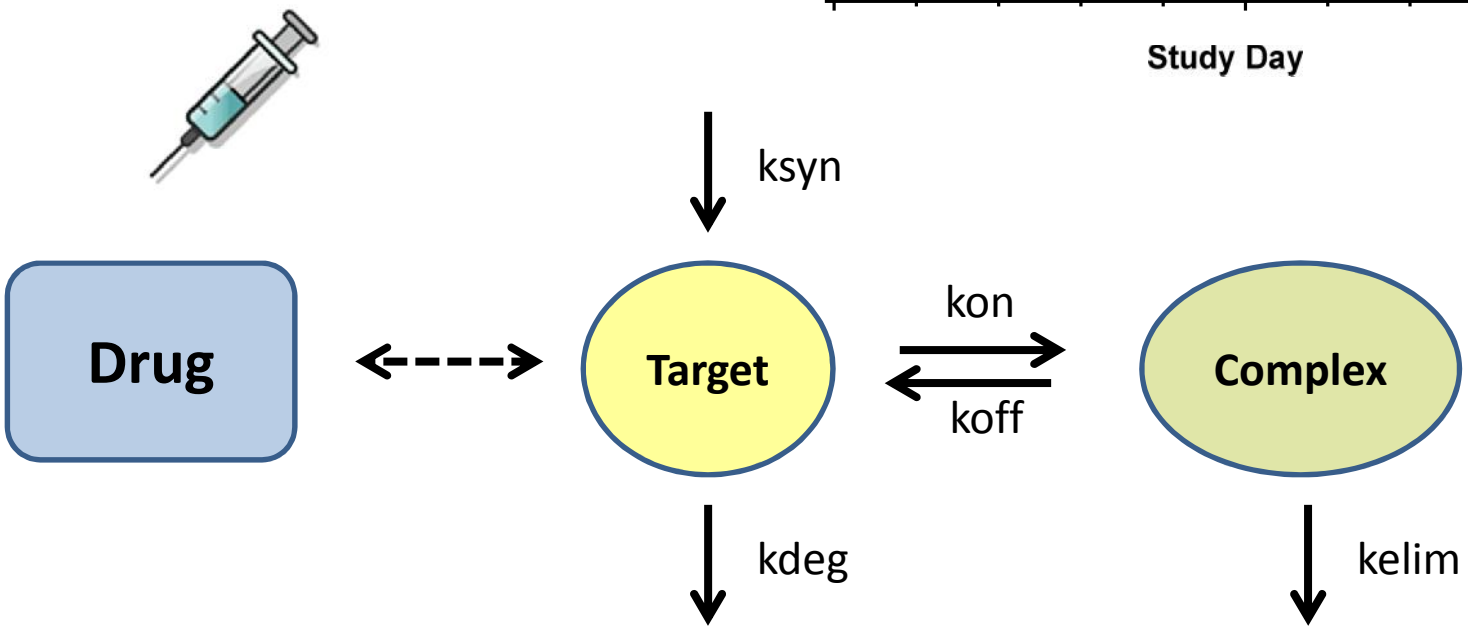
- **Total target**
  - Sandwich immunoassay
  - mAb non-competitive with therapeutic (free + bound)
    - Excess therapeutic added to favour bound
  - Range 50– 50000 pg/mL



