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Novel approaches for a neutralising anti-capsid assay to detect pre-existing antibodies

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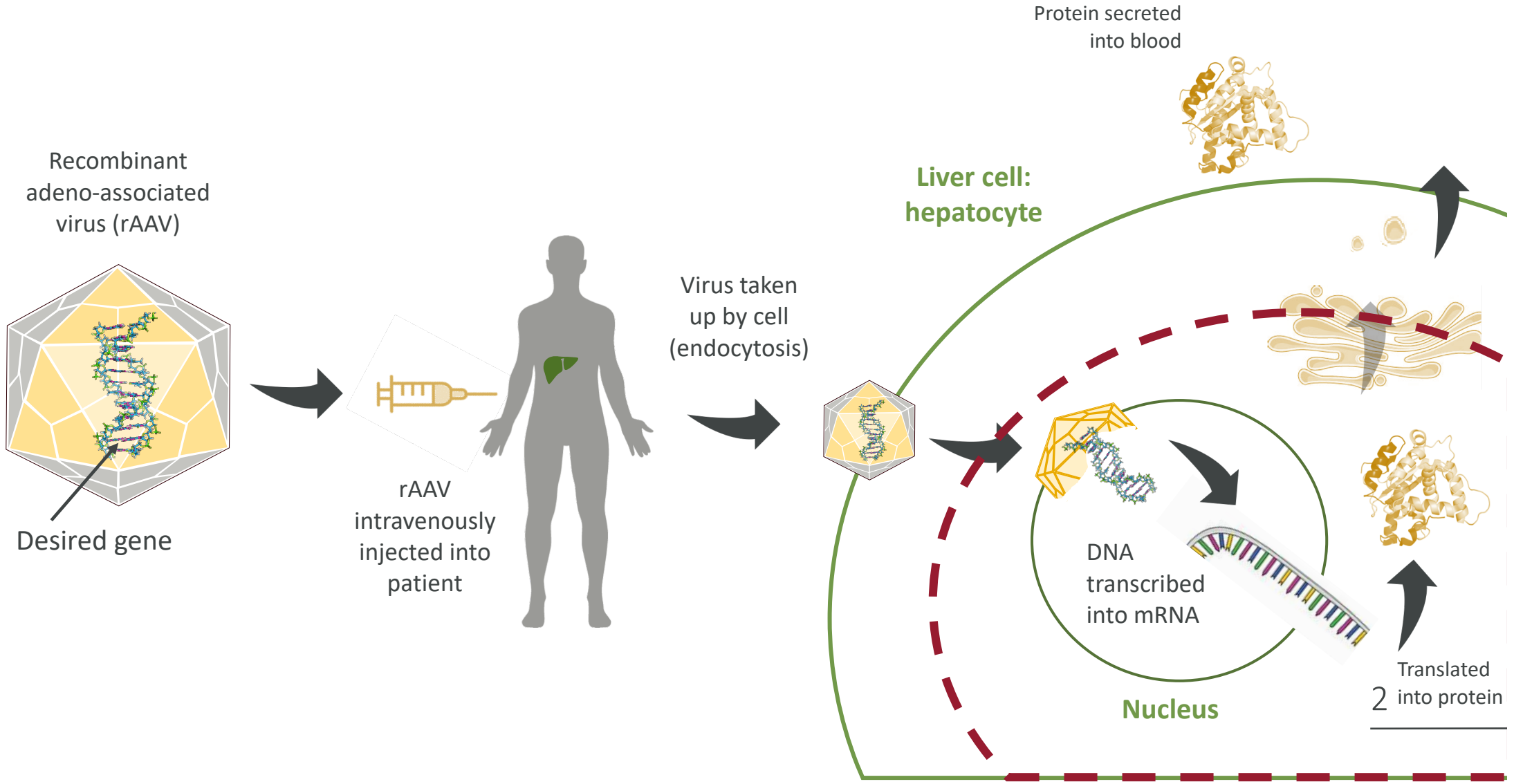
EBF Open Symposium 2021

