Active immunotherapy in neurodegenerative disease: how to define antibody responders ?

Stefanie Siegert | EBF open symposium, November 2023

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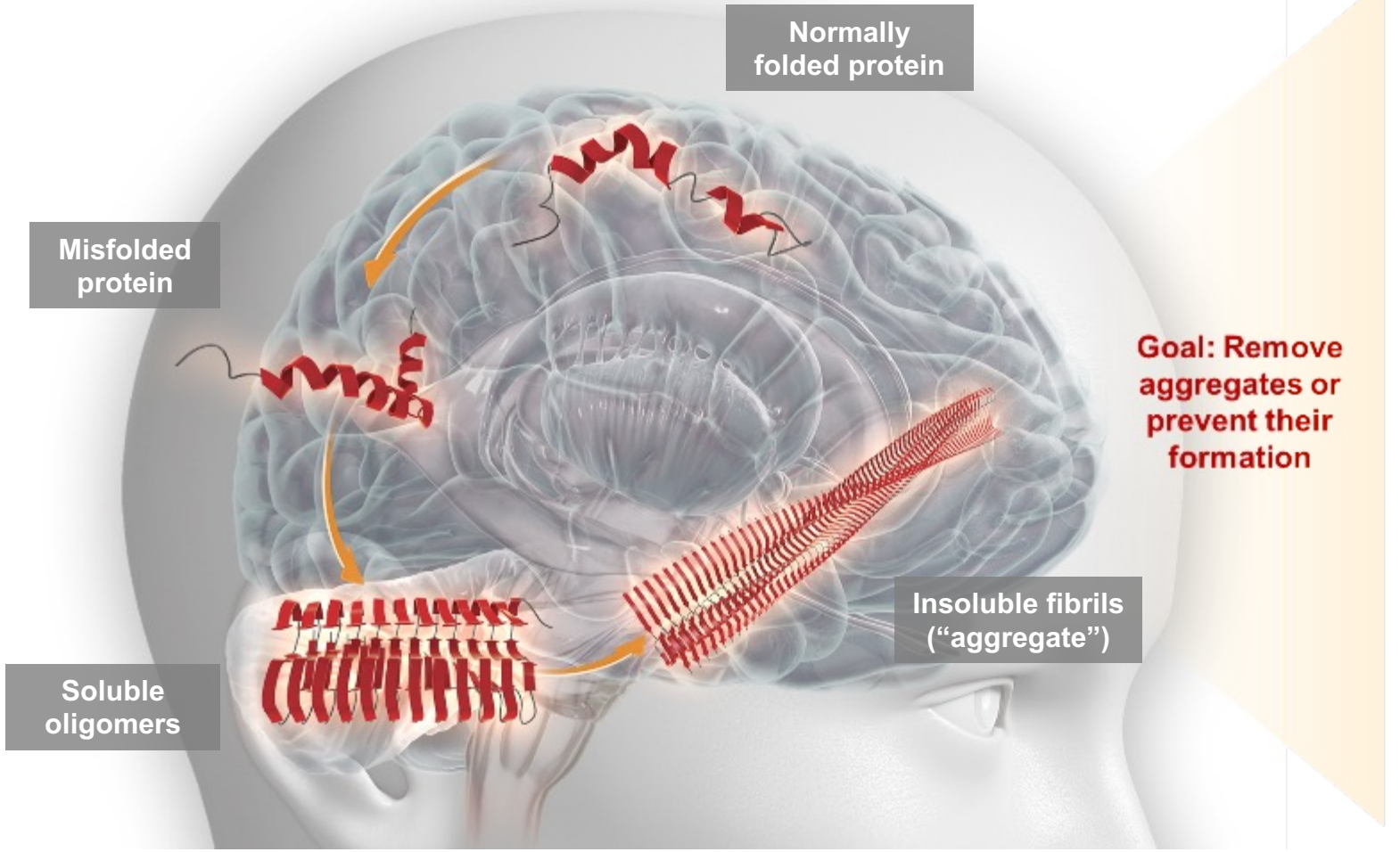
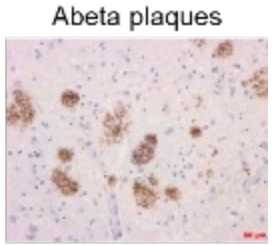
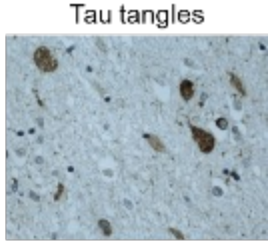
Misfolded proteins: Leading causes of neurodegenerative diseases