The assays

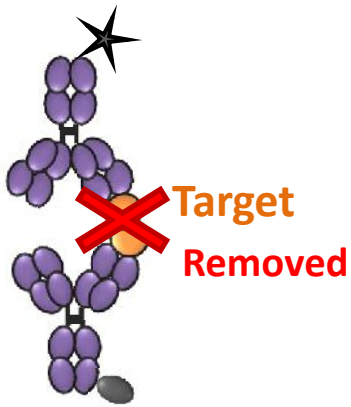
- **Total target**

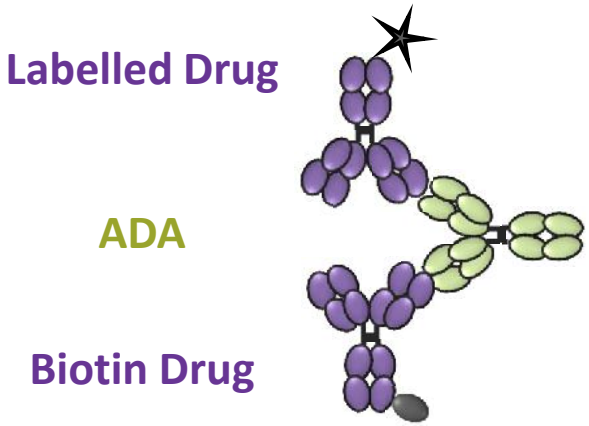


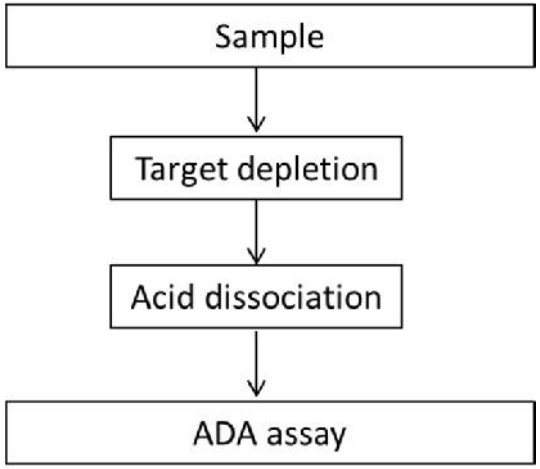


The assays

- **ADA**
  - Solution bridging immunoassay
  - SPE of target & acid dissociation
  - Sensitivity: 6.1 ng/mL (LPC at 10 ng/mL)
  - Drug tolerance: 50 µg/mL at 100 ng/mL PC level
  - Target tolerance: 1000 ng/mL

