

# Precisely Targeted Therapeutics



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# Overview

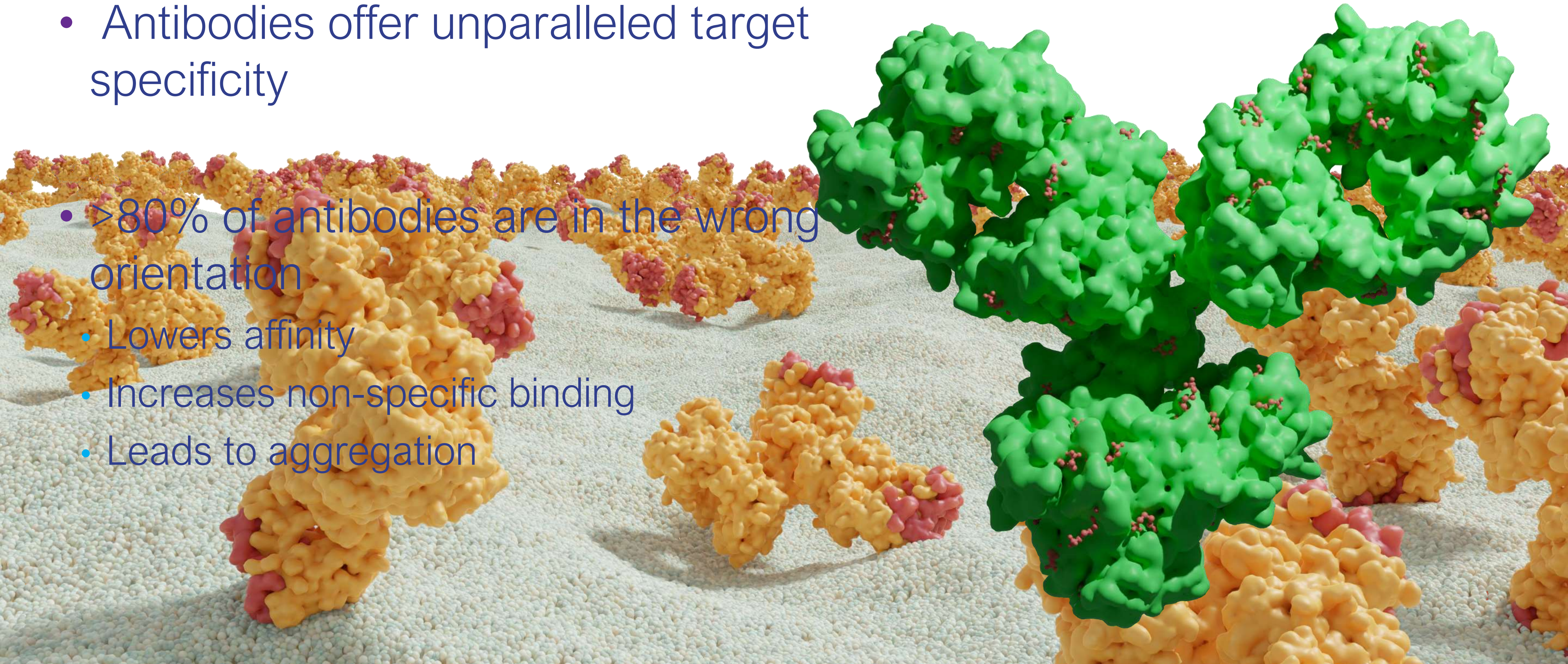


- How to do polymers and nanoparticles interact with biological systems?
  - Maximise drug delivery to the site of action inside the cell
  - Maximise drug delivery to the specific cells where activity is required
- Precise delivery of dendrimers
  - 6 year collaboration with Starpharma Ltd
  - How does targeting tumour cells improve the therapeutic effect of chemotherapies?
- Expanding precision beyond dendrimers
  - Developing optimally targeted therapeutic platforms

# Precise Delivery?

- Antibodies offer unparalleled target specificity

- >80% of antibodies are in the wrong orientation
- Lowers affinity
- Increases non-specific binding
- Leads to aggregation



