KU LEUVEN

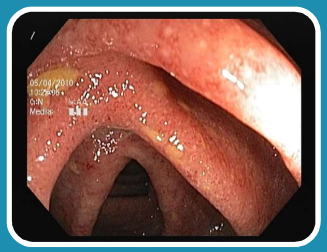
How to monitor and mitigate immunotoxicity during early phase clinical trials in inflammatory diseases?

Prof. Ann Gils
Laboratory for Therapeutic and Diagnostic Antibodies
Department of Pharmaceutical and Pharmacological Sciences,
KU Leuven, Belgium

London, May 19 2017

ann.gils@kuleuven.be

Inflammatory diseases



Inflammatory bowel diseases (IBD)

- Crohn's disease
- Ulcerative colitis

Rheumatological diseases

- Spondyloarthritis
- Rheumatoid arthritis
- Psoriatic arthritis

Dermatological diseases

- Plaque psoriasis

ann.gils@kuleuven.be

Inflammatory diseases

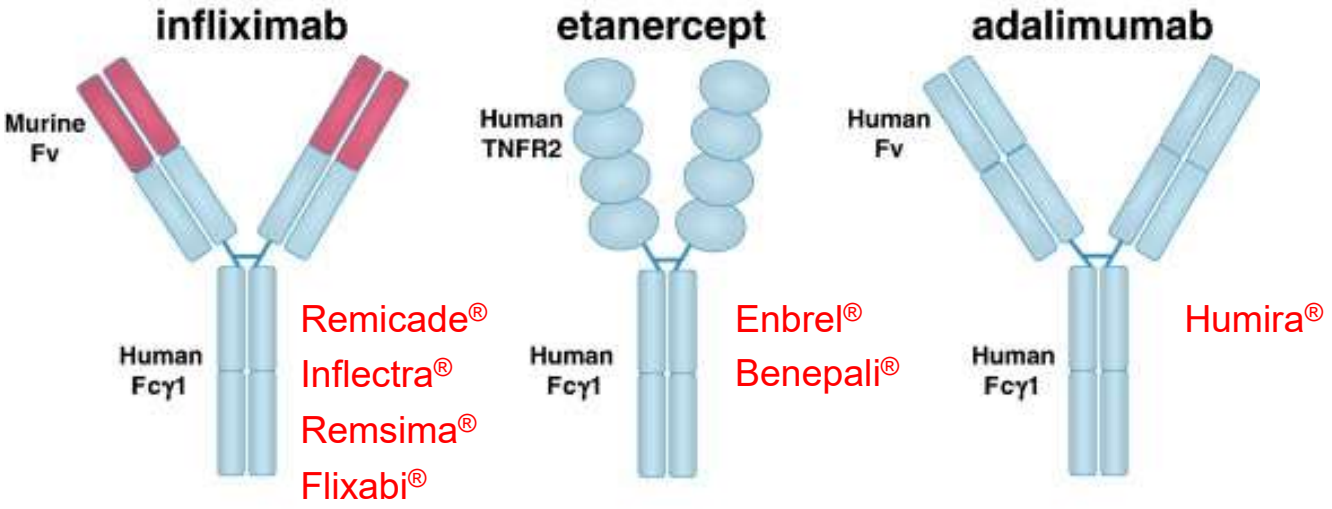
Concept:
elevated Tumor Necrosis Factor alpha (TNF) concentrations at the sites of inflammation drive disease pathology