Abeta, Tau, a-synuclein, and TDP-43[1] are important NDD[2] drug targets

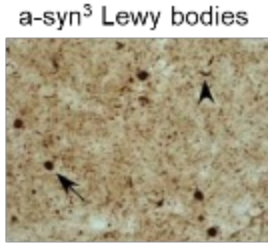




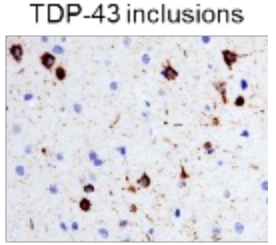
Alzheimer's disease



Alzheimer's disease



Parkinson's disease



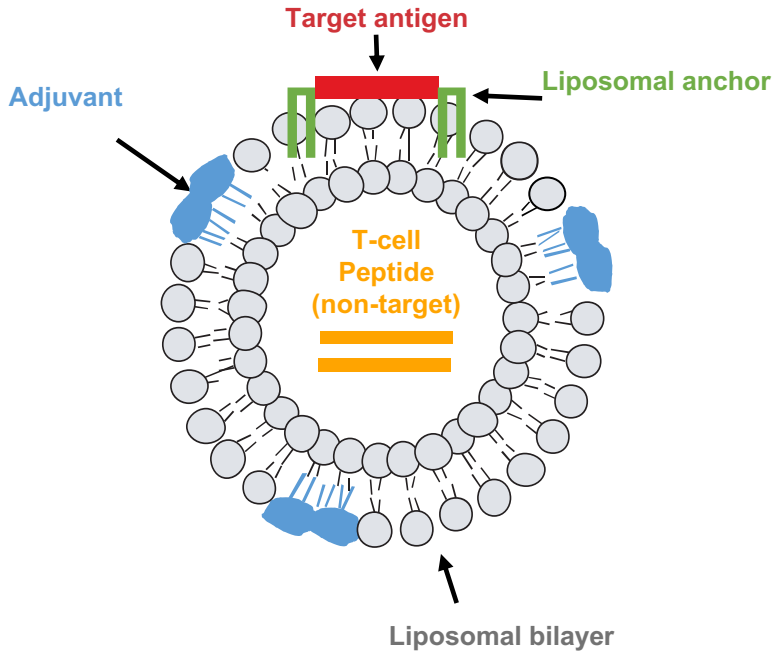
LATE[4] dementia

ALS[5]

Refs: Soto 2003, http://www.alz.org/brain; Nag *et al.* Acta Neuropathologica Communications (2018) 6:33;
(1) TAR DNA-binding protein 43; (2) Neurodegenerative disease; (3) a-synuclein; (4) Limbic-predominant age-related TDP-43 encephalopathy; (5) Amyotrophic lateral sclerosis

Disruptive potential of SupraAntigen®

Active immunotherapies delivering superior results in neurodegenerative diseases



Target-specific antibody response

Helper T-cells safely engaged **(target-unrelated)**

Unprecedented Clinical Performance

Immunogenicity	✓
Target & conformation specificity	✓
Avidity increase over time	✓
Sustainable response	✓
Boostable response	✓

- Robust immunogenicity and strong safety demonstrated in humans
- Evidence for lasting immune response supporting a disease prevention approach

