Challenges of inflammatory biomarker assay development and validation

Stéphanie TEIXEIRA

Novimmune SA

Geneva, Switzerland

novimmune

Outline

- Background
  - Biomarker utility
  - Biomarker strategy
  - Bioanalytical assay strategy
- Bioanalytical assay development challenges
  - Standard generation
    - Surrogate matrix
    - Recombinant protein
  - Parallelism
  - Endogenous QCs
- Conclusion

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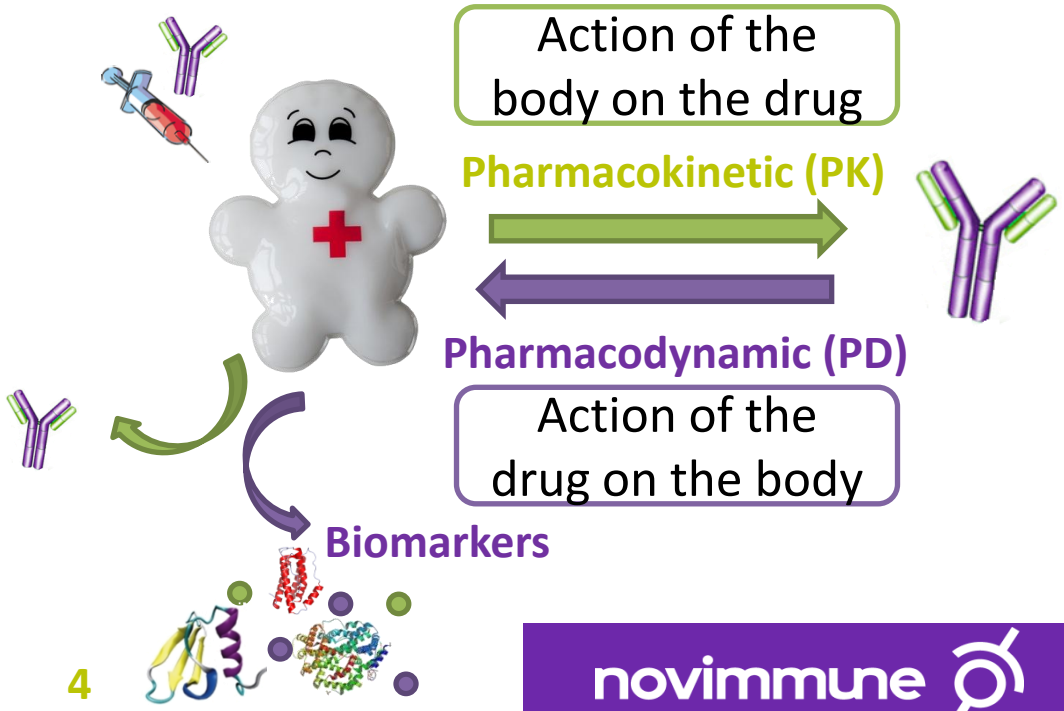
Biomarker utility