Therapeutic goal:
removal of excess TNF from sites of inflammation

Development of anti-TNF biologicals

ann.gils@kuleuven.be

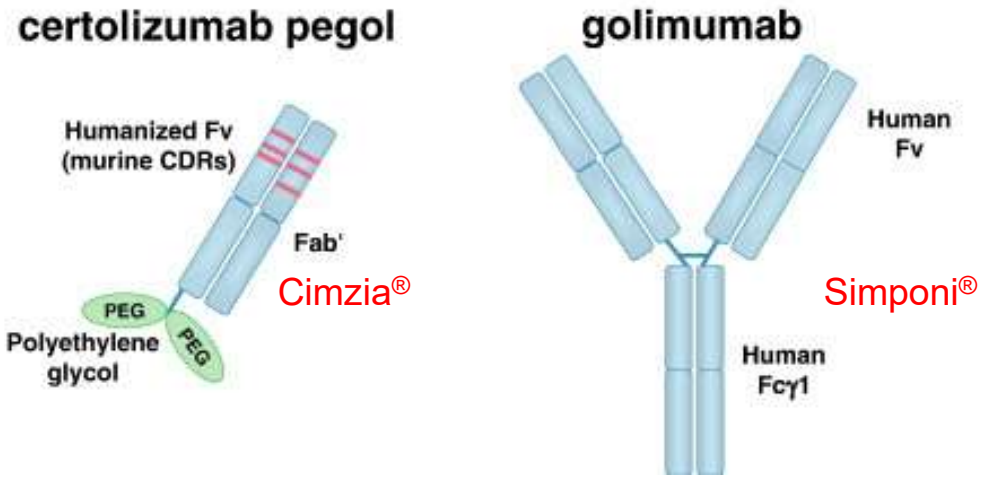
anti-TNF biologicals



Approved for treatment of IBD in Europe

Induction followed by maintenance therapy

Treatment cost: 8.000-15.000€/year

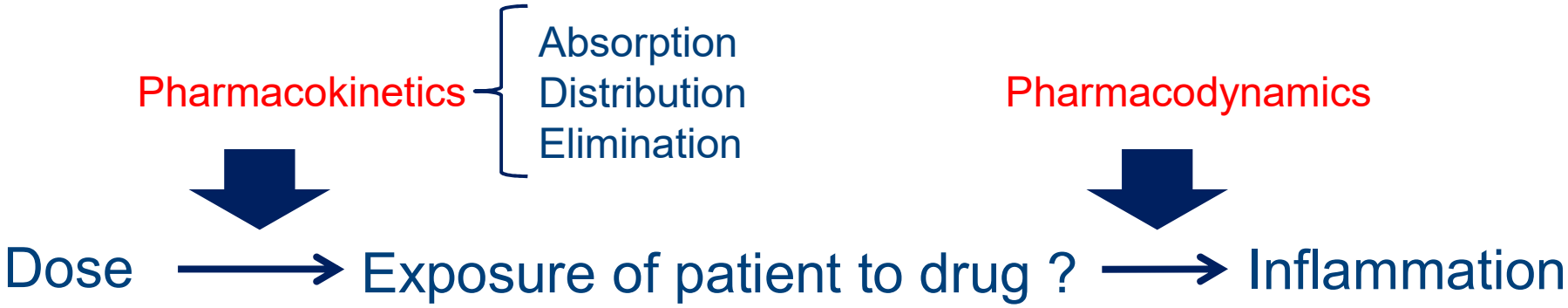


ann.gils@kuleuven.be

Tracey D. *et al.*, Pharm & Ther 2008; 117: 244-79

KU LEUVEN

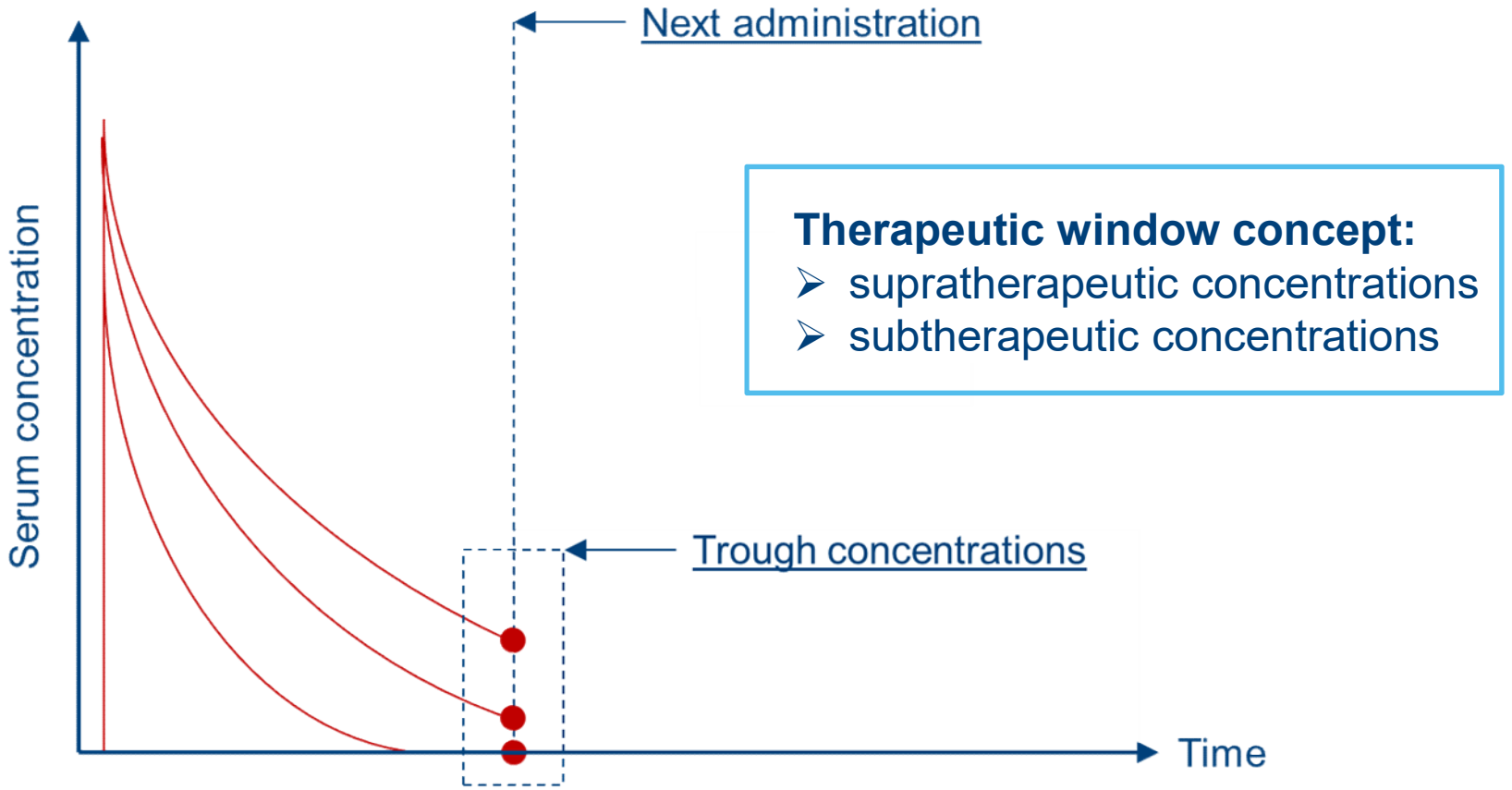
Pharmacokinetics/Pharmacodynamics



ann.gils@kuleuven.be

KU LEUVEN

Pharmacokinetic variability-IV drug



Therapeutic window concept:

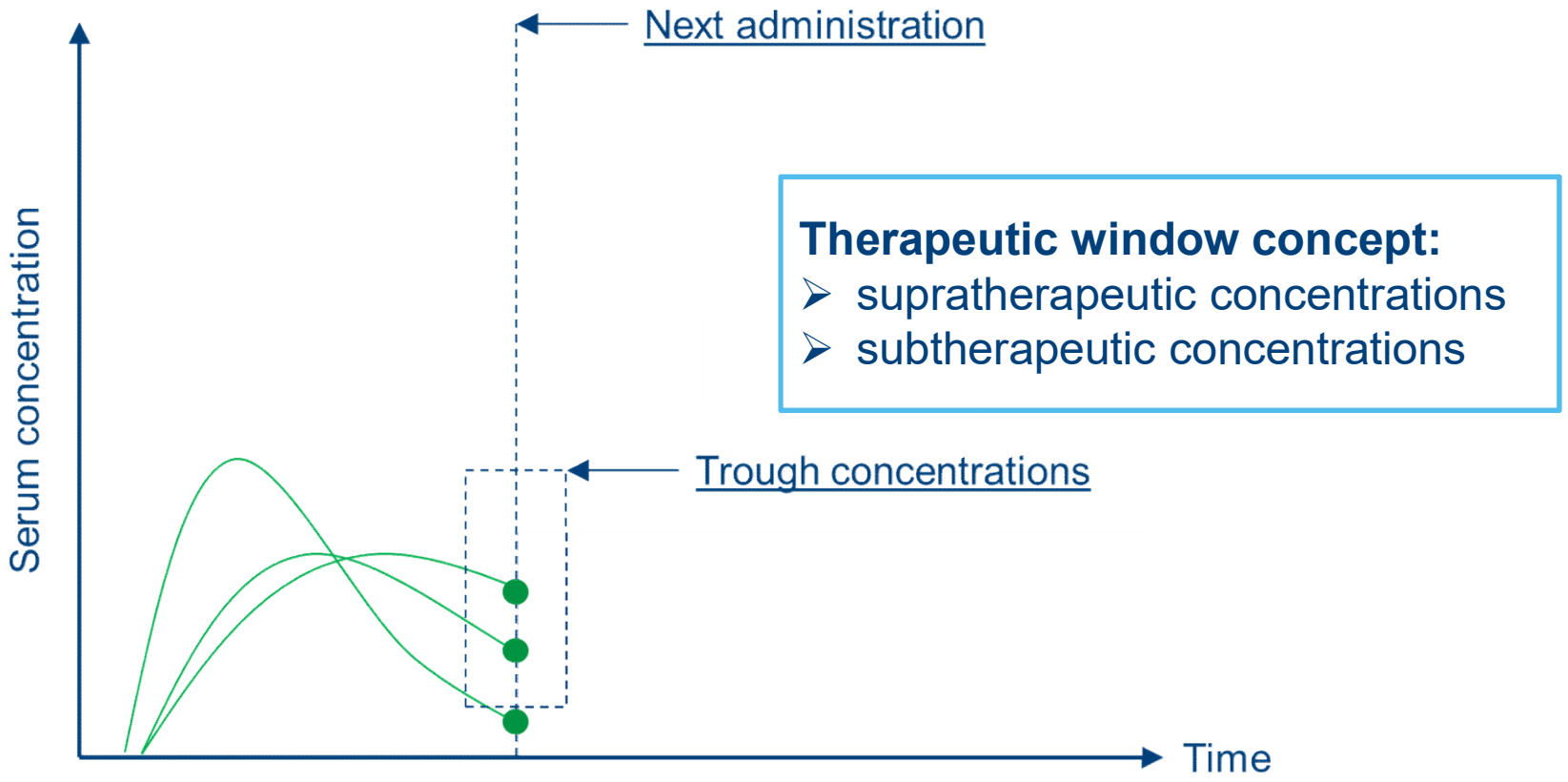
- ➢ supratherapeutic concentrations
- ➢ subtherapeutic concentrations