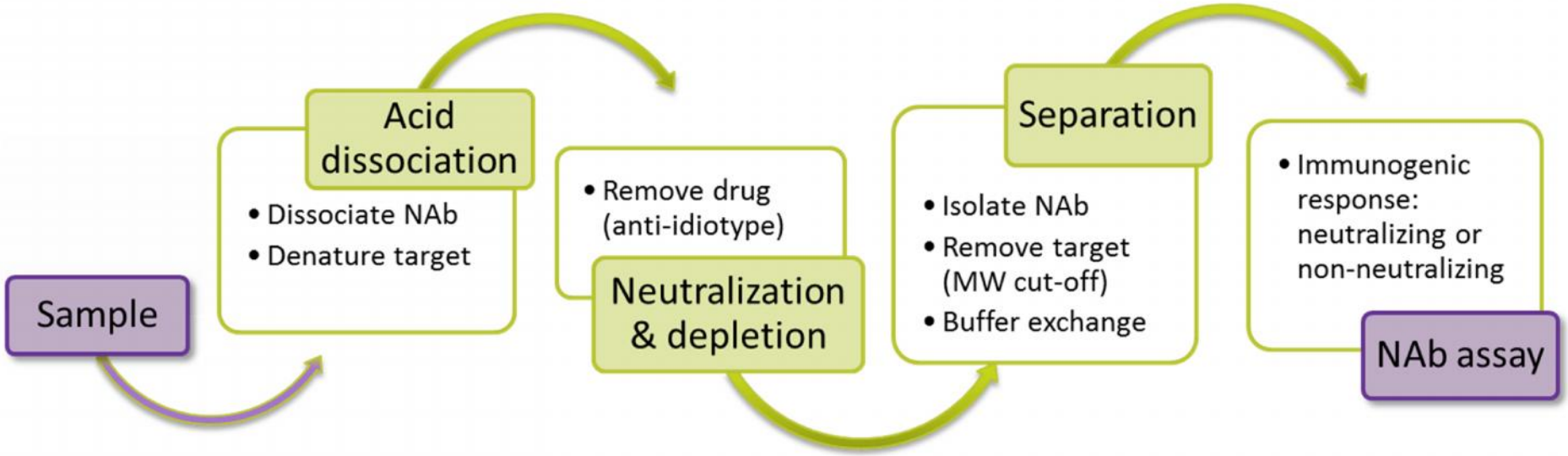






The assays

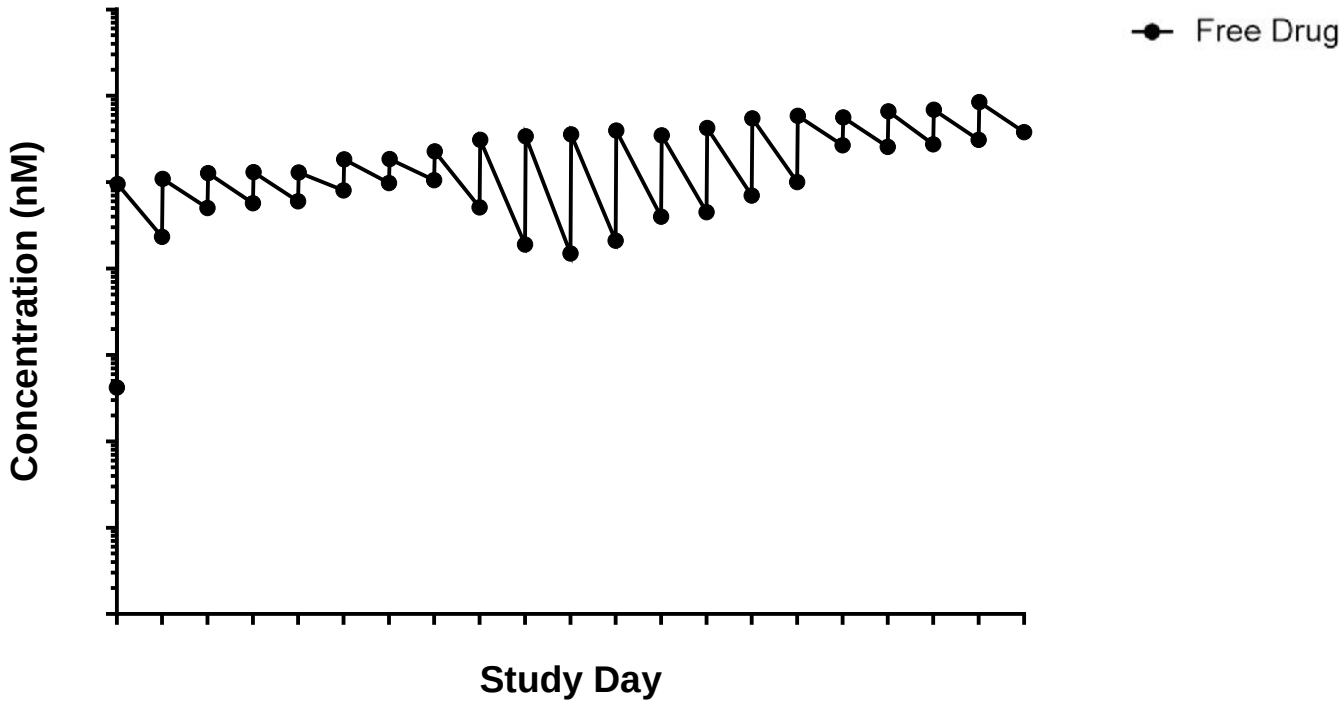
- **Neutralizing ADA**
  - Adapted from potency bioassay
  - Acid dissociation and SPE of drug