Barcelona

Adeno-associated virus gene therapy



Golgi apparatus image adapted from https://qsstudy.com/biology/describe-golgi-apparatus. Protein image adapted from https://foodscience-techn.blogspot.com/2014/07/structure-of-protein.html. mRNA, messenger RNA; rAAV, recombinant adeno-associated virus

AAV capsids can trigger a strong immune response

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BioA challenges: anti-capsid antibodies

- Neutralising antibodies (NAbs) to AAV capsids are common in the general population
- NAbs linked to reduced efficacy
- Linked to patient selection
- Companion diagnostic

First-generation assay takes 4 days to complete and employs a FACS readout

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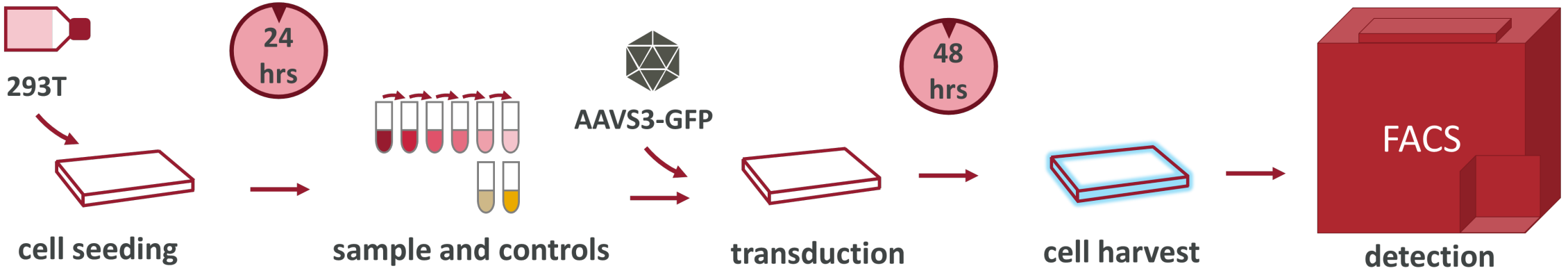
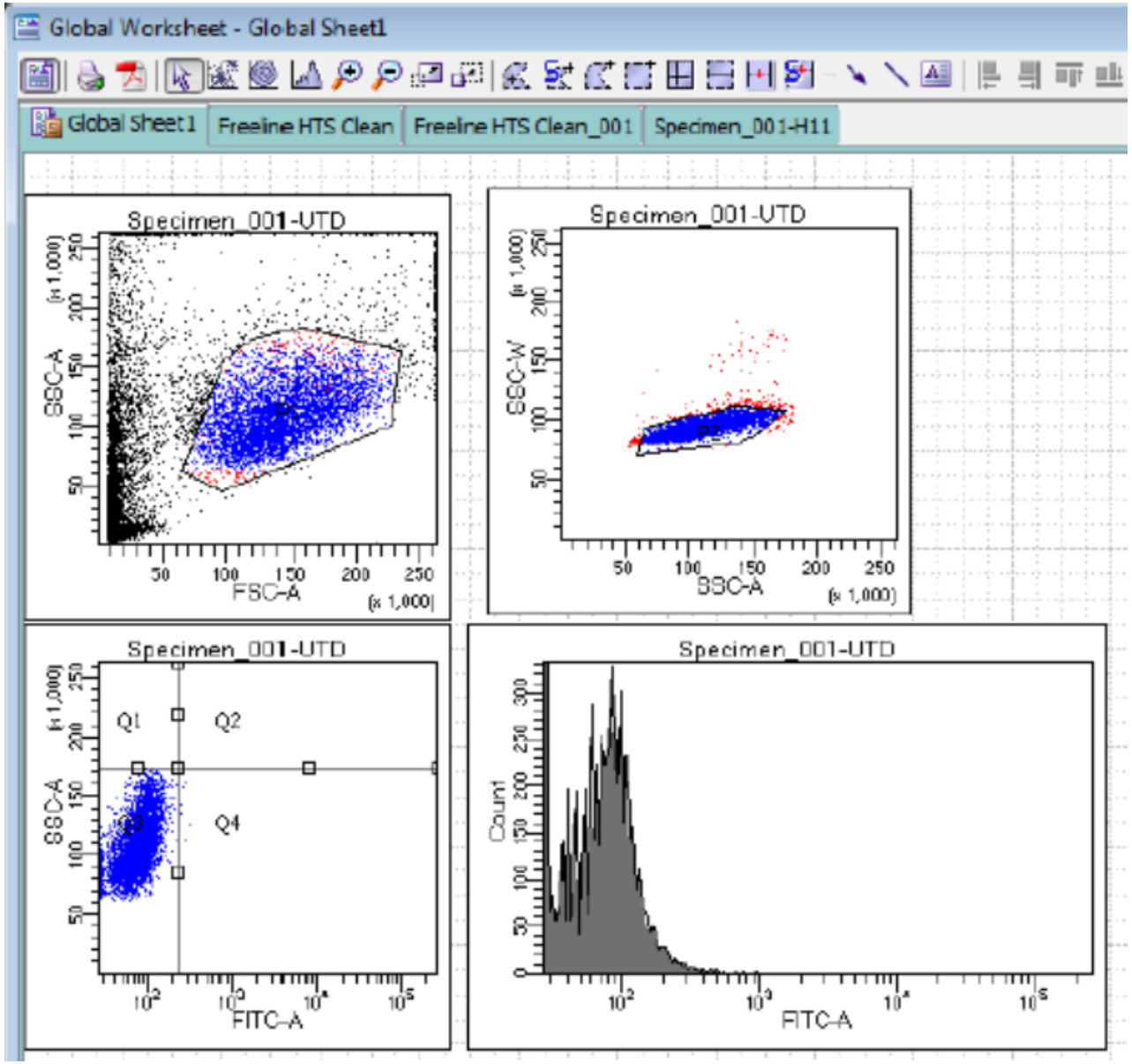


