ADCS, WHAT IS INDUSTRY DOING TODAY? AN OVERVIEW

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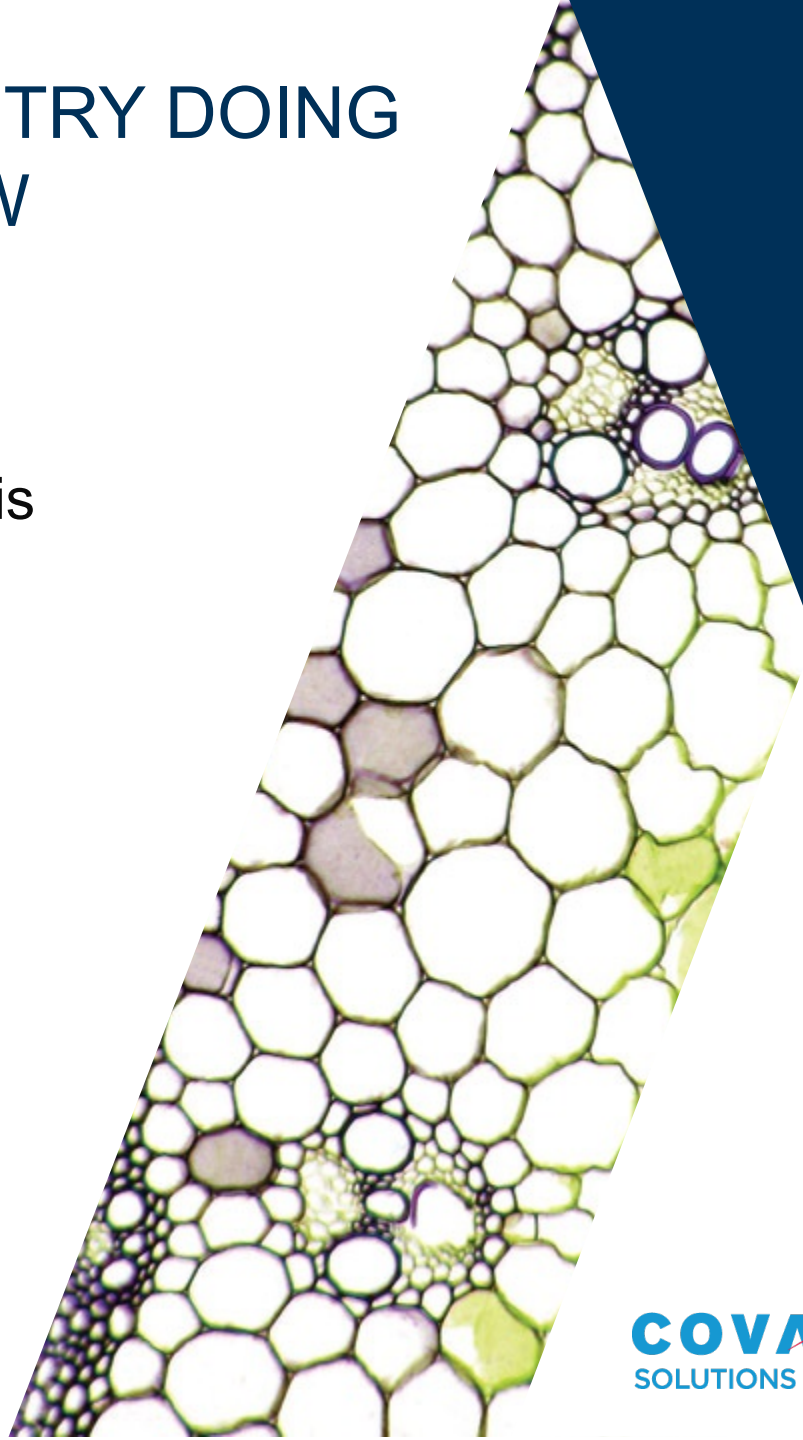
EBF ADC Training day