Integration of PK-PD-ADA

Simulated data based on real case

- **Case 1**

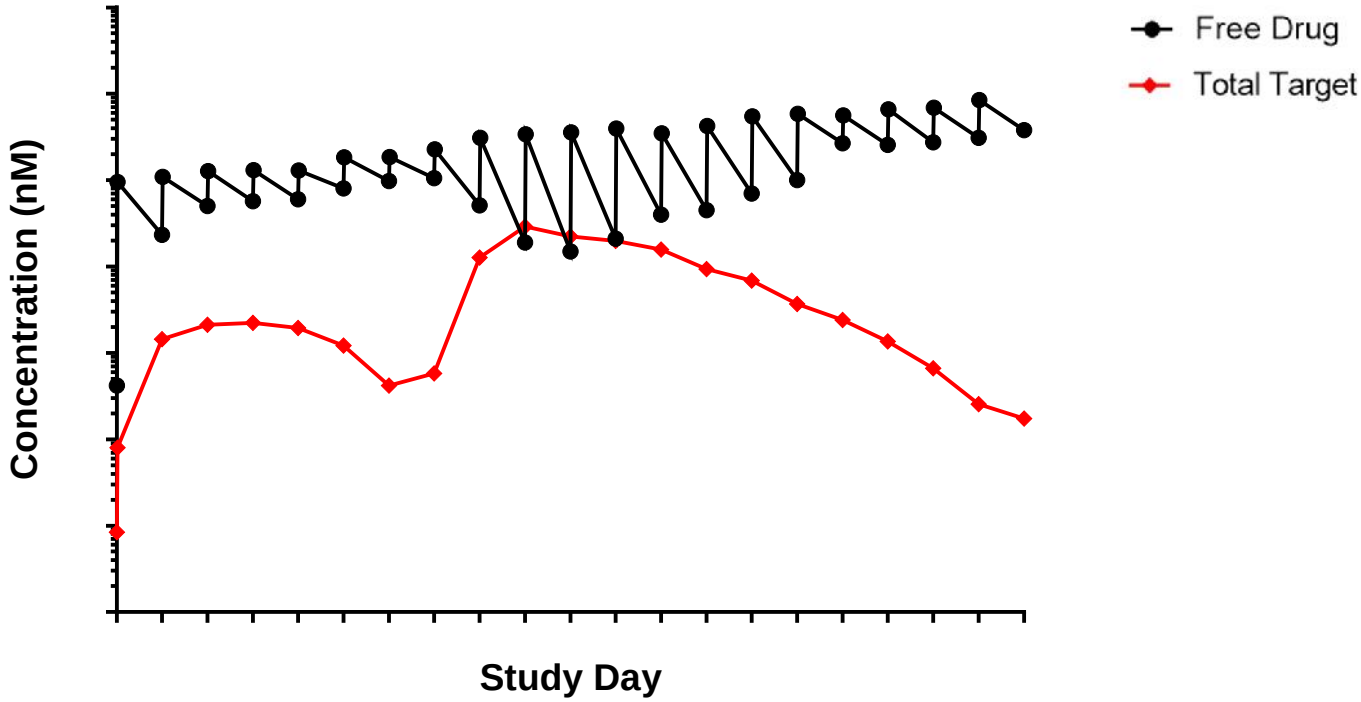


- Rapid elimination of drug – driver?