Challenges with FACS readout



Designing a next-generation assay

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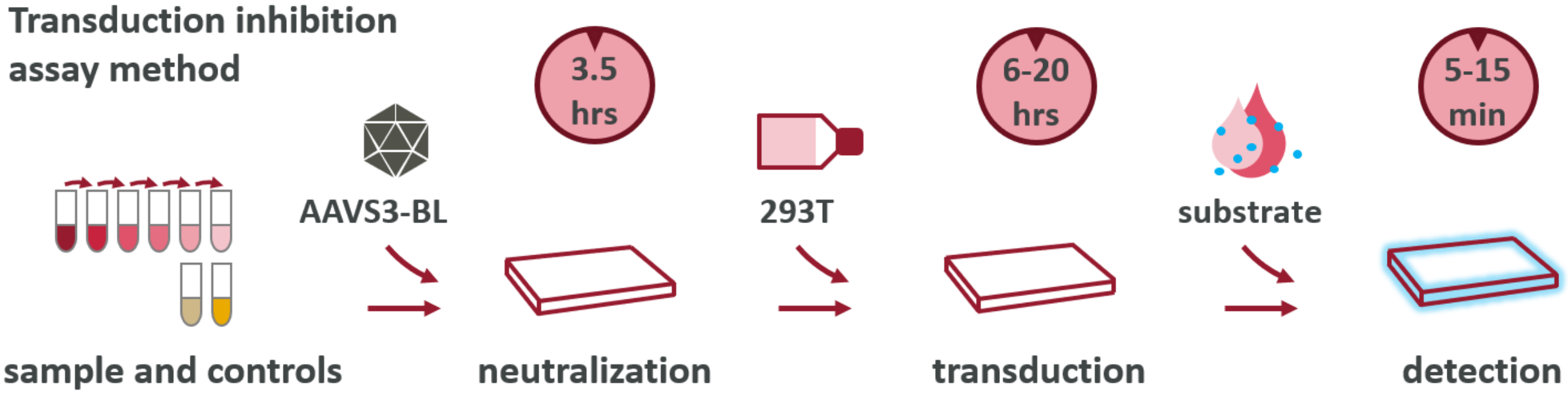
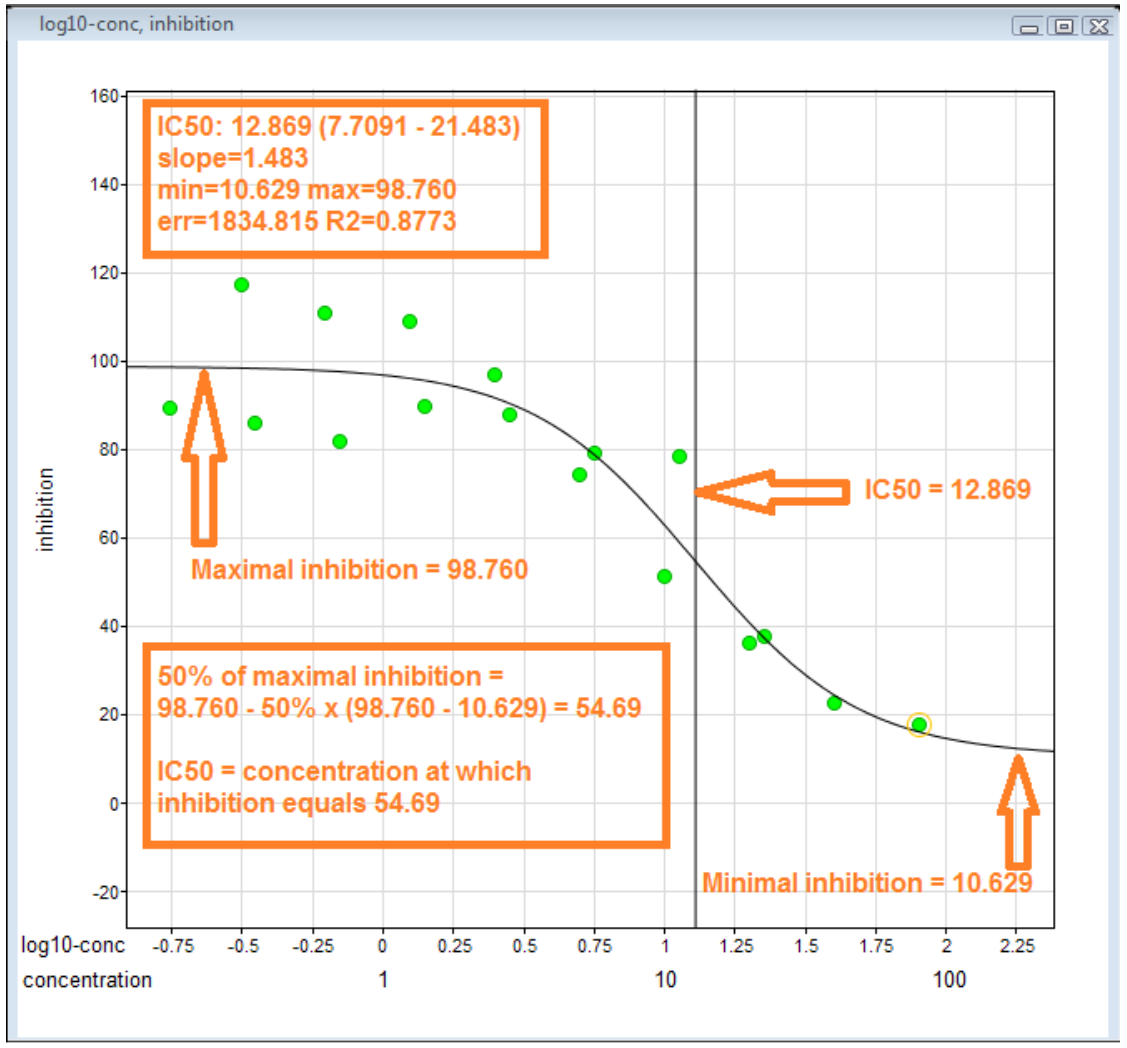
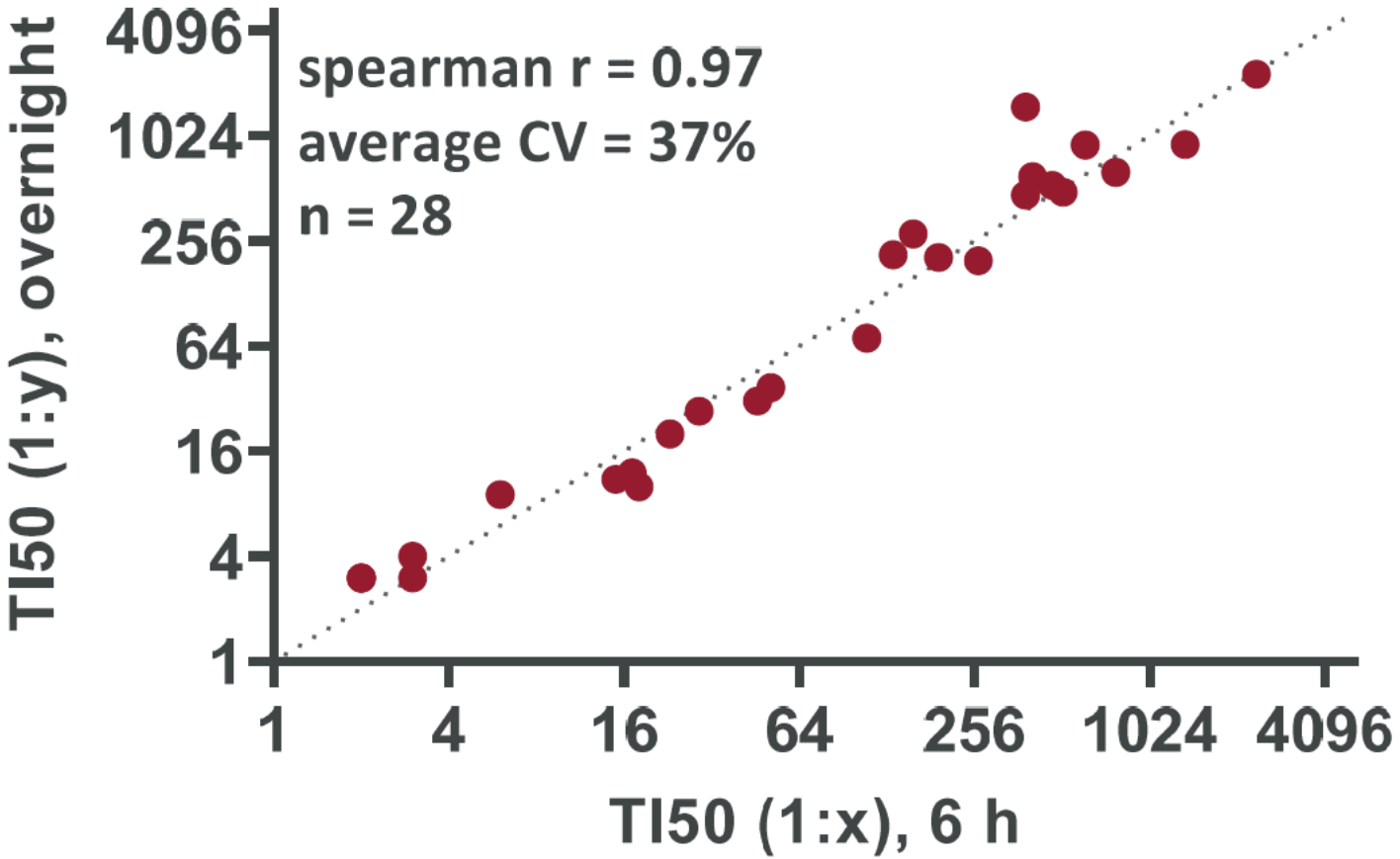