Immunogenicity assays following active immunotherapy

Bioanalytical strategy to assess wanted immunogenicity against self-antigens

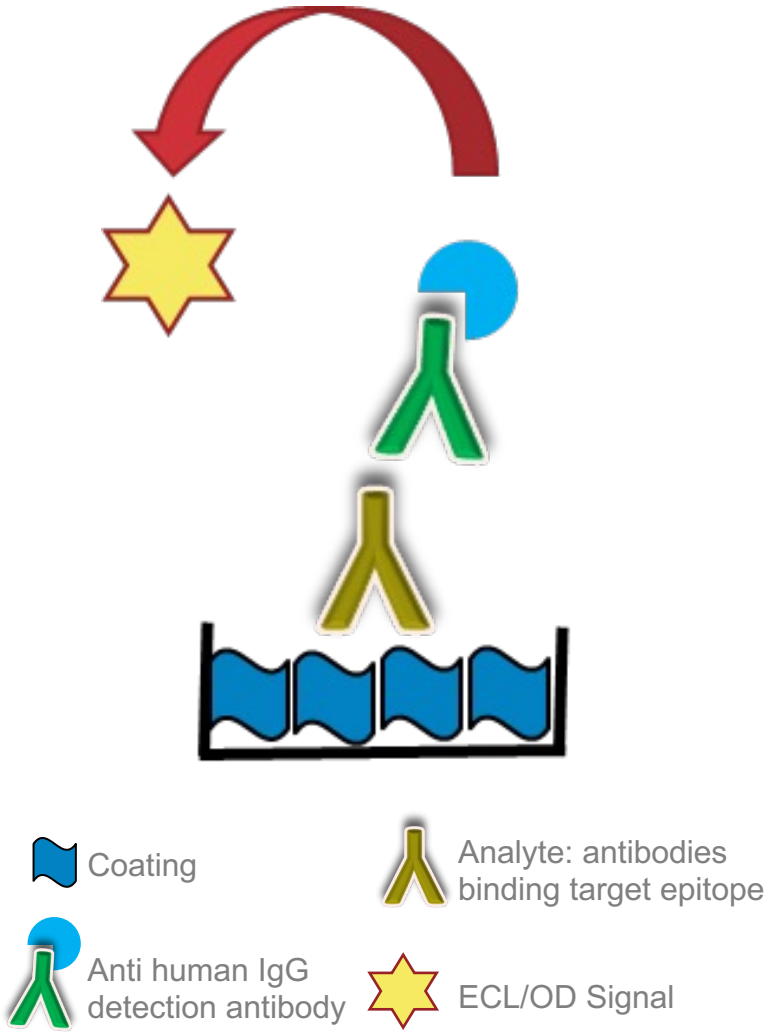
Challenges

1. Antibodies can be present before immunization → specific definition of responders
2. Even a low response against self-antigens can be relevant → highly sensitive assay are needed
3. Long duration of clinical trials (3-4 years) with frequent interim analysis → robust, assay that are stable over a long time are needed

No specific guidelines exists regarding bioanalytical assays for active immunotherapy against self-antigens

Immunogenicity assays following active immunotherapy

Typical ligand binding assay set up to determine antibody titers following immunization



