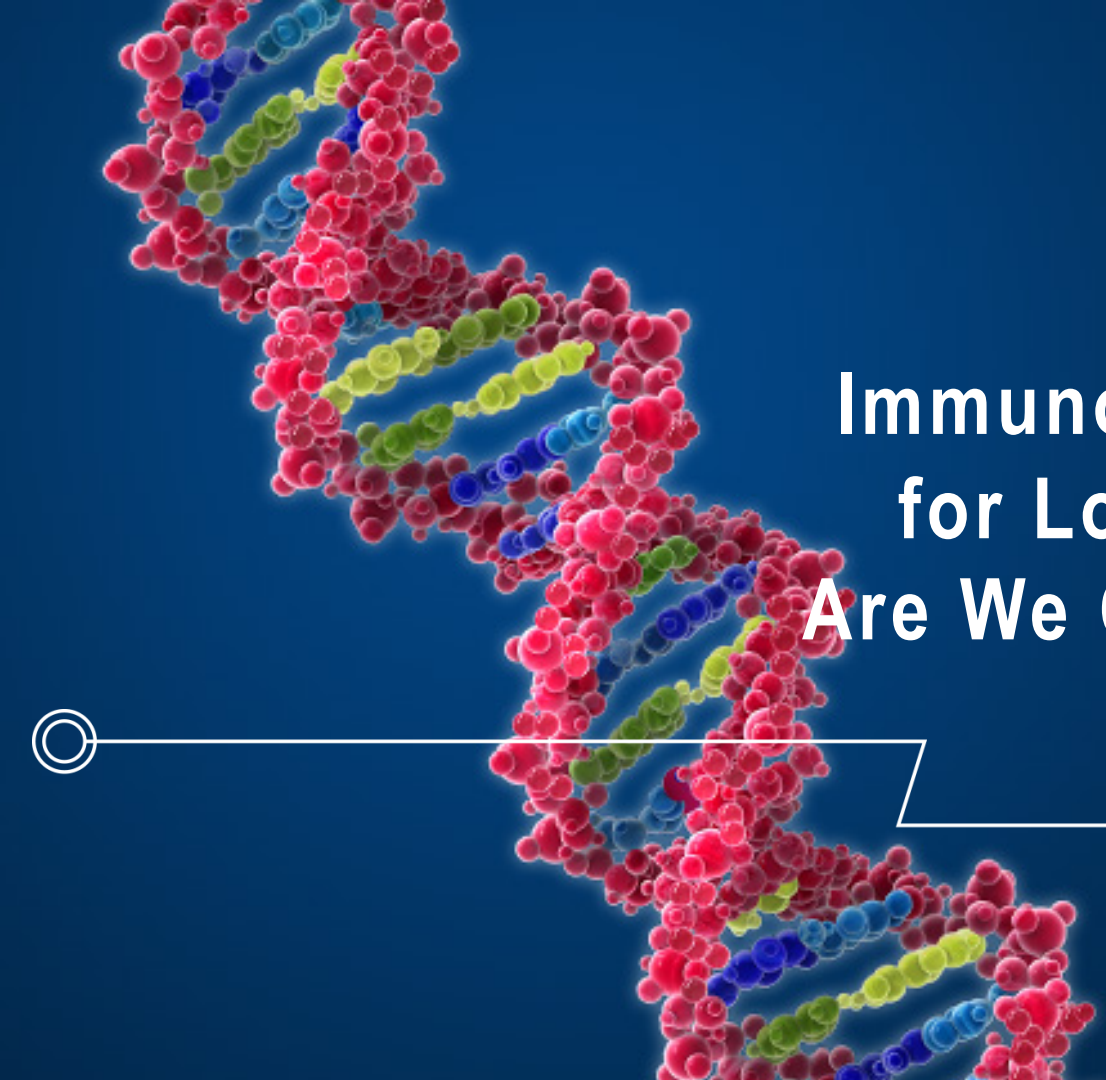

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# Immunogenicity Monitoring for Low-Risk Molecules: Are We Over Reporting ADA?