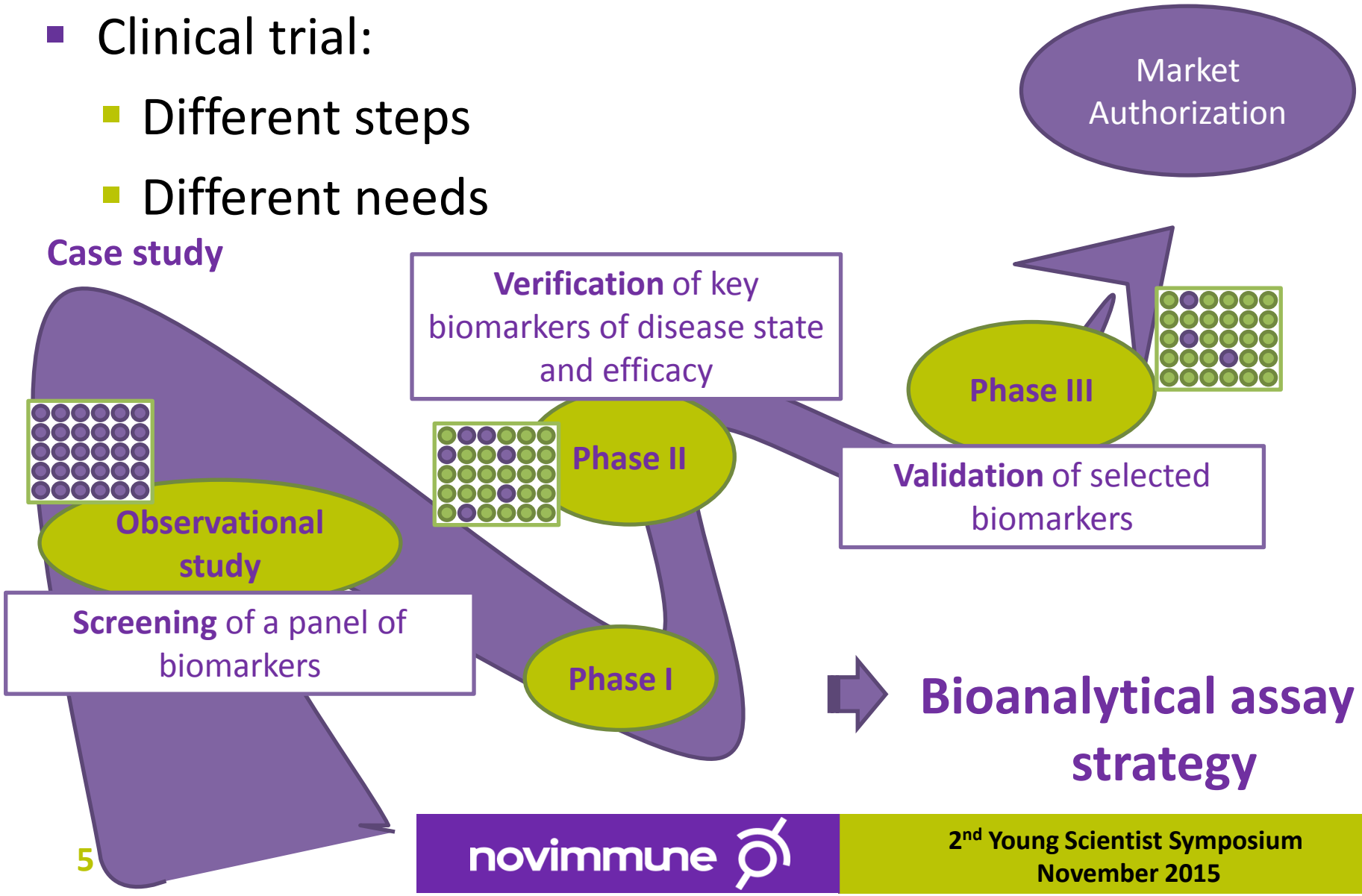
- **Why** do we need to measure biomarkers?
  - High attrition rate of new therapeutics
  - Need better translational models and **tools** to determine drug exposure, efficacy and safety