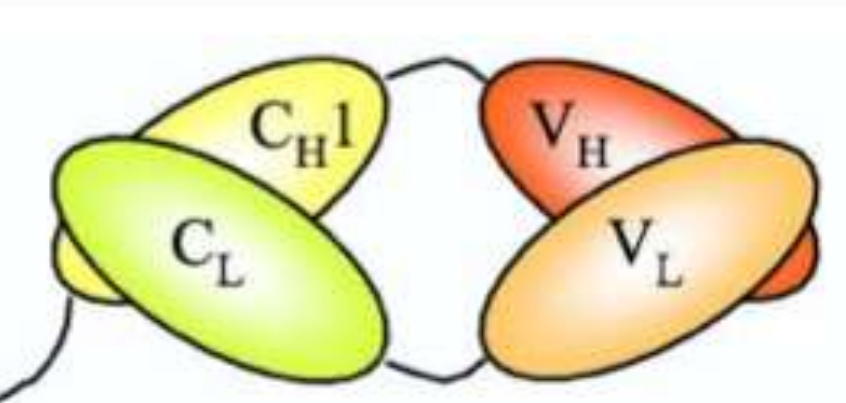
# Antibodies have limitations



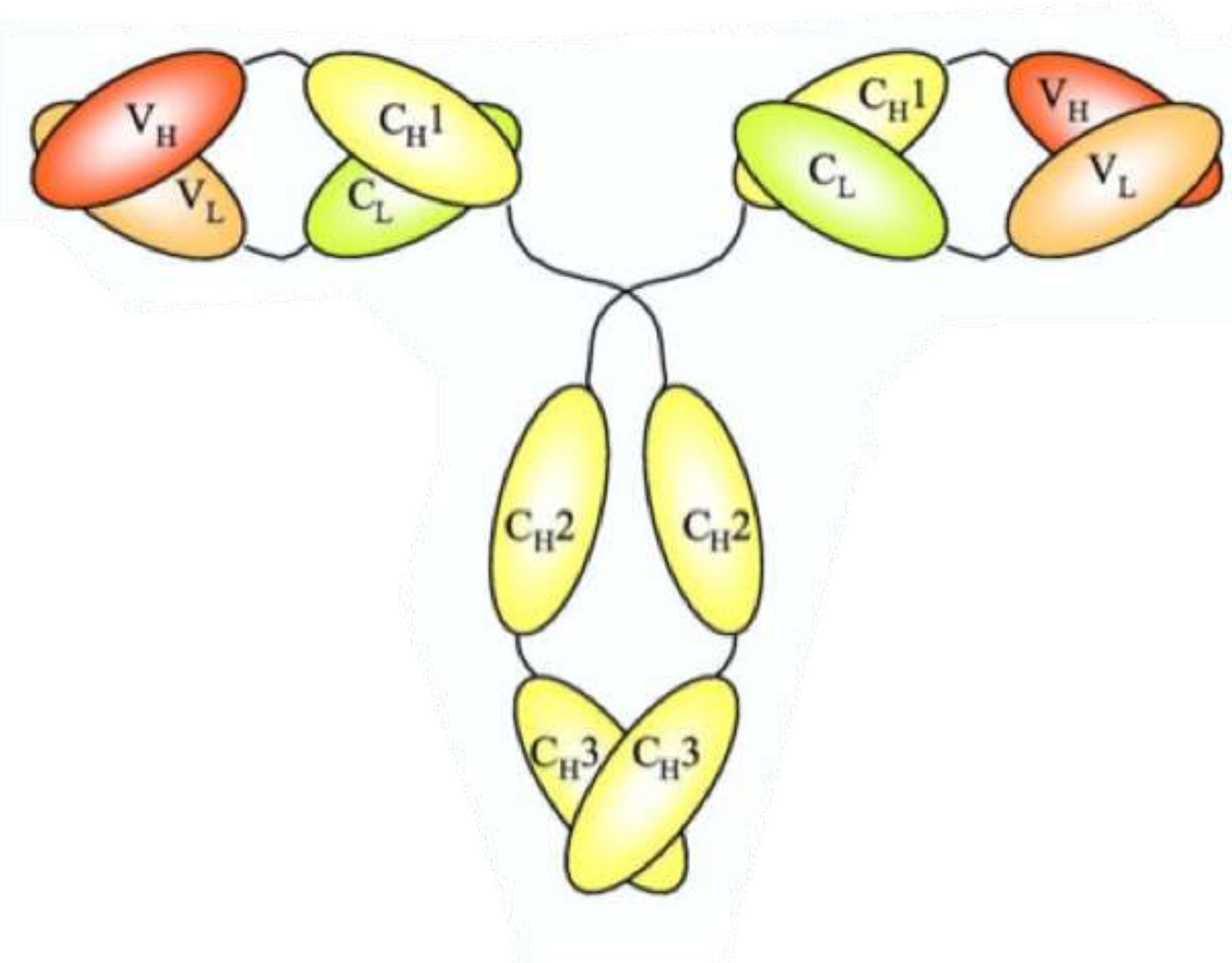
# Alpaca's Have Special