Michael Partridge

# Disclaimer

The following presentation reflects the opinions of the author and does not necessarily reflect the official position of Regeneron Pharmaceuticals

# Immunogenicity Low Risk vs High Risk

- Biological Mimic
  - EPO & TPO – non-redundant
  - ERT – CRIM negative non-self
- Anti-TNFα – Humira/Remicade
  - High immunogenicity risk
  - Efficacy or safety?
- Anaphylaxis/hypersensitivity (e.g., older drugs, cetuximab, not immunogenicity)
- Immunotoxins (efficacy)
- New modalities

# Low Immunogenicity Risk

- Biologics that are not endogenous mimics
  - Monoclonals: fully human, humanized
- Particular patient populations/disease indications (e.g., oncology, ID)
- ADA data available from early phase studies
  - Low incidence (e.g., < 5%), low titers, no PK impact
  - No immunogenicity-related safety events

- **Immunogenicity assessment is one size fits all**

# For Low-Risk Molecules What Can We Do Differently?

- What benefit do we get from confirmation and titer assays?
- Wholistic analysis of data
  - ADA assay – positive/negative, duration, titer (S/N?)
  - PK Assay
  - PD Assay
- Do we need NAb? When?
- Case Study: Marketed low risk mAb, low ADA, target capture (active) PK assay

# Recent Publications:

- ADA is one size fits all
- Clinically meaningful ADA data
  - Highly sensitive and drug tolerant assays
  - Do we always need NAb?
- Severe diseases, dense sampling

Perspective

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Bioanalysis

Assessment of clinically relevant immunogenicity for mAbs; are we over reporting ADA?

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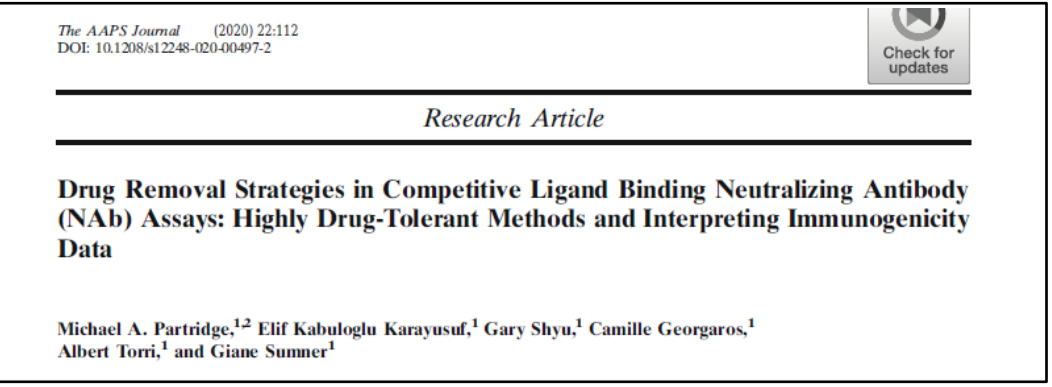
- PMC drug tolerant NAb
- Technical challenges
- More NAb positives
- NAb pos ≠ decreased drug levels/efficacy



*The AAPS Journal* (2020) 22:112
DOI: 10.1208/s12248-020-00497-2

Check for updates

*Research Article*

**Drug Removal Strategies in Competitive Ligand Binding Neutralizing Antibody (NAb) Assays: Highly Drug-Tolerant Methods and Interpreting Immunogenicity Data**

Michael A. Partridge,[1,2] Elif Kabuloglu Karayusuf,[1] Gary Shyu,[1] Camille Georgaros,[1] Albert Torri,[1] and Giane Sumner[1]

# Ongoing Discussion around ADA Assessment for Low Risk mAbs

- Event driven approach
  - Ongoing risk assessment
  - Collect and hold for phase 1/2
  - Implement for pivotal studies
- FDA Guidance
  - Full validation for high risk or pivotal studies

*The AAPS Journal, Vol. 19, No. 3, May 2017 (© 2017)*
DOI: 10.1208/s12248-017-0059-7

*Commentary*

**A Proposal to Redefine Clinical Immunogenicity Assessment**

**Daniel T. Mytych,[1,3] M. Benjamin Hock,[1] Mark Kroenke,[1] Vibha Jawa,[2] Arunan Kaliyaperumal,[1] and Yanchen Zhou[1]**

**VI. ASSAY VALIDATION**

Assay validation is a process of demonstrating, through specific laboratory investigations, that the performance characteristics of the ADA assay employed are suitable for its intended use. The extent of validation depends on the stage of product development and the risks of consequences of immunogenicity to subjects associated with the therapeutic protein product. For most products, a partial validation involving assessments of assay sensitivity, specificity, precision, cut-point, and drug tolerance — with less emphasis on robustness, reproducibility, and stability — may be adequate for the earlier stages of clinical development such as phase 1 and phase 2 studies. High-risk products may require full validation before any clinical studies. However, as stated in section VI.A, fully validated assays should be used for testing samples from pivotal and postmarketing studies.