PLHUM170113

ann.gils@kuleuven.be

KU LEUVEN

Pharmacokinetic variability-SC drug

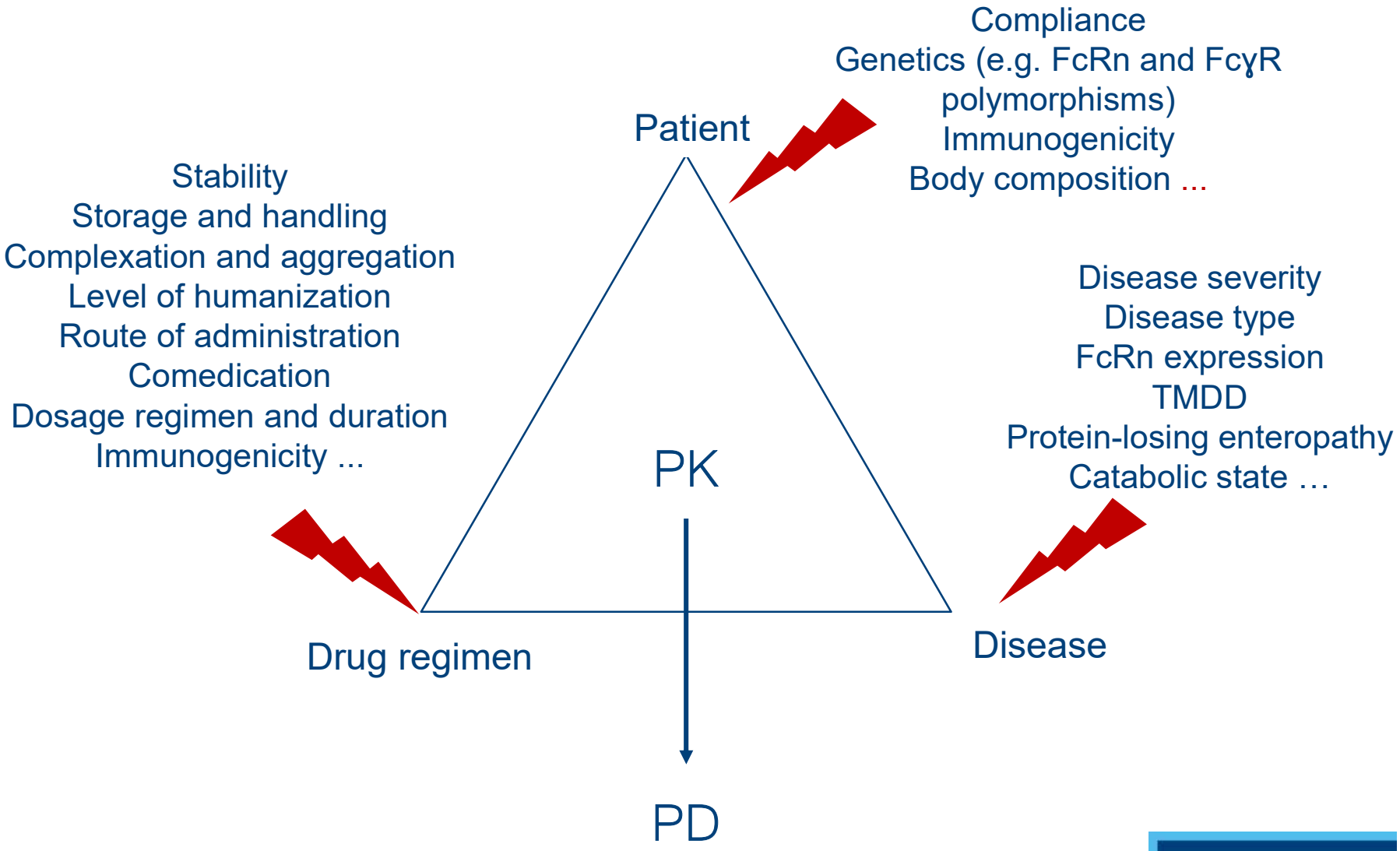


PLHUM170113

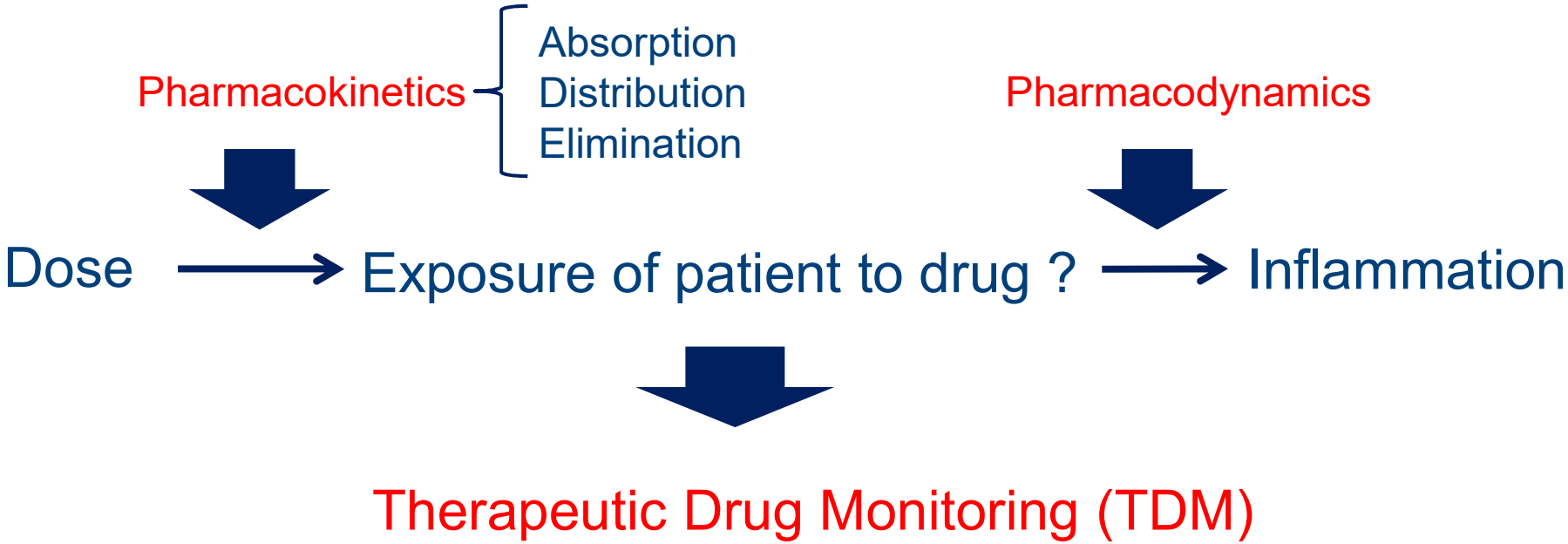
ann.gils@kuleuven.be

KU LEUVEN

What causes PK variability?