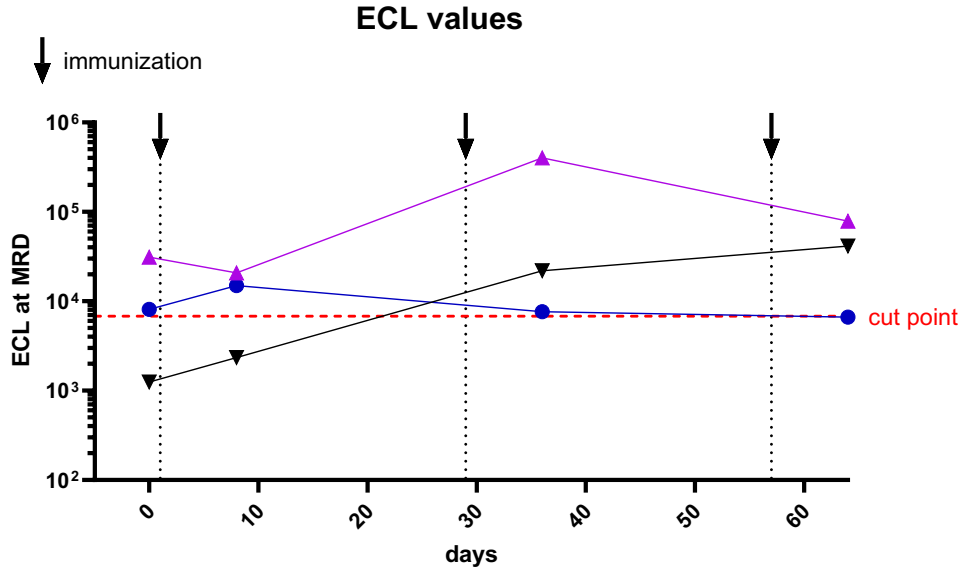
- A **standard curve*** is included on each plate to back-calculate the antibody titers in samples (≠ end-point titers)
- Samples and QC are measured in **serial dilution**
- 2 levels of QC* on each plate for plate acceptance and follow up of assay performance over time

*polyclonal non-human primate serum or monoclonal antibody

Responder definition in immunogenicity assays

Classical cut point approach

- Cut point = OD/ECL value determined during validation so that 95% of naïve human serum are evaluated as negative
- Samples at MRD* with an OD/ECL above the cut point are considered positive
- BUT in presence of endogenous auto-antibodies this doesn't reflect properly the biological response



	Responder based on cut point			
ID	predose	D8	D36	D64
1	+	+	+	+
2	-	-	+	+
3	+	+	+	-

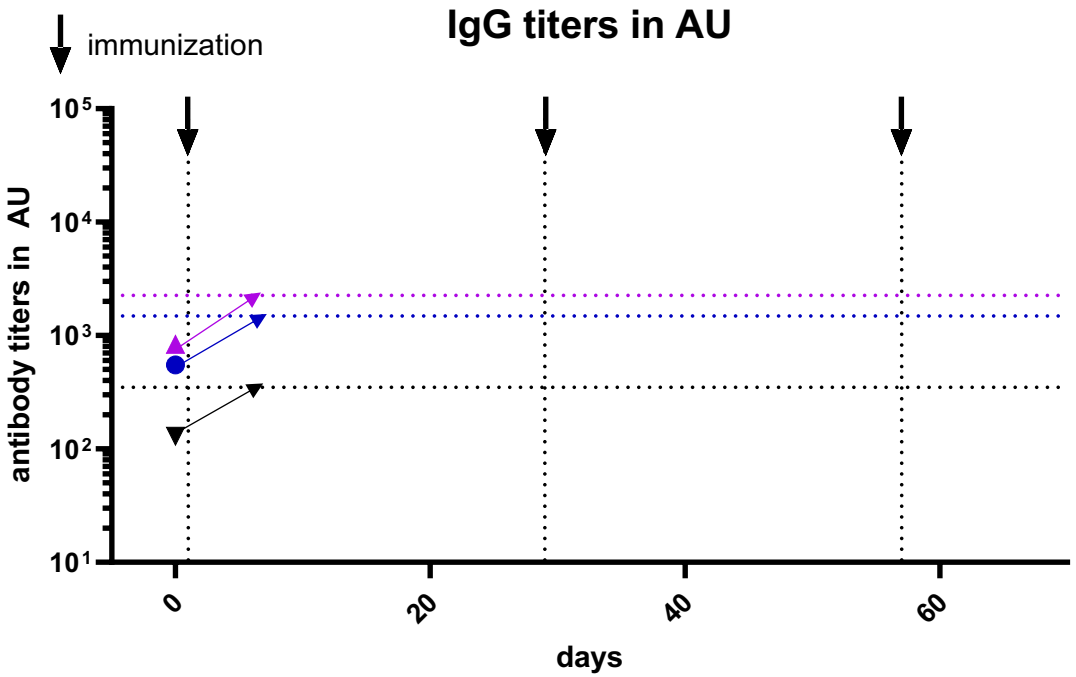
- An alternative approach is needed to define responders