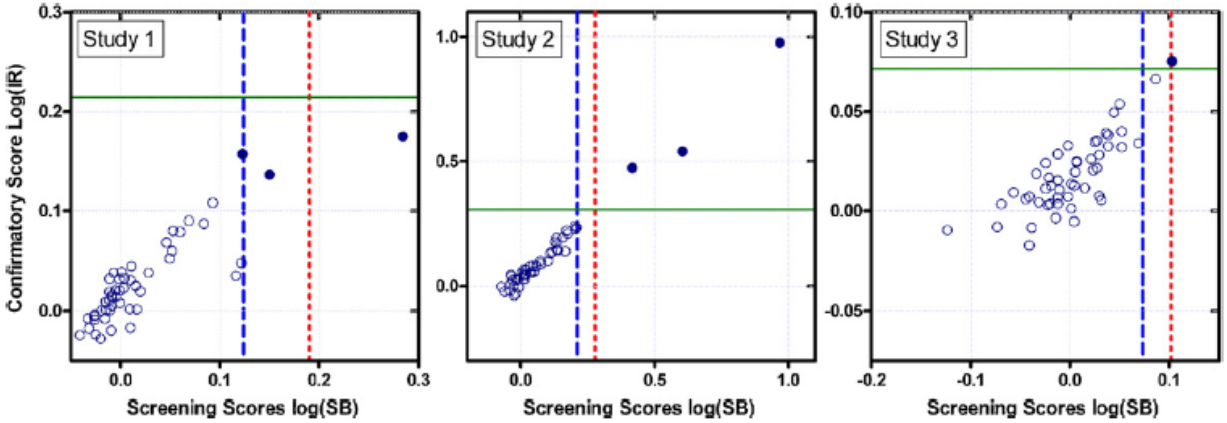
# Immunogenicity Bioanalysis Paradigm

- Four-tiered assessment (screen, confirmation, titer, NAb)
  - Safety considerations with early biologicals
  - Guidance, White Papers: Industry and health authorities are comfortable
- Industry established a conservative analysis paradigm
- Unlike most other assay types

**Do we need this approach for low-risk molecules?**

# ADA Bioanalysis Paradigm: Screen & Confirmation

- Screen and confirmation are not orthogonal assay types
  - Screen and confirmation data highly correlated
  - Statistically, current analysis is equivalent to 1% screen F/P

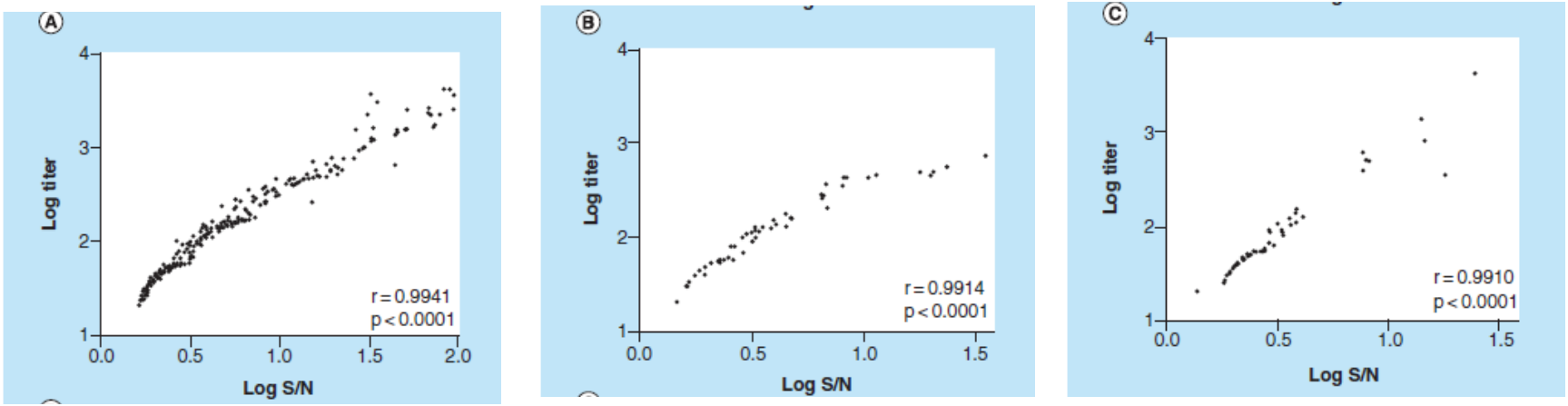




Robert Kubiak et al (2013) *Journal of Pharmaceutical and Biomedical Analysis*

# ADA Bioanalysis Paradigm: Titer & Signal:Noise

- Titer and S/N are also highly correlated
- AAPS Focus Group: Alternatives to Titer
  - Hook effect, treatment boosted etc can be resolved
  - Historical assays probably remain titer-based