Pharmacokinetics/Pharmacodynamics

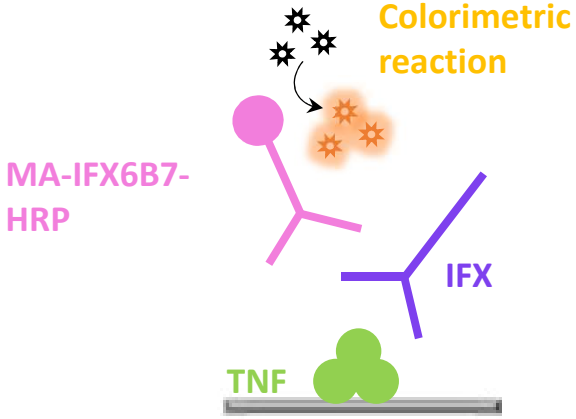


ann.gils@kuleuven.be

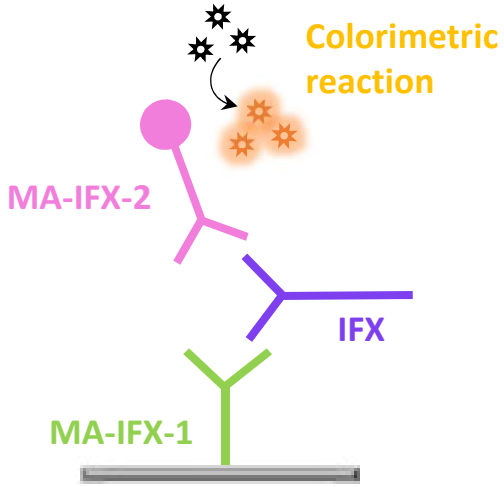
KU LEUVEN

TDM: How to measure? ELISA

TNF coated



MA/MA combination



- infliximab, adalimumab, golimumab: both TNF coated and MA/MA ELISA have been developed. Van Stappen T *et al.*, TDM 2015; Bian S *et al.*, JBPA 2016, Detrez I *et al.*, JCC 2016
- TNF coated ELISA is used in CE-labelled kit (Ridascreen-R-biopharm)

ann.gils@kuleuven.be

KU LEUVEN

TDM: How to measure? rapid assays

ELISA:

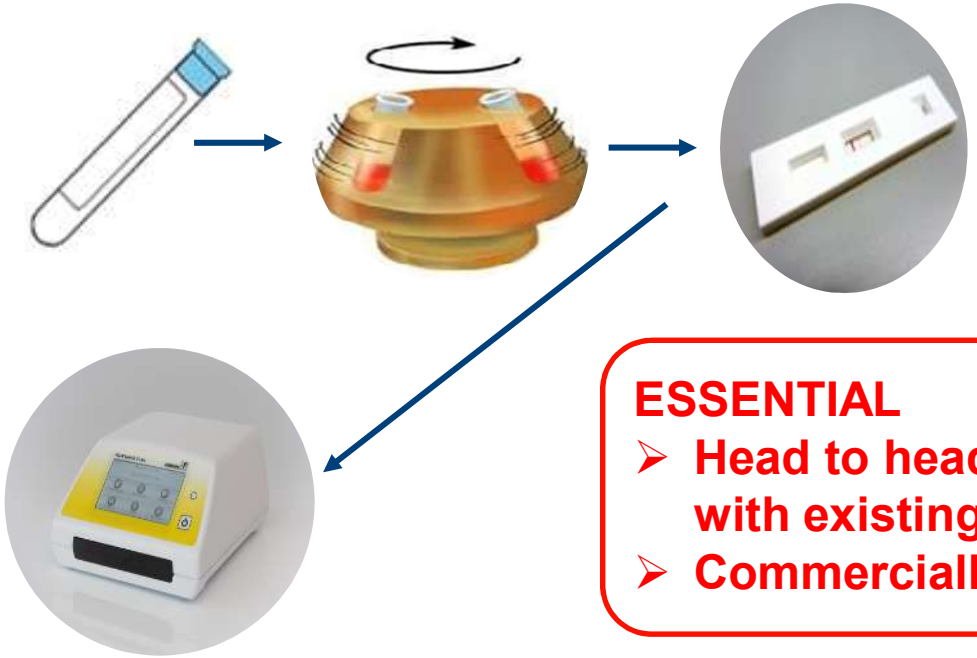
- Requires time : approximately 2h
- Requires laboratory equipment or transport to central laboratory
- Requires multiple samples in order to be cost-efficient
- Long time to result time

Rapid assays:

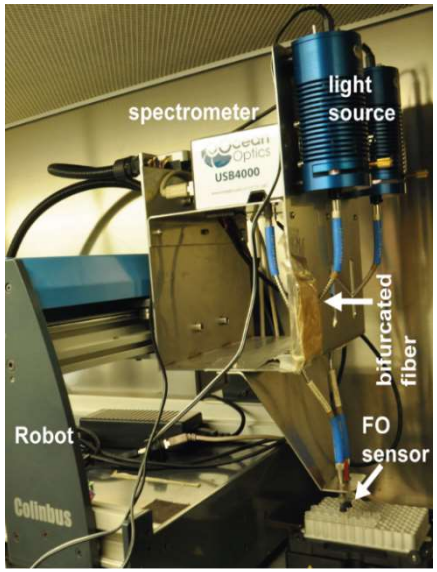
- Lateral flow technology — Van Stappen T *et al.*, Clinical and Translational Gastroenterology 2017
- Fiber optic surface plasmon Resonance: FO-SPR — Lu J *et al.*, Biosens Bioelectron 2016; Lu J *et al.*, Anal Chem 2017

Increase the speed of TDM: rapid assays

- **Lateral flow technology** (Van Stappen T *et al.*, Clin Transl Gastro 2017)



- **Fiber optic Surface Plasmon Resonance (**FO-SPR) (Lu J *et al.*, Biosens Bioelectron 2016; Lu J *et al.*, Anal Chem 2017)



ESSENTIAL
- **Head to head comparisons with existing assays**
- **Commercially available**

Ridaquick infliximab monitoring (R-biopharm)

ann.gils@kuleuven.be

KU LEUVEN

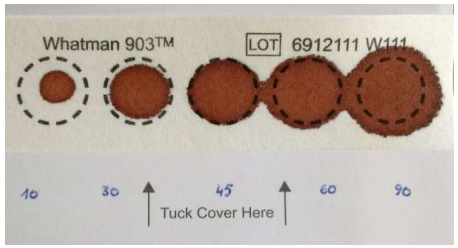
Increase the speed of TDM: rapid assays

Improvement possible?