* MRD = minimal required dilution

Responder definition in immunogenicity assays

Threshold approach

- For each participant, an individual threshold is defined based on the pre-treatment titer
- Only titers post-treatment that are above the individual threshold are considered positive



Pre-treatment baseline titers is multiplied by the threshold factor to determines the individual threshold

Responder definition in immunogenicity assays

Threshold approach

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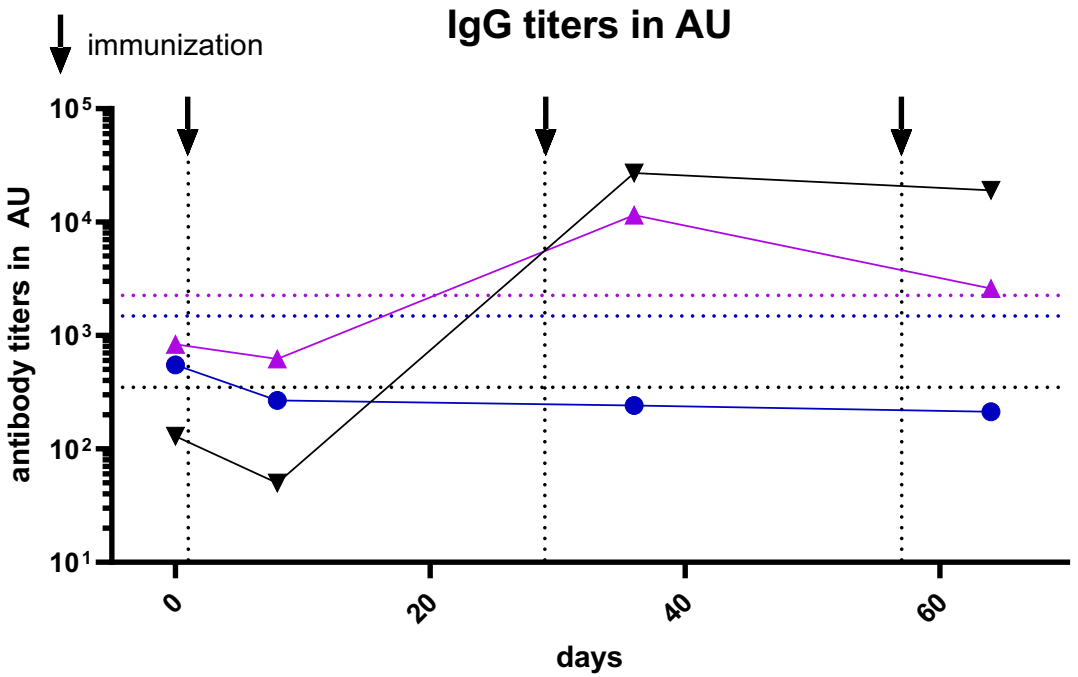
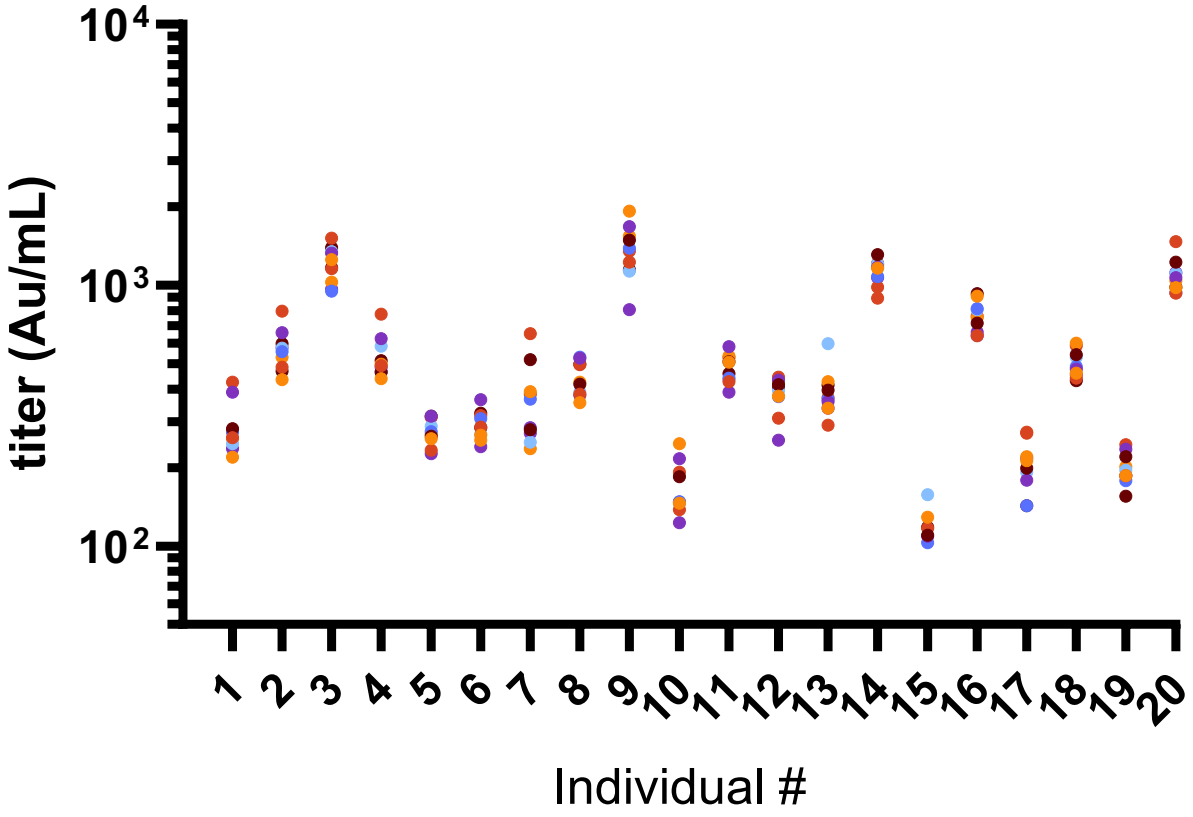