June 2017



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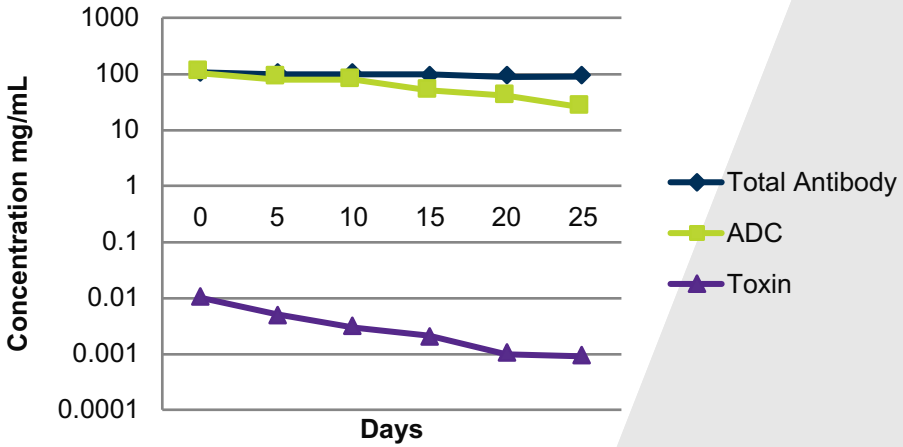
ADC Bioanalytical PK Assays

Assay	Purpose	Technology
PK Total Antibody DAR = 0	Assess overall Antibody PK behaviour	Ligand Binding
PK Conjugated Antibody (ADC) DAR ≥ 1	Assess level of active drug	Ligand Binding
PK Unconjugated Drug	“Free” drug level	LC-MS/MS

Example data (Covance):



2 ADCs, what is industry doing today? June 2017

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Analytical Considerations For Nonclinical Safety Assessment Of ADCs

Analytical consideration	Small molecules	Large Molecules	ADCs
Manufacturing	Chemical synthesis	Biologically-derived	Biologically derived + conjugation from chemical synthesis
Toxicity	On- and off-target	• Low toxicity due to selectivity • Complex pharmacology	• Ag-independent • on- and off- target
Pharmacokinetics	• Short half-life • High Volume of distribution	• Long half-life • Lower Volume of distribution	• Long Ab half-life • Toxin: rapid clearance • Lower Volume of distribution
PK assays	• Total drug product • metabolites	Total Ab	• Conjugated Drug (ADC) • Total Antibody DAR=0 • unconjugated toxin
Immunogenicity assays	No	Yes	Yes

Ways To Mitigate Risks Of ADC Development Program

Build a panel of analytical assays to fully understand the mode of action:

- Full Bio CMC data package (Physiochemical characterisation)
- Full Pharmacokinetic characterisation (ADC, Unconjugated and toxin)
- Full immunogenicity package with possible epitope mapping

Validated Toxin Bioanalytical assays

LC-MS/MS

- Solid Phase Extraction
- API 5000
- Limits of Quantification
  - Rat: 10 pg/mL
  - Monkey: 10 – 20 pg/mL
  - Human: 10 pg/mL
- Freeze Thaw
  - 2 – 4 (linker dependent)

(Image: Covance)

Validated LBA Bioanalytical assay formats

Total antibody	ADC
Preclinical	
Generic: Capture: Antigen Detection: Anti-Human IgG	Capture: Anti-tox mAb (71%) Detection: Anti-Human IgG, anti-ID mAb
Selective: Capture and Detection: Anti-ID mAb	Capture: Antigen Detection: Anti-tox mAb
Human	
Capture and Detection: Anti-ID mAb	Capture: anti-tox mAb Detection: anti-ID mAb