Biomarker assays are not PK assays

Biomarker strategy

- Clinical trial:
  - Different steps
  - Different needs

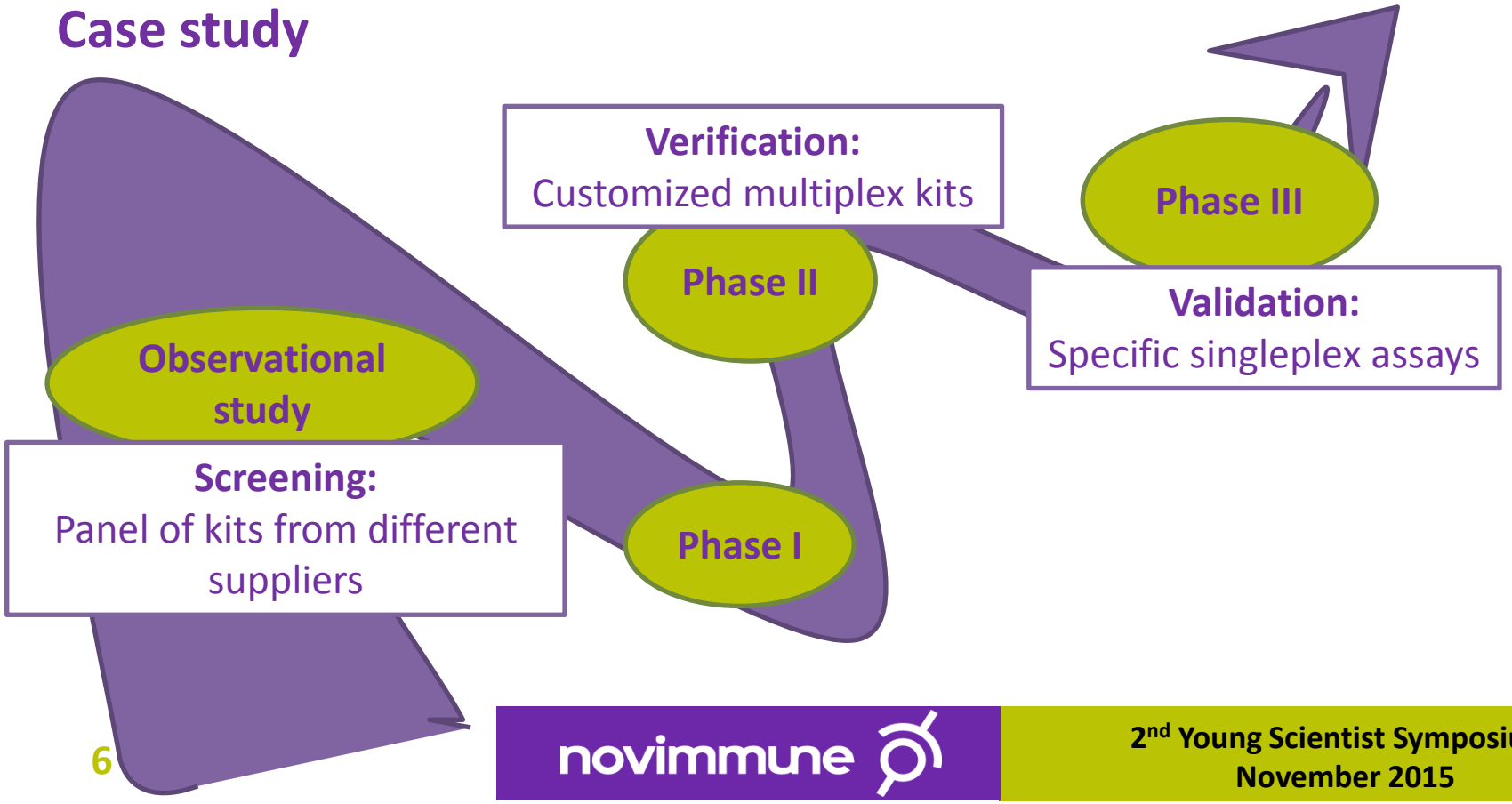


Bioanalytical assay strategy

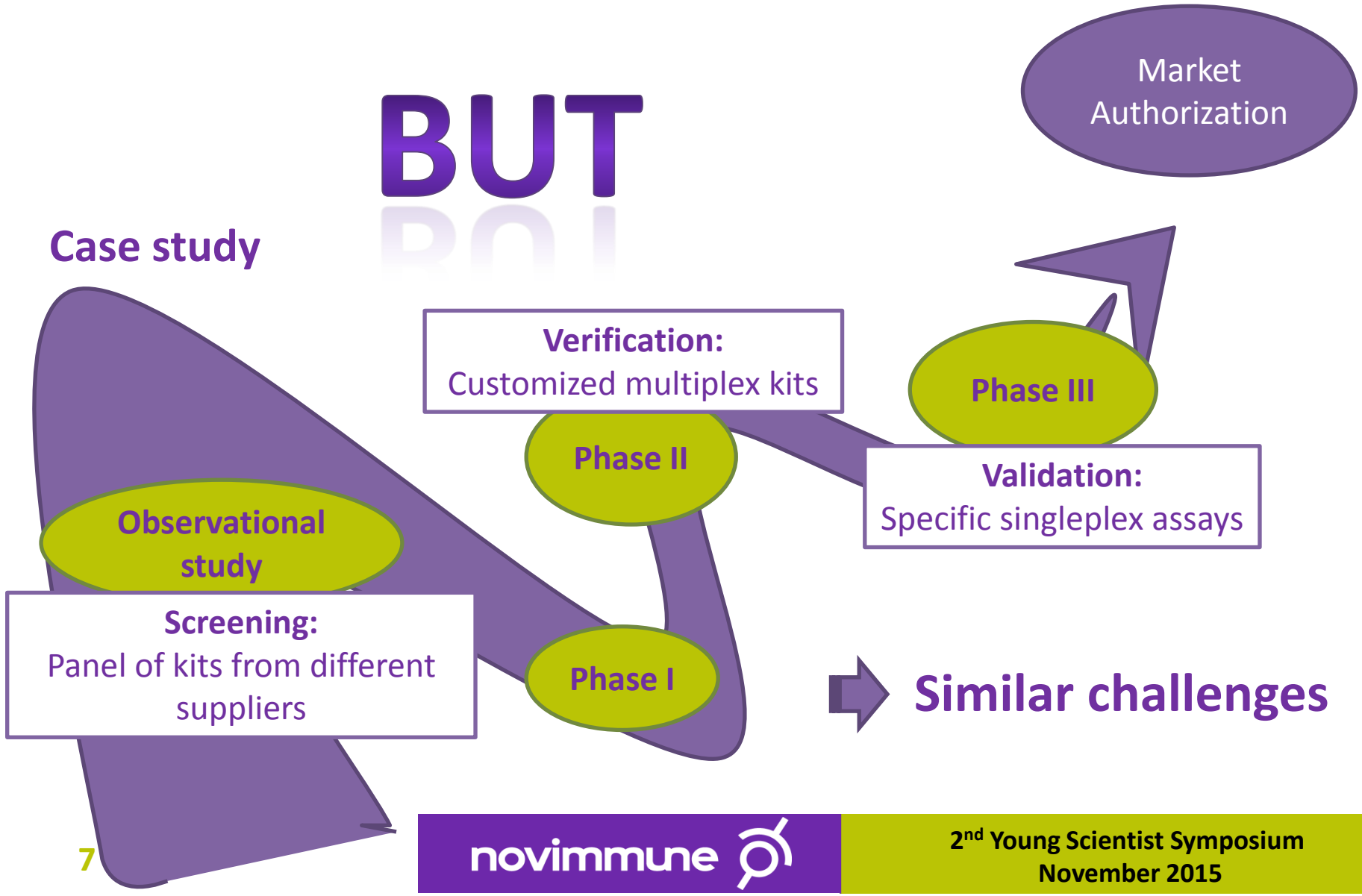
- Assay development:
  - Different kind of assays
  - Different technologies

Market Authorization