- **Full blood** *versus* **serum**
  - Validation with existing assays using serum

Other alternative forms

- **Dry blood spots** collection followed by extraction: increases speed and accessibility of collecting samples

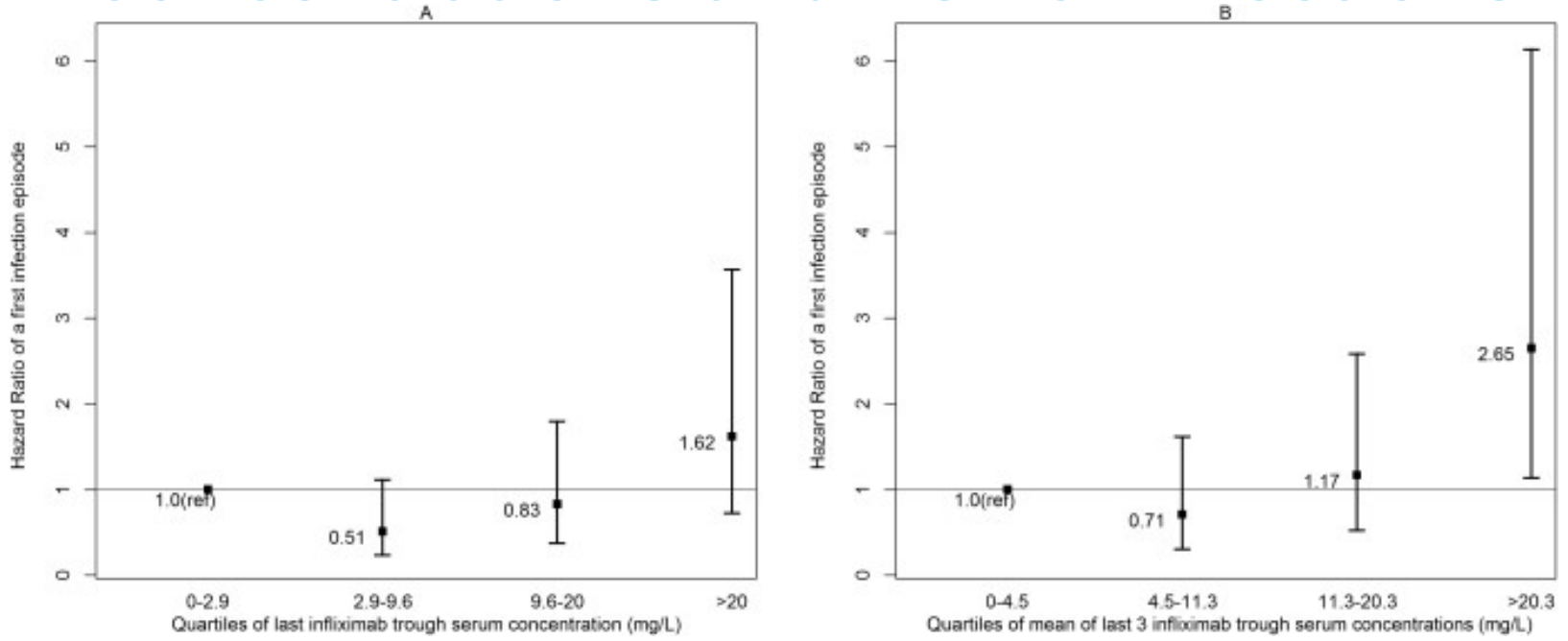


- **FO-SPR technology**: all matrices (full citrated blood, plasma, serum, dry blood spot extracts) validated (Lu J *et al.*, Anal Chem 2017)

ann.gils@kuleuven.be

KU LEUVEN

Relationship between high serum infliximab concentrations and risk of infections



Estimated hazard ratios and 95% confidence intervals for a first infection episode in spondyloarthritis patients in each quartile of trough serum IFX concentration (A) or mean of the last 3 trough serum concentrations (B) Bejan-Angoulvant T *et al.*, Arthritis & Rheumatology 2017

- High IFX concentration (>15-20 µg/ml) are correlated with a higher risk of first infection episode

ann.gils@kuleuven.be

KU LEUVEN

Relationship between immunogenicity and low concentrations of anti-TNF biologicals

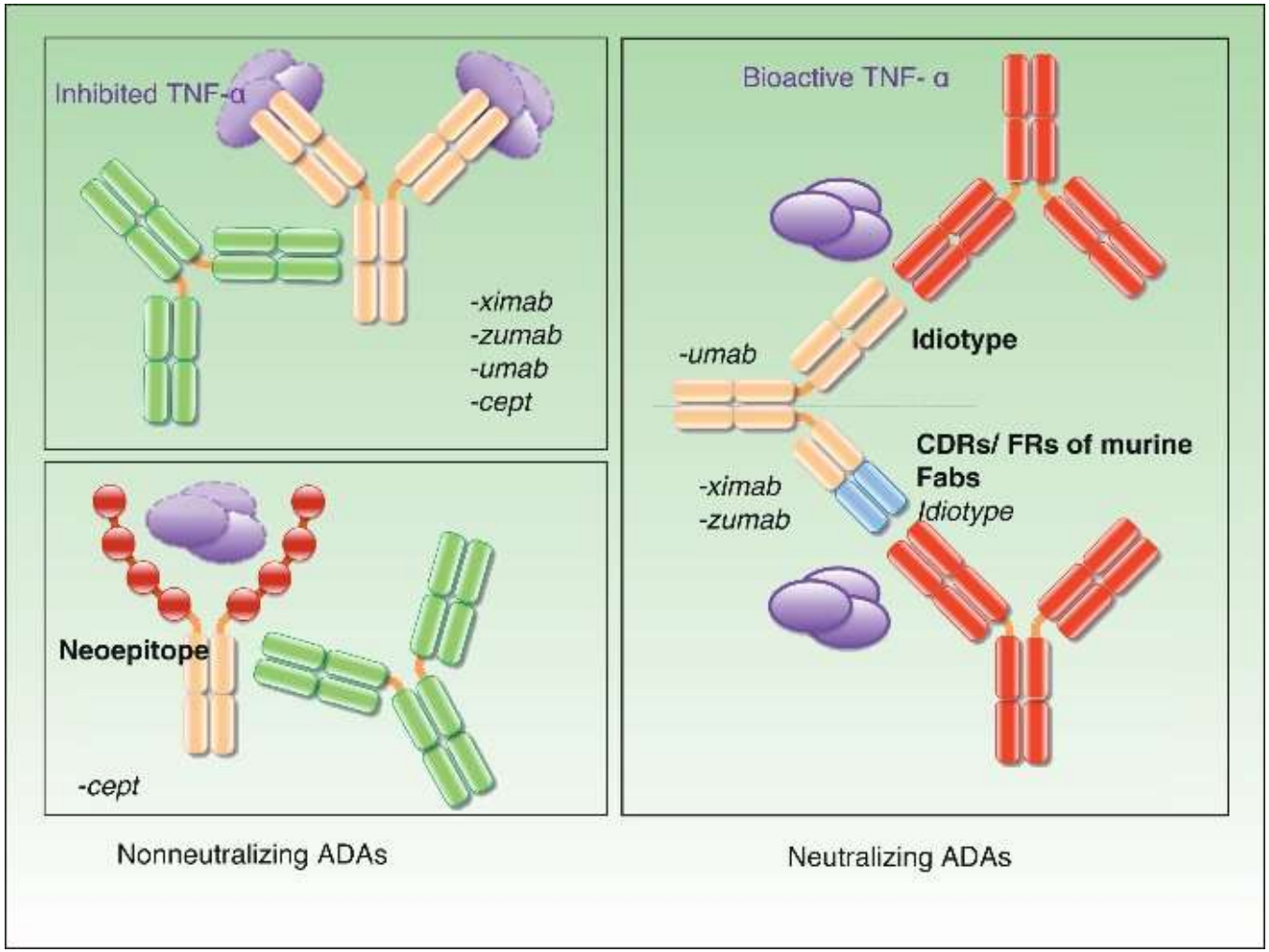
- All biologicals can evoke an immune response
  - infliximab: chimeric
  - adalimumab & golimumab: fully human

- Resulting in a formation of anti-drug antibodies (ADA)
  - Infliximab: > 90% neutralizing ADA
  - Adalimumab: 97% neutralizing ADA