Integration of PK-PD-ADA

Simulated data based on real case

- **Case 1**

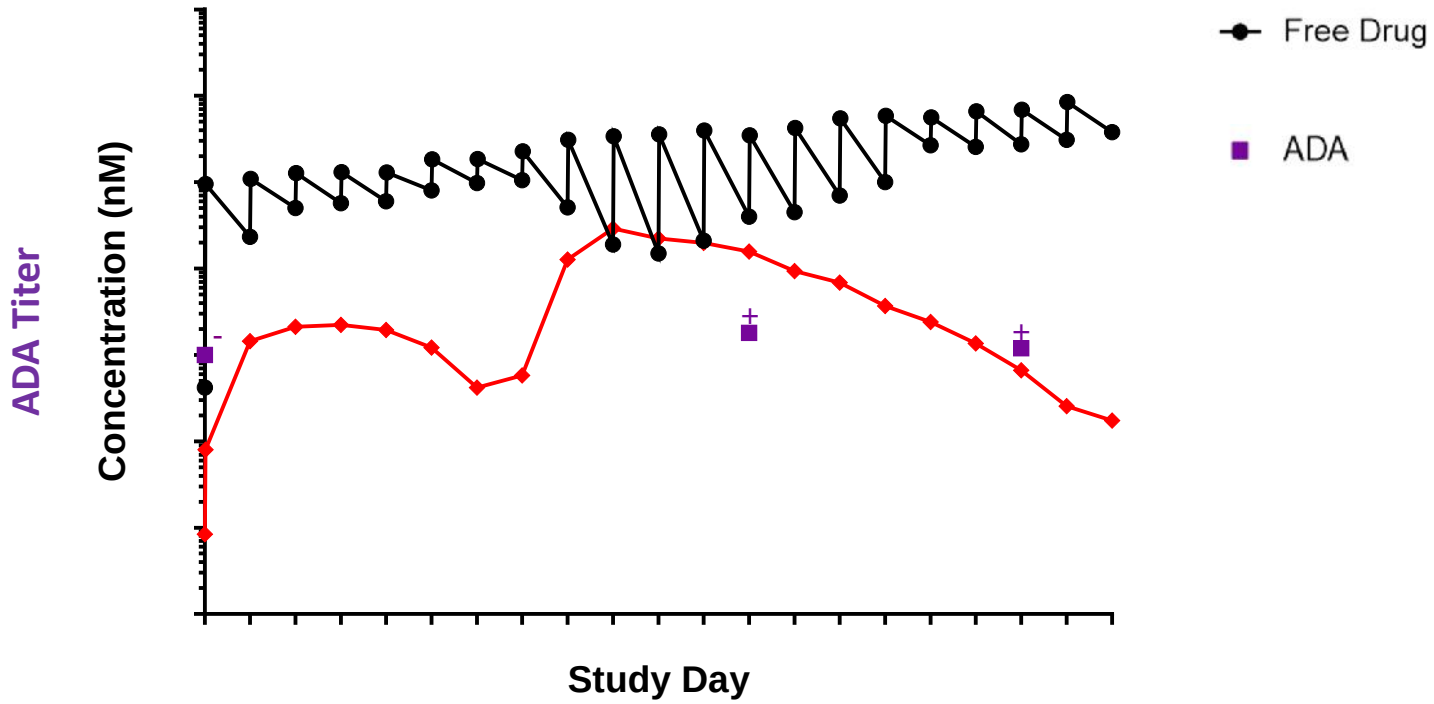


- Elimination of drug driven by increase in target levels
  - After this period, drug returned to normal elimination profile