Case study



Bioanalytical assay strategy



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Standard generation

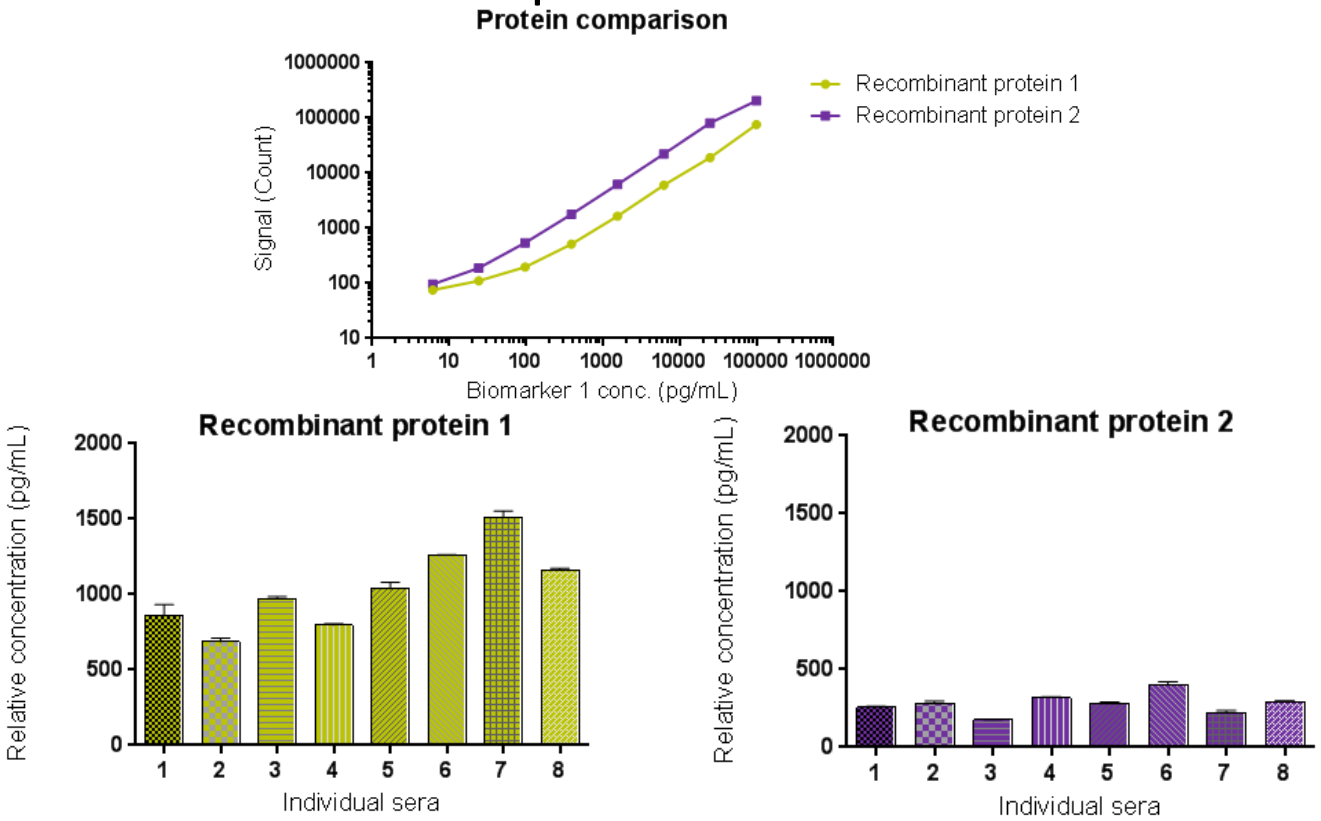
- **Surrogate matrix:**
  - **Why ?** Mimic sample matrix without endogenous biomarker
  - **When ?** Used for calibration standard, sample dilution, (QCs)