# Example from Non-Clinical ADA Assessment

- **Historical Approach**
  - Full validation according to clinical guidance
  - 3-tier analysis (titer assay often challenging)
- **Current Approach**
  - ADA not always required (e.g., only for BLA-enabling studies)
  - Condensed assay “qualification” (defined in SOP)
  - Screen analysis only
  - 1% FP cut point
  - Report S/N

# Neutralizing Antibody Testing in Low-Risk Molecules

- Substantial information is obtained from other assays
  - ADA status (positive, transient/persistent, titer)
  - PK, PD and efficacy

- What additional information does NAb analysis provide for human mAb drugs?
  - We know ADA matures over time and tends to become neutralizing
  - For low risk mAbs where ADA impacts PK/efficacy, do we need to know if it is clearing or neutralizing?

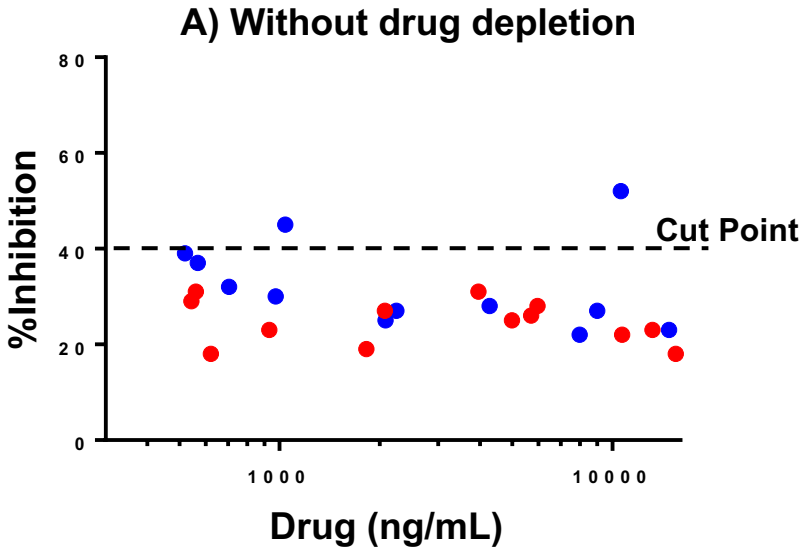
"mAbs are not expected to induce antibodies that cross-react and neutralize an endogenous counterpart…" and can "thus be considered a lower risk class"