Integration of PK-PD-ADA

Simulated data based on real case

- **Case 1**



- ADA was observed
  - Low titer, neutralizing

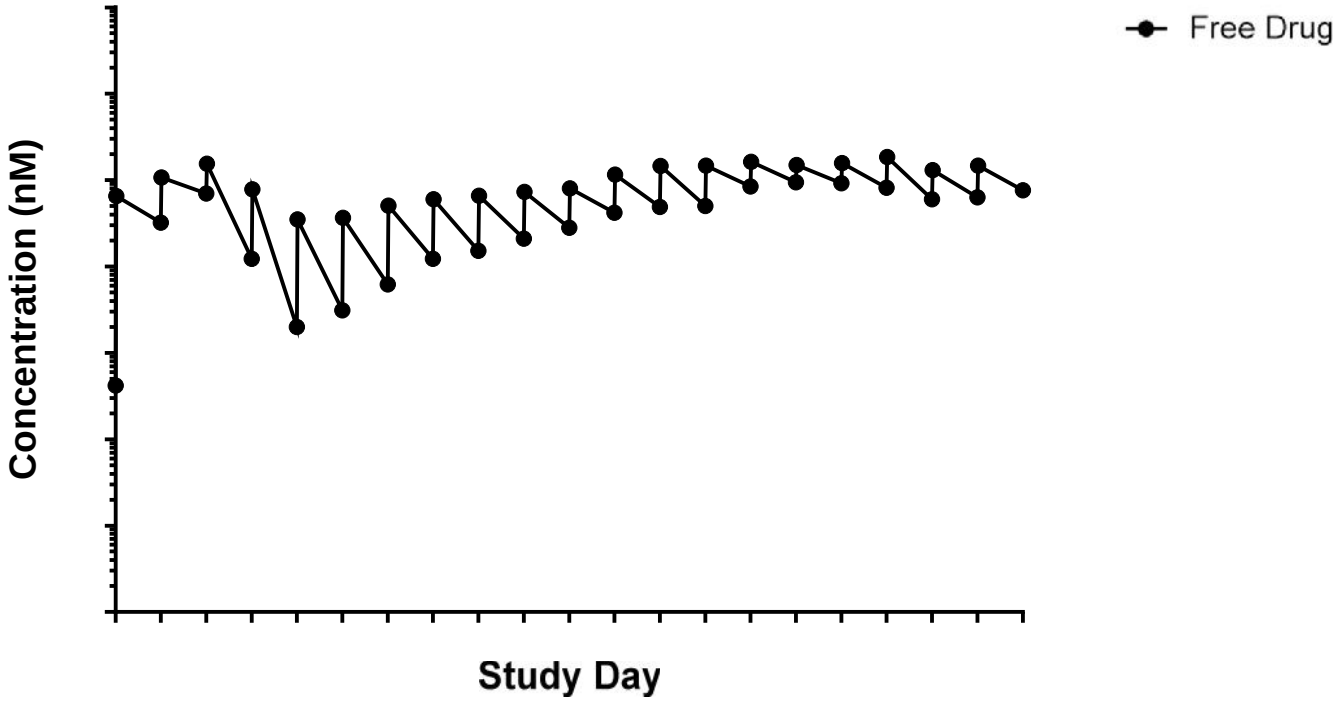
Integration of PK-PD-ADA

- **Case 1 summary**
  - Changes in concentration-time profile of therapeutic
    - Driven by production of target
  - ADA response was observed
    - Characterized as low titer, neutralizing, sustained
    - Did not impact the binding to the target or the drug elimination

Integration of PK-PD-ADA

Simulated data based on real case

- **Case 2**

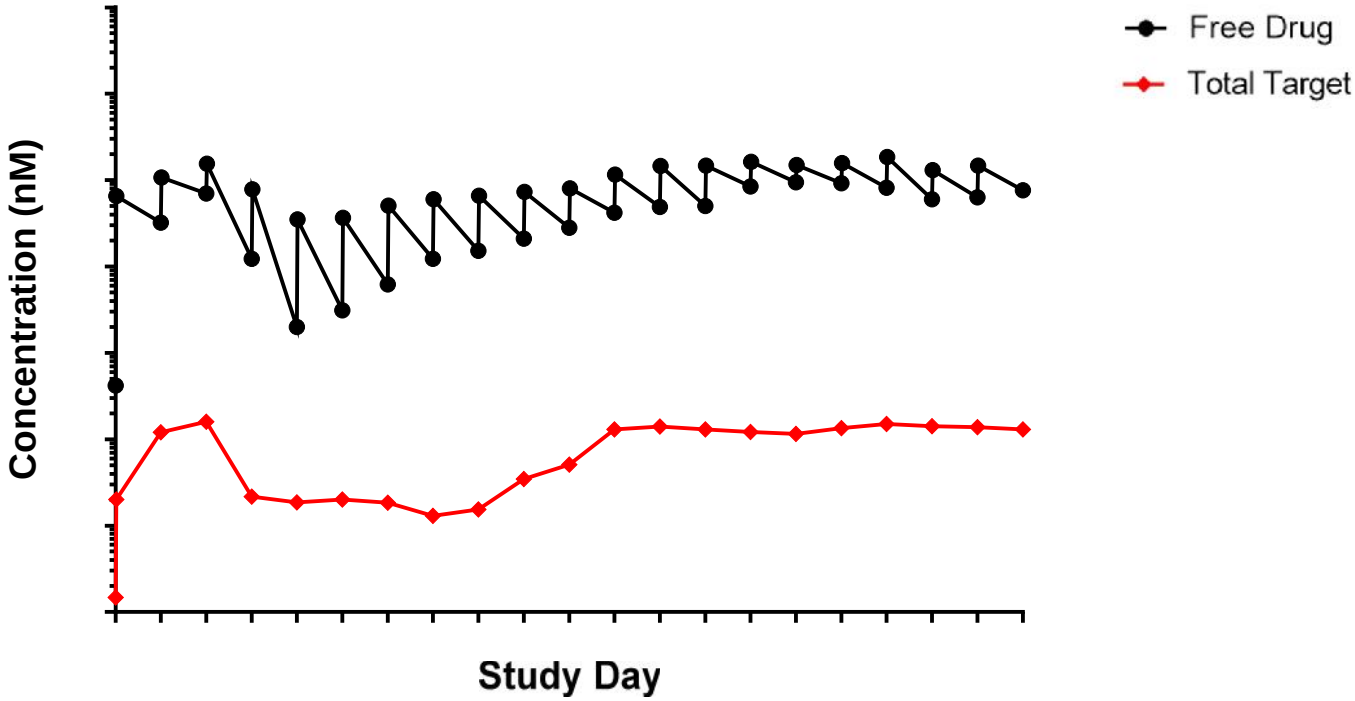


- Rapid elimination of drug – driver?