- **Recombinant protein**
  - **Why ?** For *relative* biomarker quantification
  - **When ?** Used as calibration standard, (QCs)

- Need to be tested in the assay

Standard generation

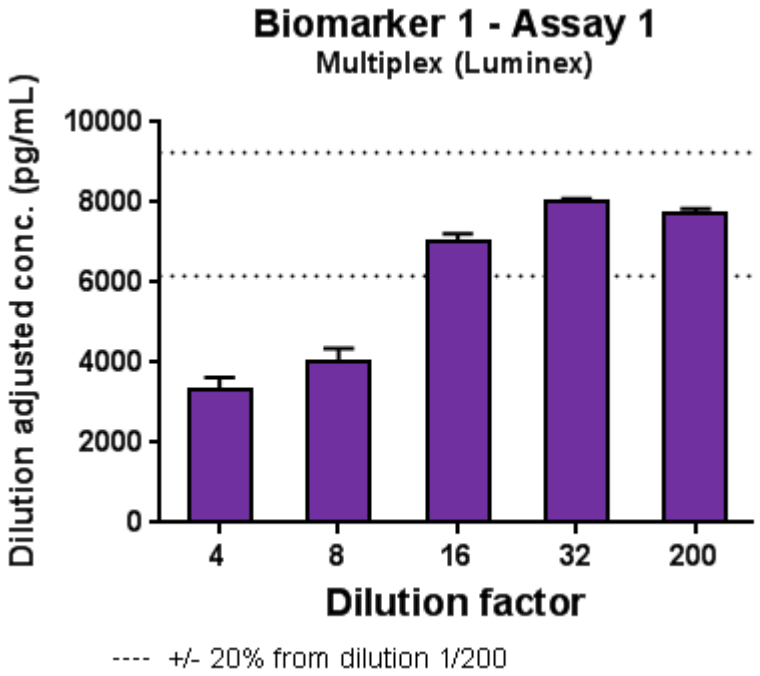
- **Case study**
  - 2 different recombinant proteins for the standard