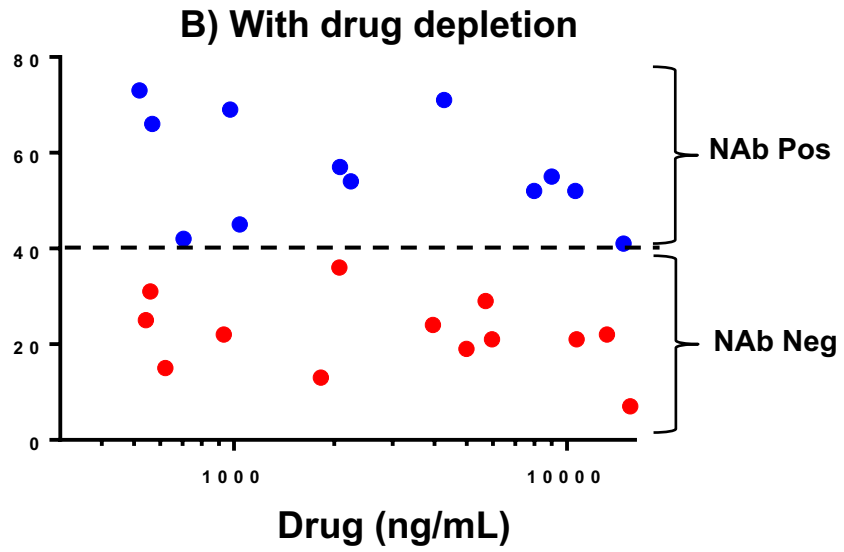
*EMA 2012 & Wu 2016*

**For mAb drugs, why is NAb testing be the default?**

# More NAbs Detected with Drug Tolerant Assay

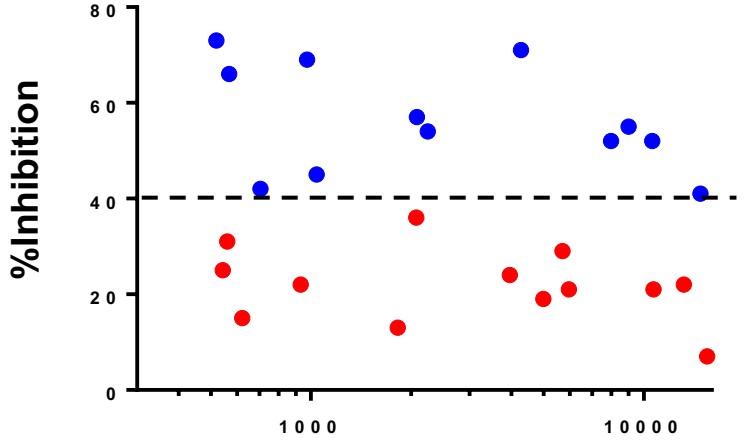
- Human mAb, low overall ADA
- Post-marketing commitment to develop a more drug tolerant NAb assay
- Tested ADA+ clinical samples with drug conc > drug tolerance



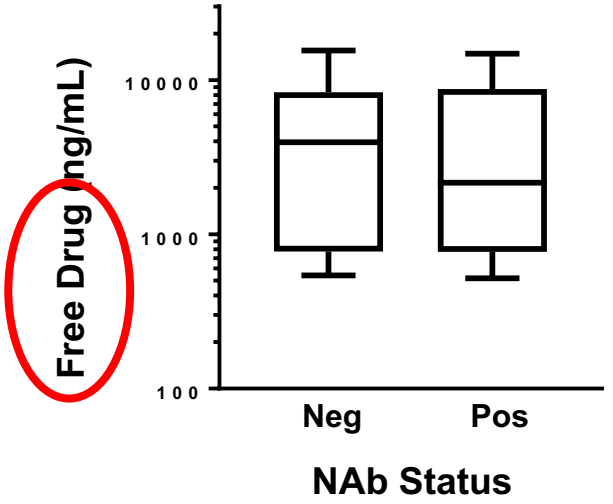



# Clinical Relevance of NAbs Detected With Drug Tolerant Assay

**NAbs Detected after drug depletion**
**All low titer ADAs, 67% > D29**




**Drug concentration are similar in**
**NAb positive and negative samples**




**Drug tolerant assay does not detect clinically relevant NAbs**



See also: van Schouwenburg et al 2013; Van Stappen et al 2017

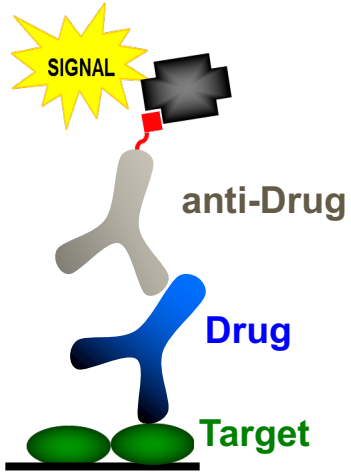
# Case Study: Marketed mAb #1 combination with mAb #2

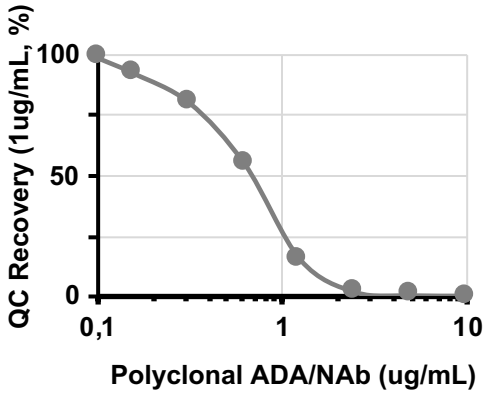
- Low ADA rate as monotherapy
- Low risk indication (severe disease)
- Phase 2 POC study in new indication
- Target capture “active” PK assay

**What immunogenicity assessment is needed for mAb #1?**

- Do we need NAb?
- Can we bank samples?

**Target Capture “Active” PK Assay**



# Rethinking Immunogenicity Assessment

- Immunogenicity currently one-size-fits-all
- Event driven approach
  - Collect and hold for phase 1/2
- Consolidate screen, confirmation, titer
  - Assays correlated: Screen & confirmation; S/N & titer
- Requirement for NAb
  - Is NAb always required?
  - When (post marketing)?

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# Questions?