Van Schie K *et al*., Ann Rheum Dis 2015

ann.gils@kuleuven.be

nonneutralizing *versus* neutralizing ADA

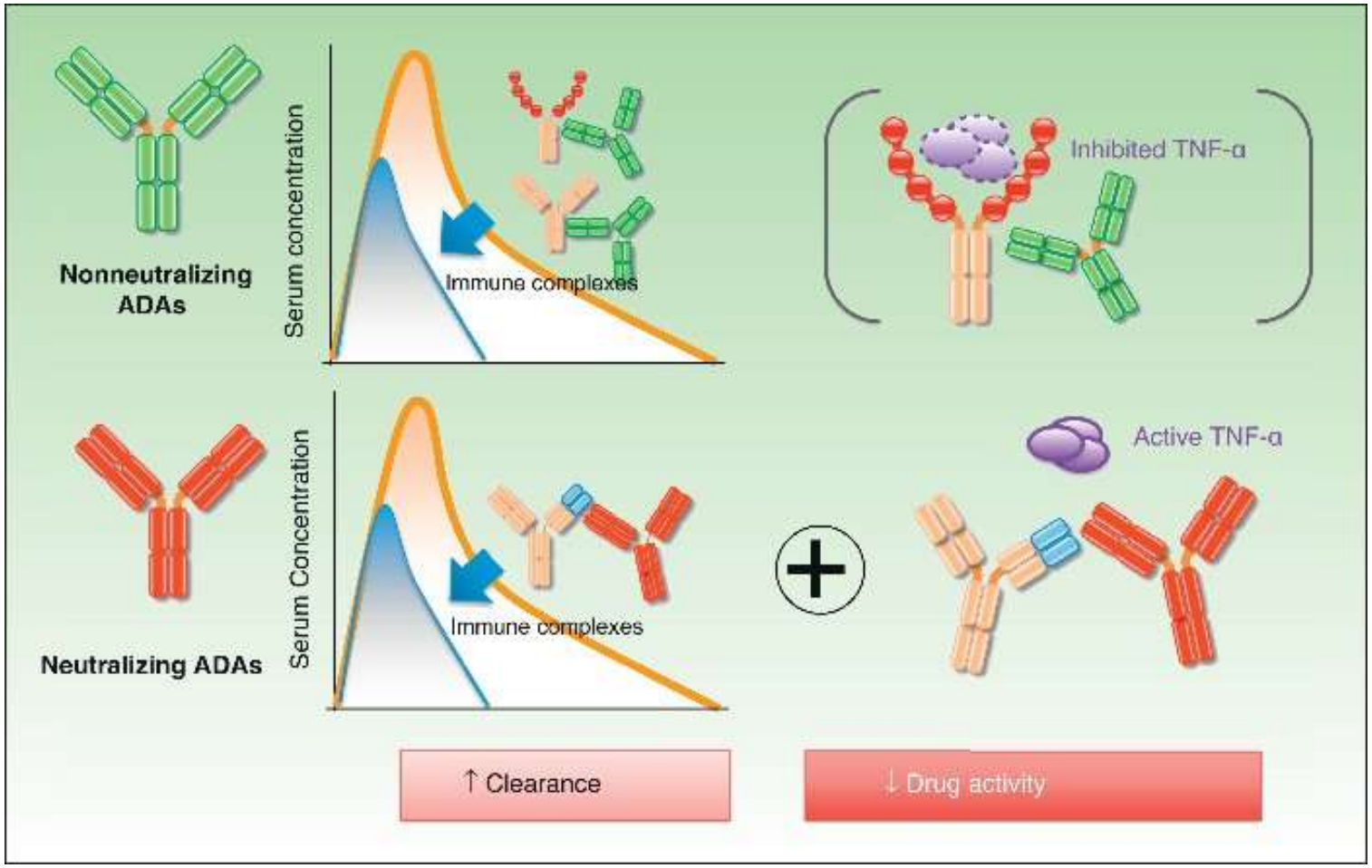


Carrascosa JM, Actas dermisifiliogr. 2013

ann.gils@kuleuven.be

KU LEUVEN

The effect of (non)neutralizing ADA?



Carrascosa JM, Actas dermisifiliogr. 2013

ann.gils@kuleuven.be

KU LEUVEN

Relationship between immunogenicity and low concentrations of anti-TNF biologicals

- Transient *versus* persistent ADA
  - persistent ADA are associated with loss of clinical response whereas transient ADA are not

    Vande Casteele N *et al*., Am J Gastroenterol 2013

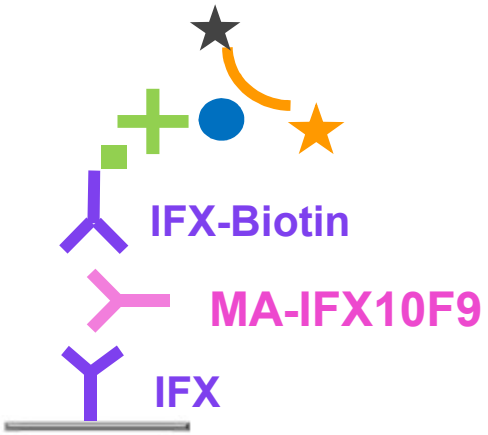
- Size and titer of immune complexes
  - large immune complexes: favor further ADA induction through complement activation and larger uptake by antigen presenting cells: large immune complexes are found in patients with acute severe infusion reactions

    Van Schouwenburg P *et al.,* Nat Rev Rheumatol 2013

ann.gils@kuleuven.be

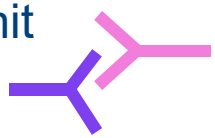
How to measure ADA : bridging ELISA

Van Stappen T *et al,*. IBD 2015



Drug sensitive: in presence of excess of IFX, ATI can not be detected

➡ only determine ATI when IFX is below detection limit



IFX: infliximab; ATI: antibodies towards infliximab

KU LEUVEN
ann.gils@kuleuven.be

ADA assays: bridging ELISA: drug tolerant?

Van Stappen T *et al.*, IBD 2015
Van Stappen T *et al.*, DTA 2016

Drug-sensitive *versus* drug-tolerant assay

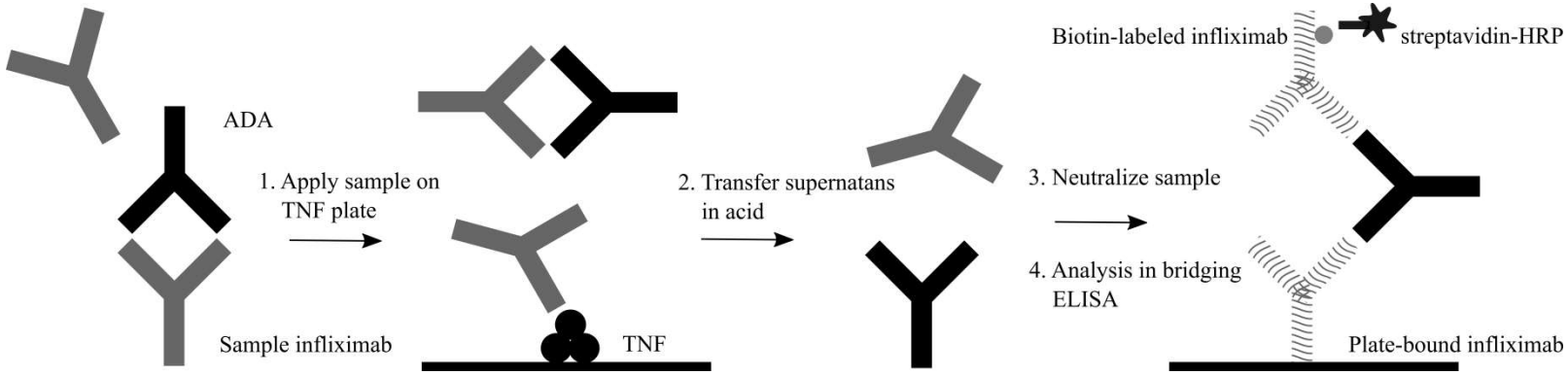
No detection of ADA in presence of drug

Detection of ADA in presence of drug

Pretreatment steps: removal of excess of drug & dissociation of drug/anti-drug complex