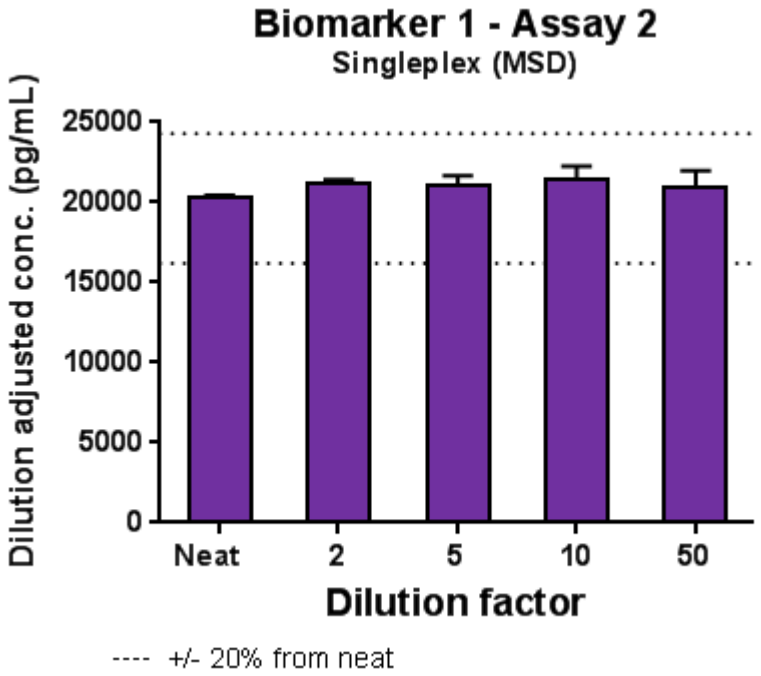


Relative concentrations are different depending on the recombinant protein used

Parallelism

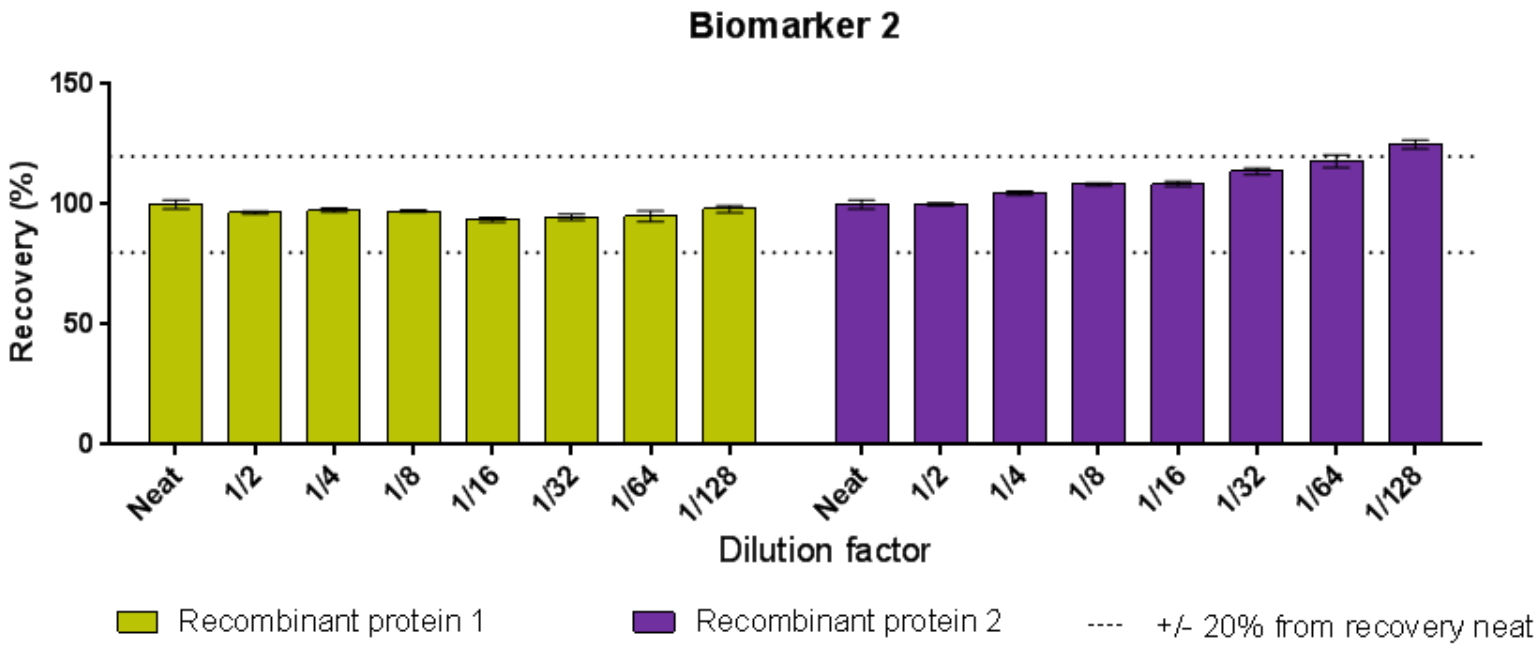
- Most important parameter
- Need to be tested for every assay, with multiple samples
- Could differ according to:
  - Assay:





Parallelism

- Recombinant protein used as calibration standard:



A good biomarker assay needs good parallelism between recombinant and endogenous protein

Endogenous QC

- **What ?**

  - Non-spiked sample corresponding to the endogenous biomarker in the biological matrix

- **Why ?**

  - To monitor the performance of the bioanalytical method
  - Assess the integrity and validity of the results

- **How ?**

  - Sample matrix or clinical sample (if possible)
  - Healthy volunteer containing endogenous biomarker
  - *Ex vivo* generation (e.g. whole blood activation)
  - Recombinant protein in target matrix

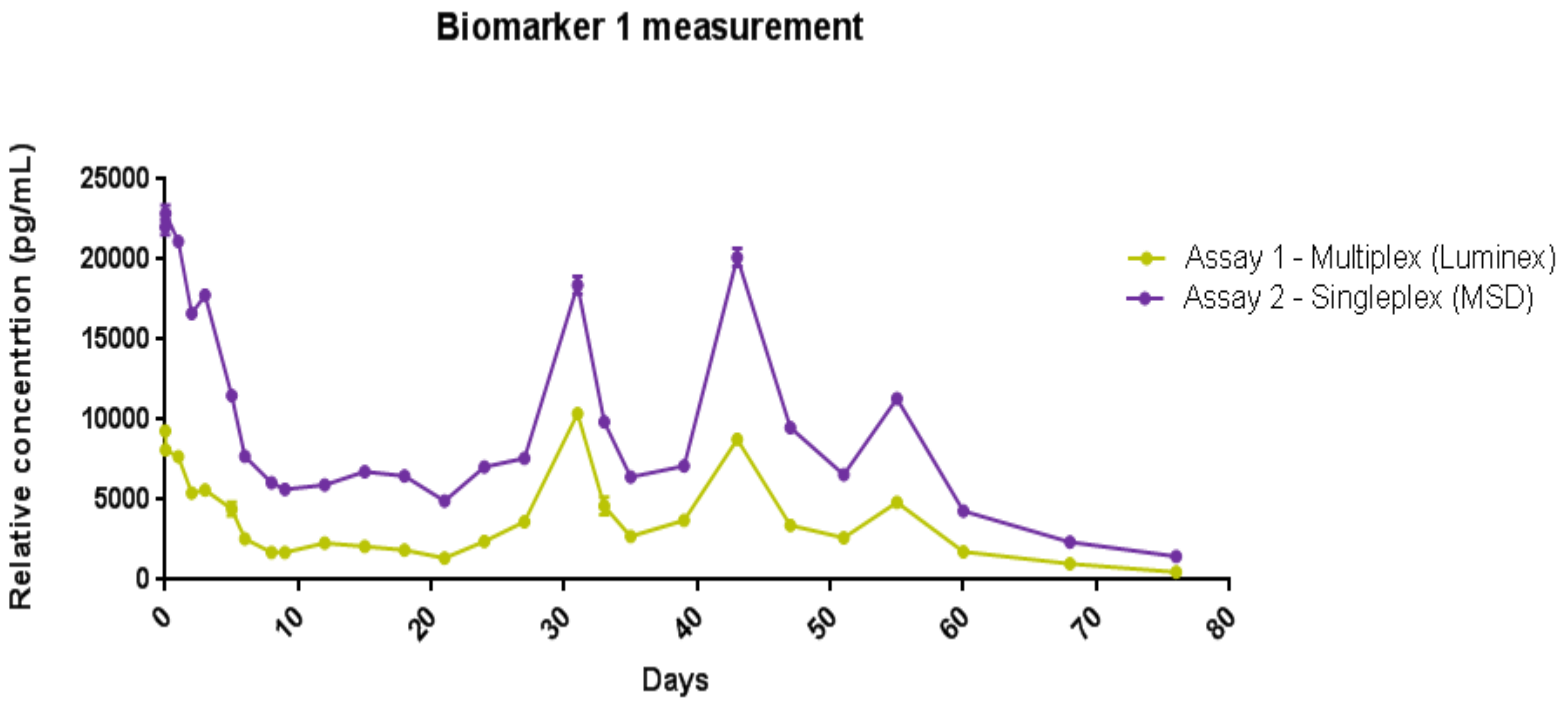
Need endogenous biomarker to validate biomarker assays