IMMUNOGENICITY

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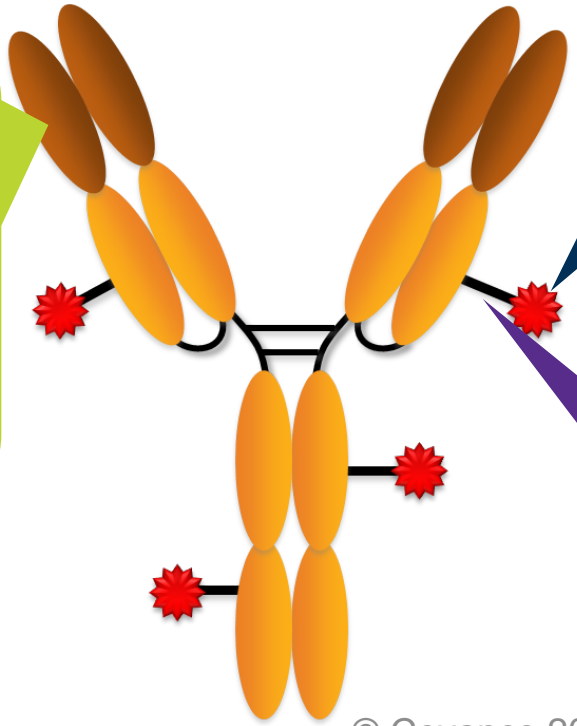
Specific ADC Components That Can Be Affected By Immunogenicity

Monoclonal Antibody

ADA to CDR > Neutralise antigen binding

ADA to Fc-gamma R > Inhibit ADCC or CDC

ADA to FcRn > Inhibit exposure



Cytotoxic Agent

- reduce efficacy
- immune complex

Linker

- reduce efficacy
- lead to epitope spreading
- immune complex

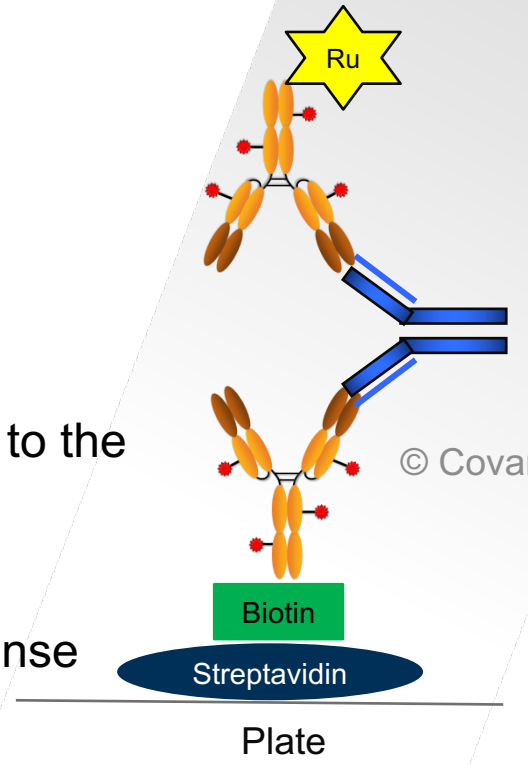
Validated ADA assay formats

CLINICAL AND PRE-CLINICAL

Bridging assays

3 Tiers

- Screening
  - Detect the presence of anti-ADC
- Confirmatory
  - demonstrate the specificity of the binding to the ADC
- Titer
  - The highest dilution factor to give a response greater than the assay cut point