Integration of PK-PD-ADA

Simulated data based on real case

- **Case 2**

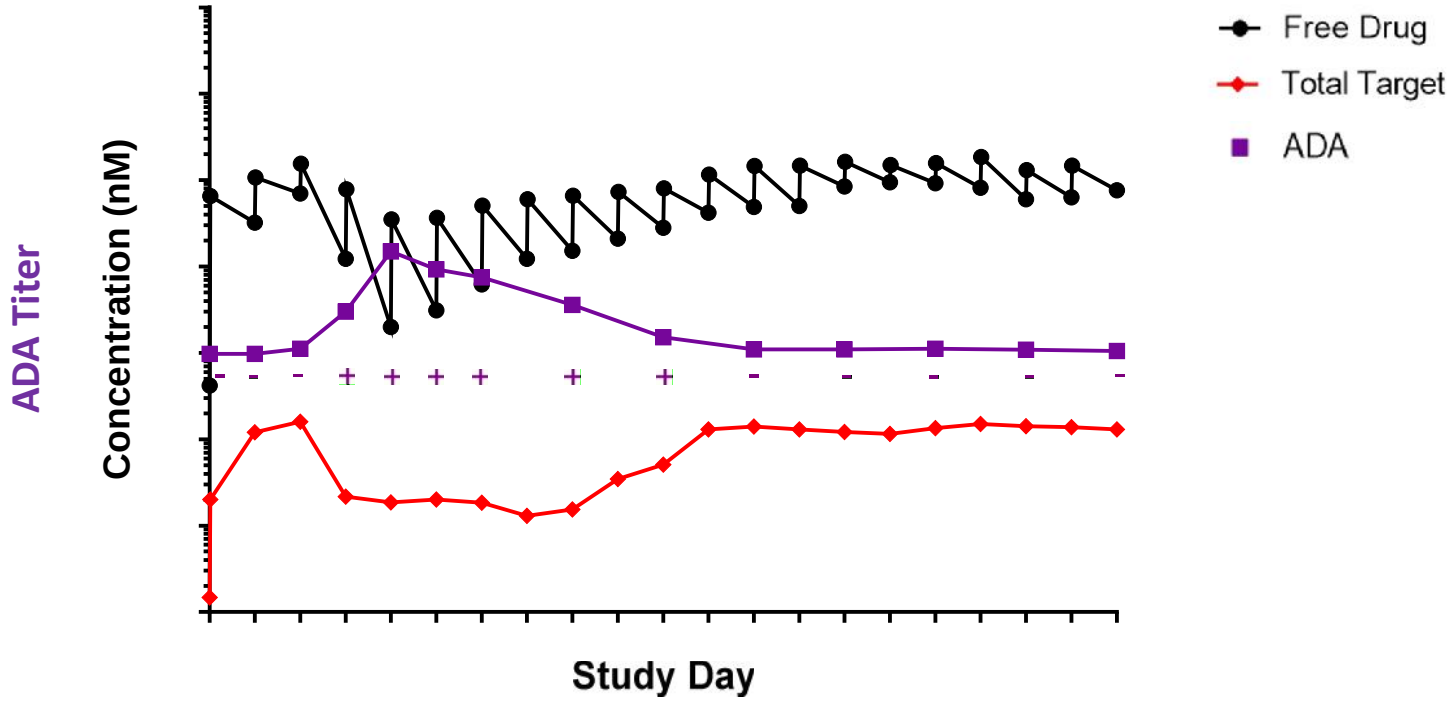


- Concurrent alteration in target engagement

Integration of PK-PD-ADA

Simulated data based on real case

- **Case 2**



- ADA observed
  - moderate titer, transient, non-neutralizing

Integration of PK-PD-ADA

- **Case 2 summary**
  - Changes in concentration-time profile of therapeutic
    - Could not be explained by target levels
  - ADA response was observed
    - Characterized as non-neutralizing, transient
    - Impacted the drug elimination and its ability to sequester target

Conclusions

- Interpretation of immunogenicity requires more than just ADA and NAb assessment
  - Integration of PK and PD data helps build the picture of impact and relevance of ADA

- Understand your bioanalytical assays
  - What they measure
  - Inter-dependencies
  - What the data mean

Acknowledgments

- Novimmune Bioanalytical Sciences team
- CRO Partners

Thank you for your attention!