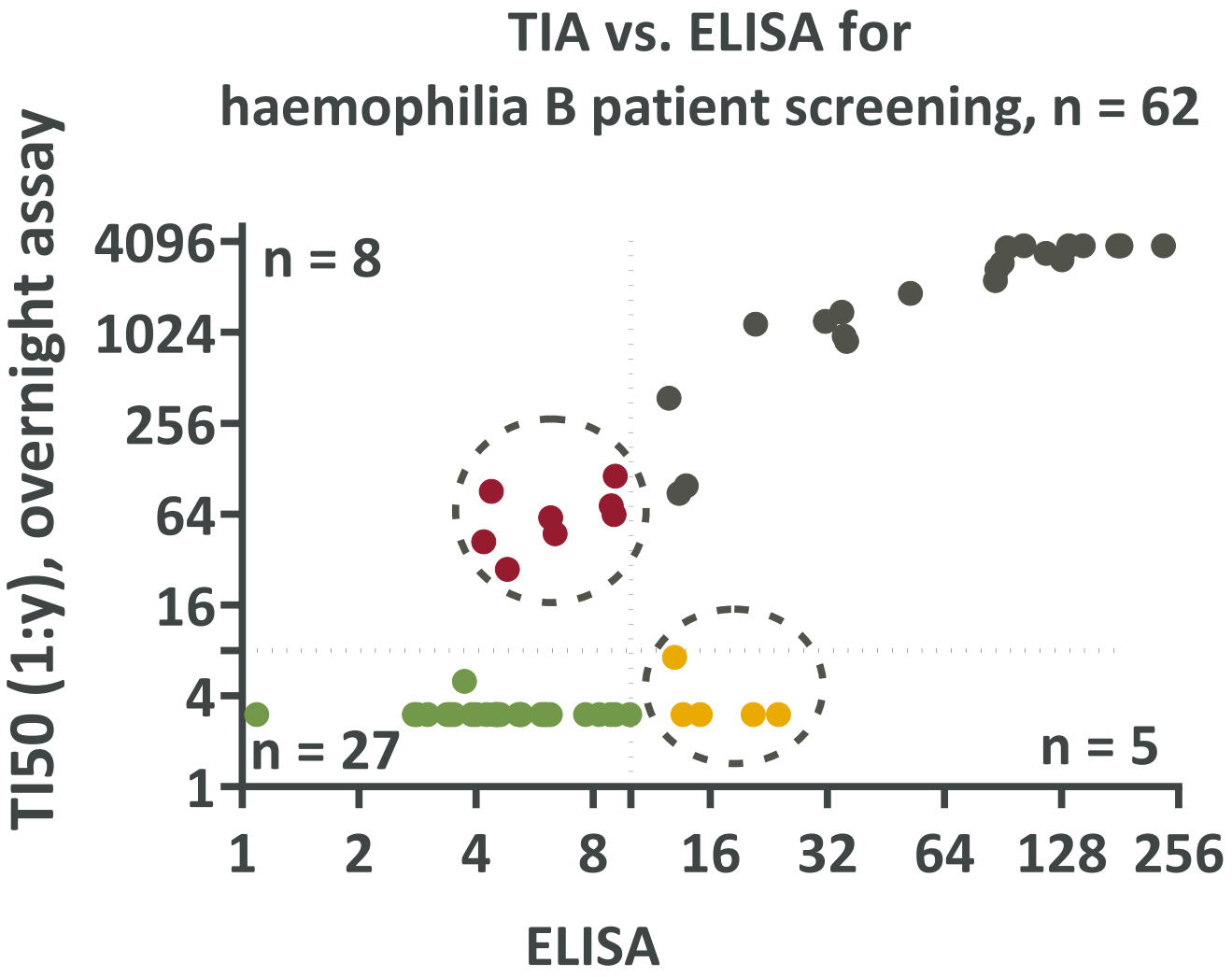
Inhibition profile determination



Transduction inhibition assay (TIA) titres are identical using 6-hour and 20-hour incubations



Functional TIA result provides true antibody status



Regulatory requirements for clinical trial inclusion/exclusion

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United States

- Assays are subject of an Investigational Device Exemption (IDE) application
- For Phase 2b/3 clinical study the final candidate IVD assay is submitted to FDA through a modular Premarket Approval (PMA) application as a companion diagnostic (CDx)

European Union (EU/UK)

- Under the current regulatory landscape (IVDD) in the EU and UK, CE marked is needed and EC declaration of conformity (Annex III of the In VitroDiagnostic Directive (IVDD) 98/79/EC)
- From 26 May 2022 compliance with EU Regulations for in vitro diagnostic medical devices (IVDR)

Conclusions

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- The immunogenicity guideline isn’t always the only source of guidance
- Different approaches for cut-point determination can be acceptable
- Lifecycle management of assays needs to start early
- Funding needs to be secured
- Impact on entire clinical development planning
- Bioanalytical and Diagnostic regulatory experts needed

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Questions ?