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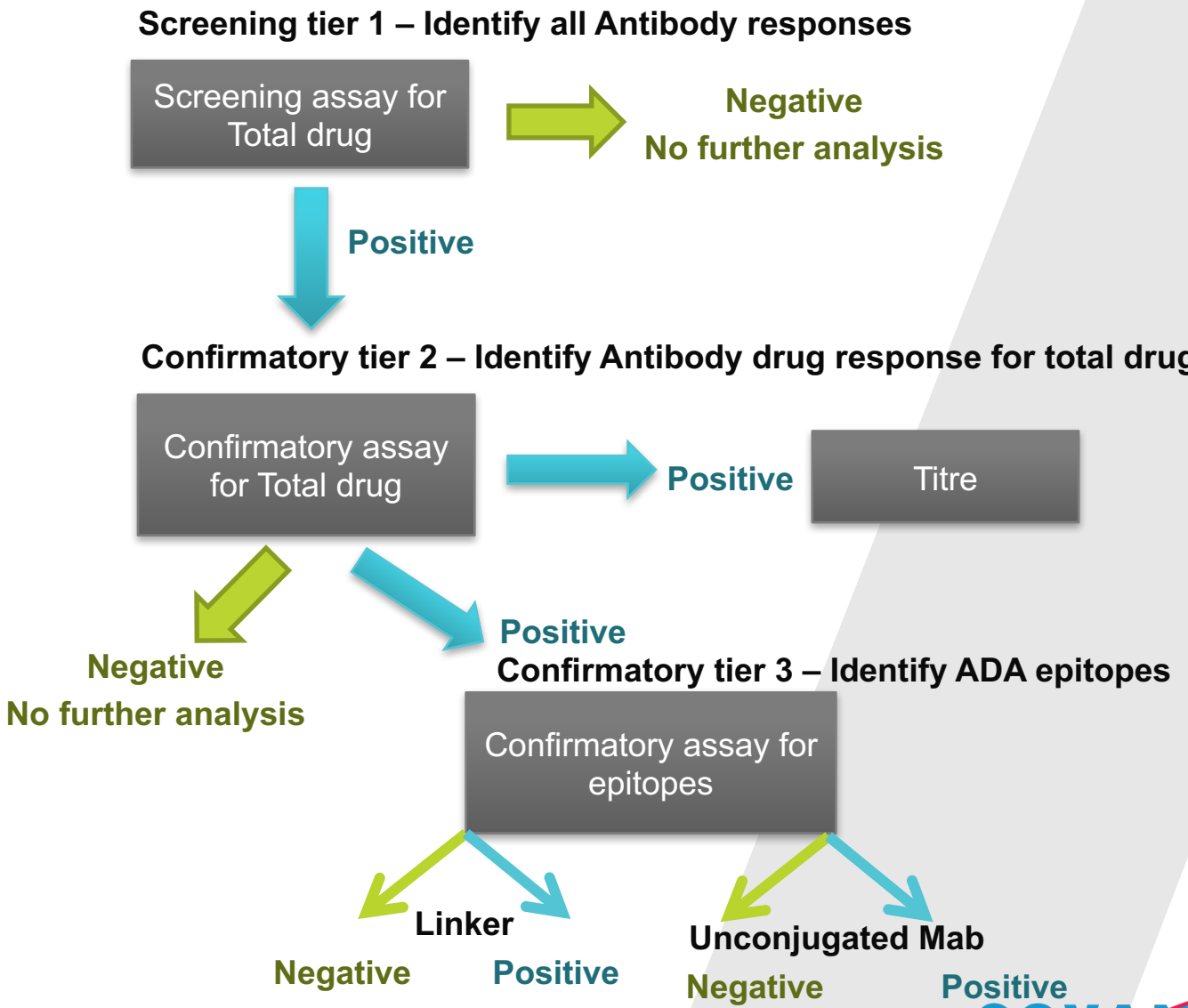
Animal Data Do Not Always Predict Clinical Outcomes, But Is Still Of Value

- For immunogenicity assessment in pre-clinical, the main purpose is to confirm appropriate interpretation of PK and PD
- The greater the difference between the foreign protein and the human protein sequence, the bigger the immunogenic reaction
- ADC reagents can introduce neo-epitopes
- ADC regents can introduce immune complex formation
- Work done in Pre-clinical to develop bioanalytical assays can be helpful for clinical program

Triage Of ADA Data For ADC Antibodies



Interpretation Of Immunogenicity

Immunogenicity *must be* considered with other endpoints

- ADA…onset of immune response & kinetics
- PK….pharmacokinetics (drug exposure)
- PD….pharmacodynamics (drug activity/efficacy)
- AE….adverse events/clinical observations (drug toxicity)

….all are important when interpreting study results!

ADA + PK + PD + AE = Immunogenicity Assessment

Conclusion

- No single package can be applied to all ADCs but there are trends
- Bespoke approaches necessary to answer specific questions
  - DAR profile
  - Epitope mapping
- Understanding the impact of immunogenicity on the mode of action can de-risk the development pathway