Conclusion

- Biomarker assay is not a PK assay
- Select appropriate surrogate matrix and recombinant protein
- Need endogenous biomarker to develop and validate a biomarker assay:
  - At the beginning (endogenous in healthy and/or disease state subjects) or during the study (measured samples)
  - Parallelism and stability
  - Endogenous QCs

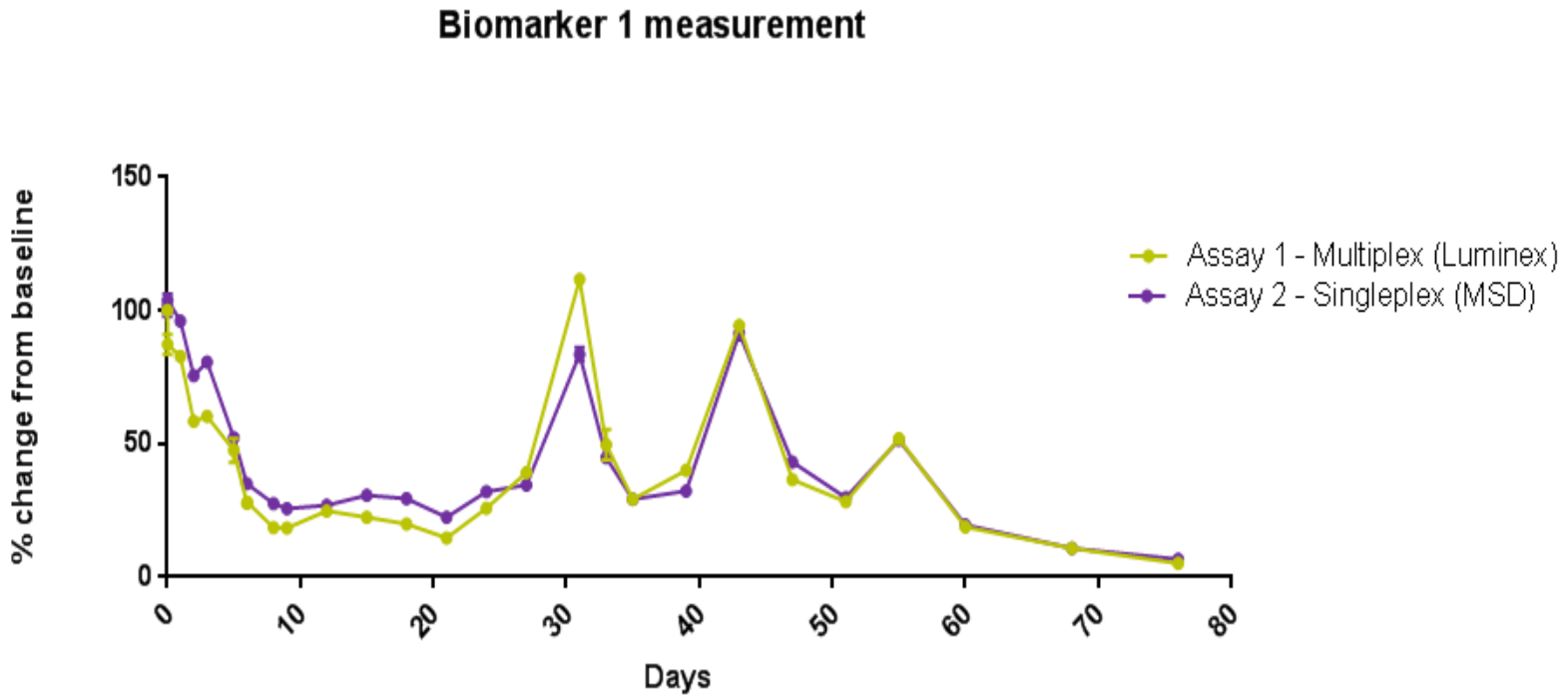
Conclusion

- Case study



Conclusion

- Case study



A good biomarker assay allows the monitoring of the relative change of the biomarker which is an important information during the clinical trial

Thank you for your attention

steixeira@novimmune.com

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