Bridging assay

Drug tolerant protocol



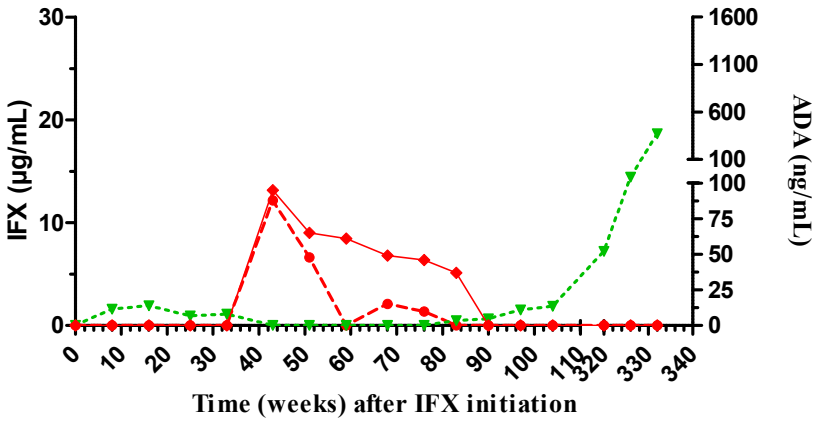
ann.gils@kuleuven.be

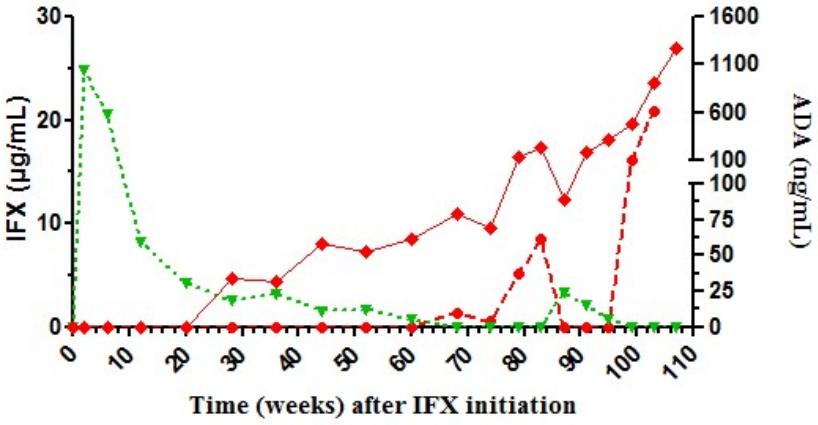
KU LEUVEN

ADA assays: bridging ELISA: drug tolerant?

Van Stappen T *et al*., DTA 2016

Comparison of the bridging ELISA with and without the sample pre-treatment protocol for the detection of anti-drug antibodies (ADA) in two patients treated with infliximab.





The infliximab concentration is presented as a dotted line with triangles indicating the date of infusion. ADA levels are represented with a dashed line (circles indicating the date of infusion) and a full line (diamonds indicating the date of infusion) for the bridging ELISA without and with the sample pretreatment protocol, respectively.

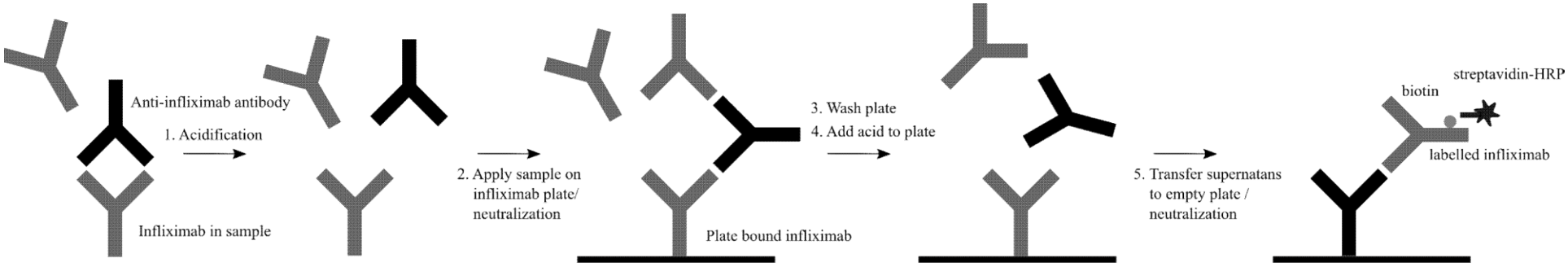
- predict formation of ADA providing opportunities for early treatment optimization

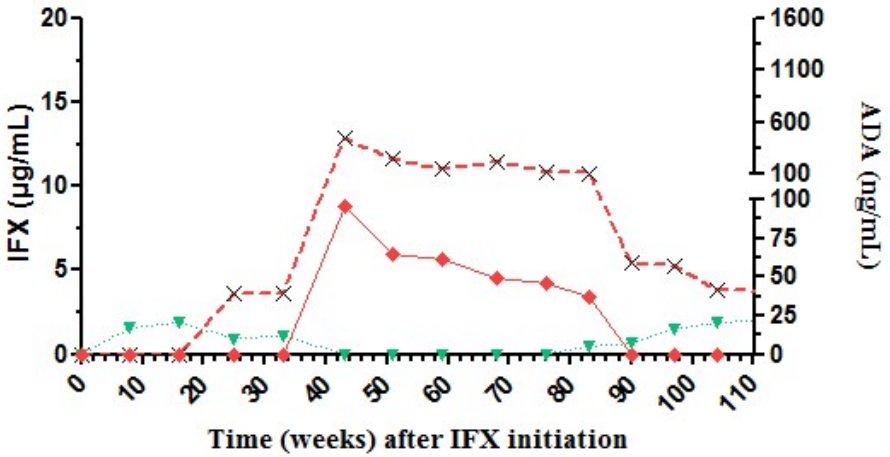
ann.gils@kuleuven.be

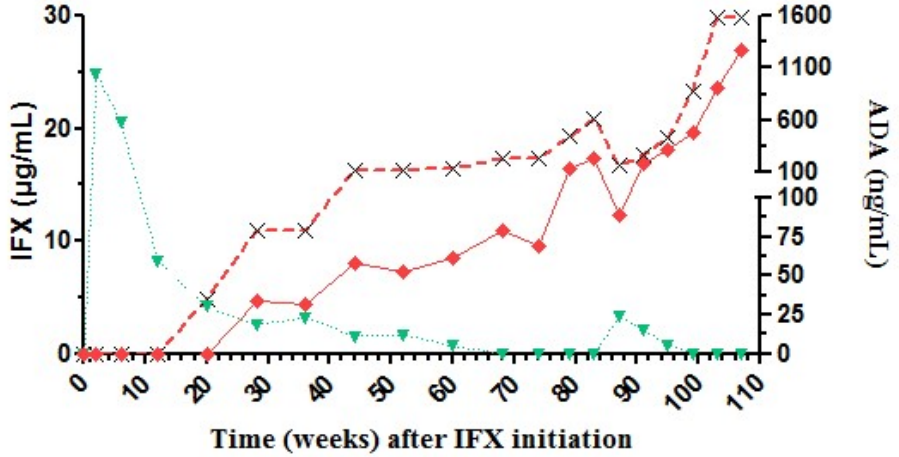
KU LEUVEN

ADA assays: Affinity Capture ELISA: increase drug tolerance

Van Stappen T *et al.,* Clin Transl Gastro 2017, Van Stappen T *et al*., Gut 2017