	Responder based on threshold			
ID	predose	D8	D36	D64
1	NA	-	+	+
2	NA	-	+	+
3	NA	-	-	-

- Responder definition based on an individual threshold reflects the biological response to the vaccine better compared to a cut point approach

Determination of the threshold factor

- The threshold factor is determined based on the assay precision
- At least 20 individuals (treatment naïve human sera) are measured in 10 separate plates on at least two different days, by at least two different, trained operators

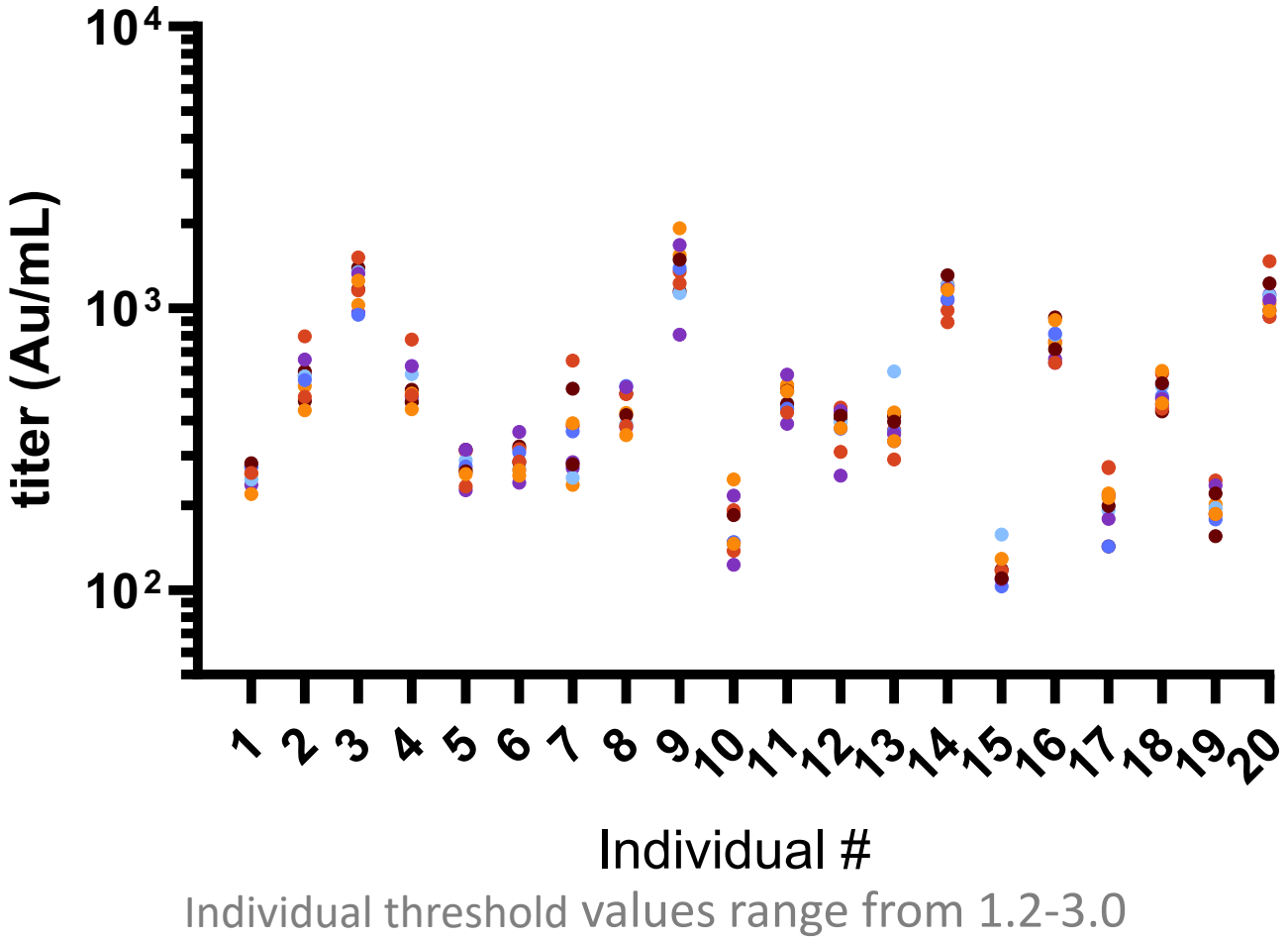


Determination of the threshold factor

- Far outlier values are excluded
- The threshold factor is determined for each individual as

$$\frac{95\ percentile}{average\ of\ the\ two\ lowest\ titers}$$

- Conservative approach: highest individual threshold is used in clinical trial data evaluation



Individual threshold values range from 1.2-3.0

Immunogenicity assays following active immunotherapy

Summary and conclusion

- No clear guidelines for bioanalytical assay characterizing wanted immunogenicity following active immunotherapy are published
- A classical cut point approach is not meaningful to define responders in patients with potential auto-antibodies
- The threshold factor is determined based on assay precision and allows to evaluate whether the difference between the pre-and post-treatment titer of the same patient is truly different

The threshold approach allows to reliably define responders and quantify antibodies titers due to the active immunotherapy, independent of present endogenous auto-antibodies

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