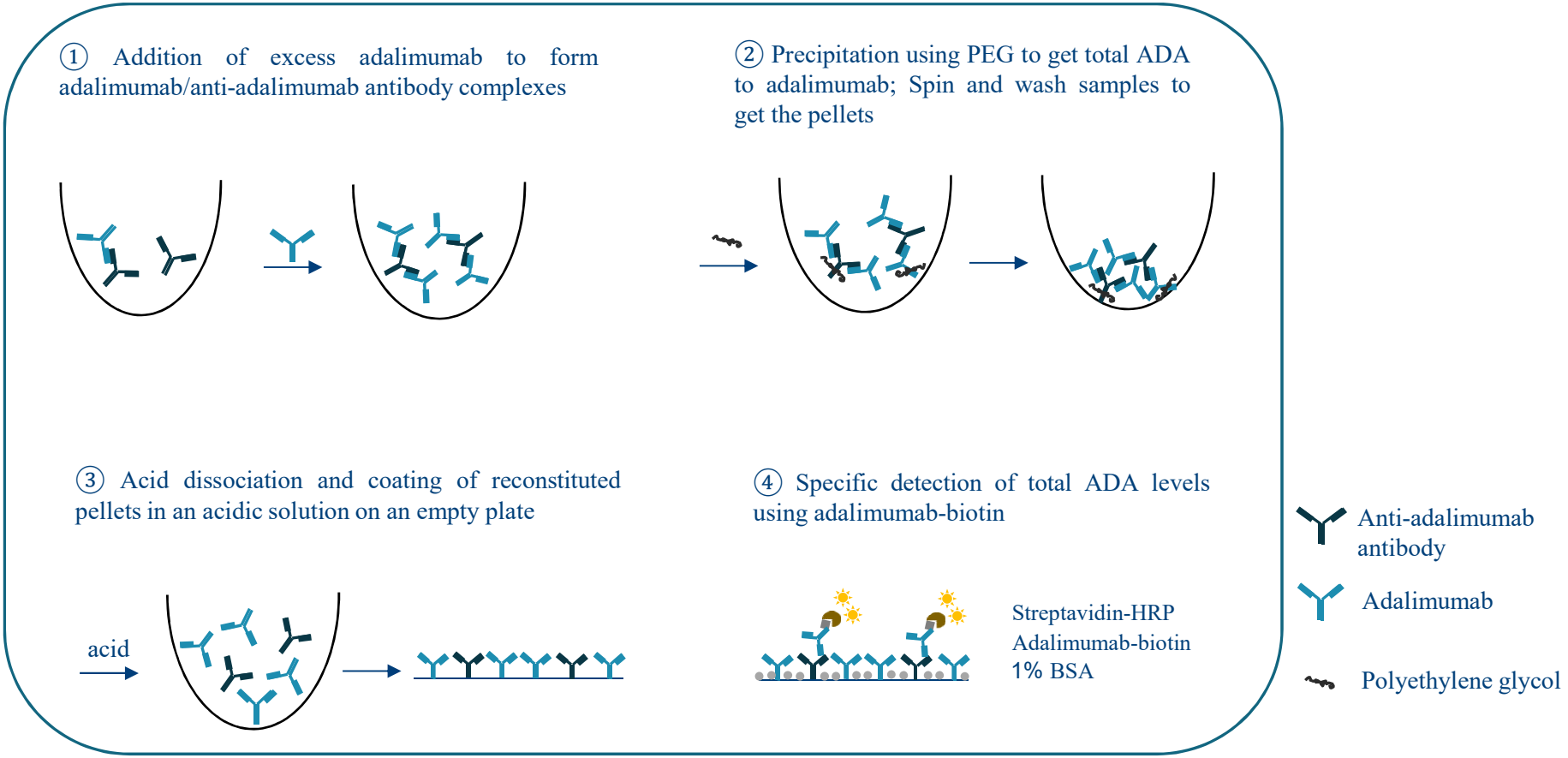
- **No bridging format**
- **Increased drug tolerance**

ann.gils@kuleuven.be

KU LEUVEN

ADA assays: drug resistant

Bian S *et al.*, AAPS 2017



- **No bridging format**
- **Drug resistant assay**

ann.gils@kuleuven.be

KU LEUVEN

How to monitor ADA formation

Drug-sensitive bridging assay
(Bian S *et al*., J Pharm Biomed Anal 2016; Van Stappen T *et al*., Inflam Bow Dis 2016; Detrez I et al., J Crohn Col 2016)

Drug-tolerant bridging assay.
(Van Stappen T *et al*., Drug Test Anal 2016)

Drug-tolerant ACE assay
(Detrez I *et al*., JCC 2016; Van Stappent T *et a*l., Clin Transl Gastro 2017, Van Stappen T *et al*., Gut 2017)

Drug-resistent PANDA assay
(Bian S *et al*., AAPS 2016)

Increased incidence of anti-drug antibody detection

Occurrence of transient ⬇ and persistent antibodies ⬆

Detection of ADA is not always associated with loss of response

ann.gils@kuleuven.be

KU LEUVEN

How to mitigate ADA formation

- De-immunizing the molecule
  - Removing or masking or substitution known immunogenic epitopes Jawa V *et al*., Clinical Immunol 2013
- Avoid patients with high disease activity and comorbities
  - In patients with acute bacterial infections or systemic inflammatory activity, dendritic cells may express higher levels of co-stimulatory molecules, decreasing threshold for T cell activation Atzeni F *et al.,* Autoimmunity reviews 2013
- Add concomitant drugs
  - Methotrexaat reduces ADA due to immune suppressive nature or due to anti-inflammatory effect Ungar B *et al*., AP&T 2017

ann.gils@kuleuven.be

How to mitigate ADA formation

- Adapt therapeutic regimen
  - tolerance induced by high dosing van der Maas A *et al.*, BMC Musculoskelet Disord 2012

- Desensitization or tolerance techniques
  - Gradually increasing doses to reach the full treatment dose over approximately 4 to 6 hours Mourad A *et al.*, 2015 Ann Allergy Asthma Immunol

ann.gils@kuleuven.be

Acknowledgements

Laboratory for Therapeutic and Diagnostic Antibodies http://pharm.kuleuven.be/biotech
Leuven IBD research group http://www.ibd-kuleuven.com

Prof Séverine Vermeire
Prof Marc Ferrante
Prof Gert Van Assche
Prof Paul Rutgeerts

ann.gils@kuleuven.be

KU LEUVEN