Antibodies



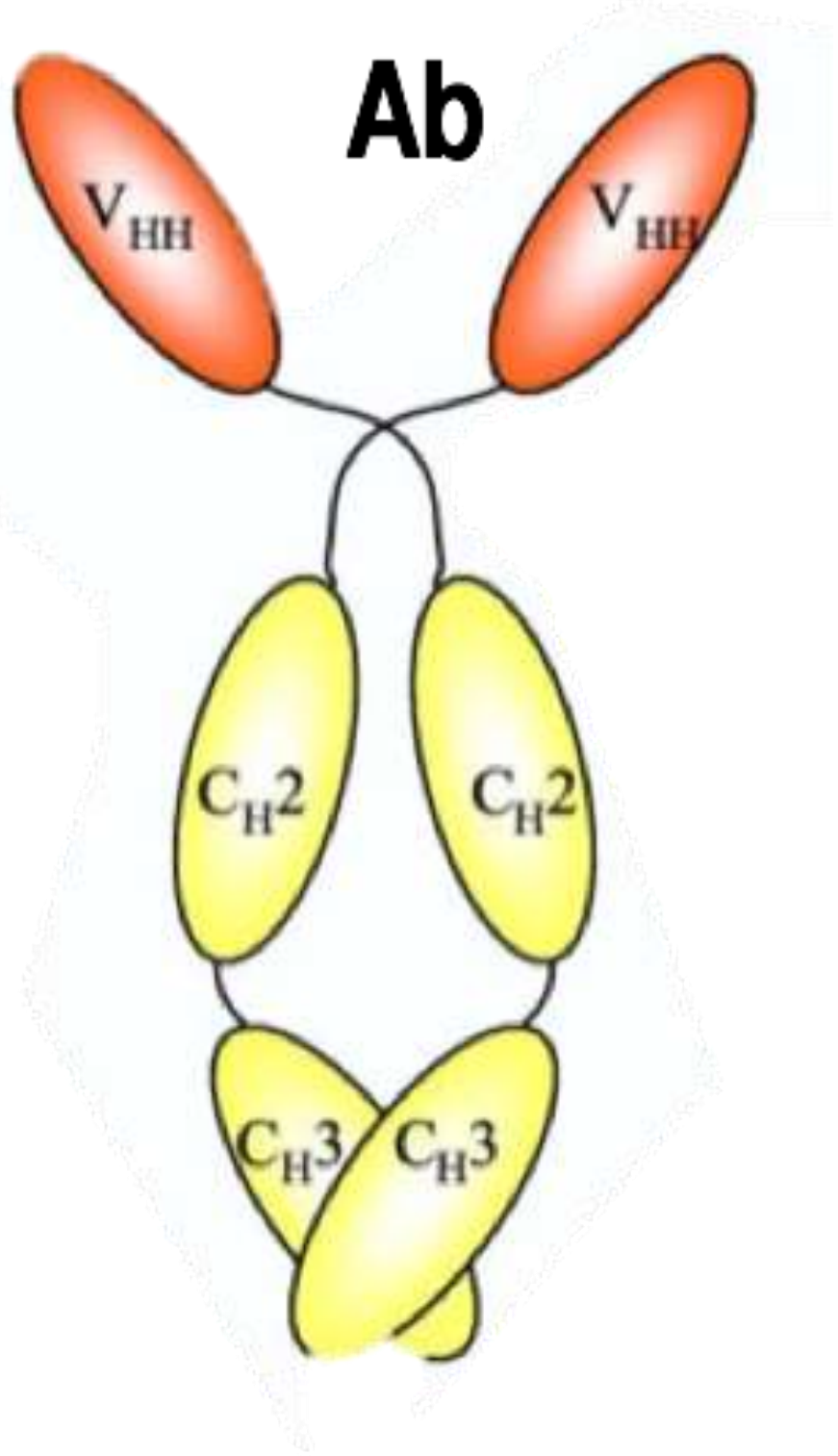
**scFv**



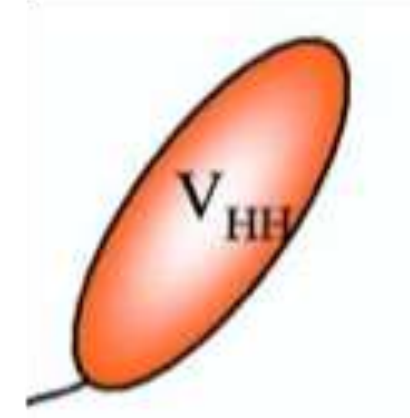
**Antibody**



**Camelid**

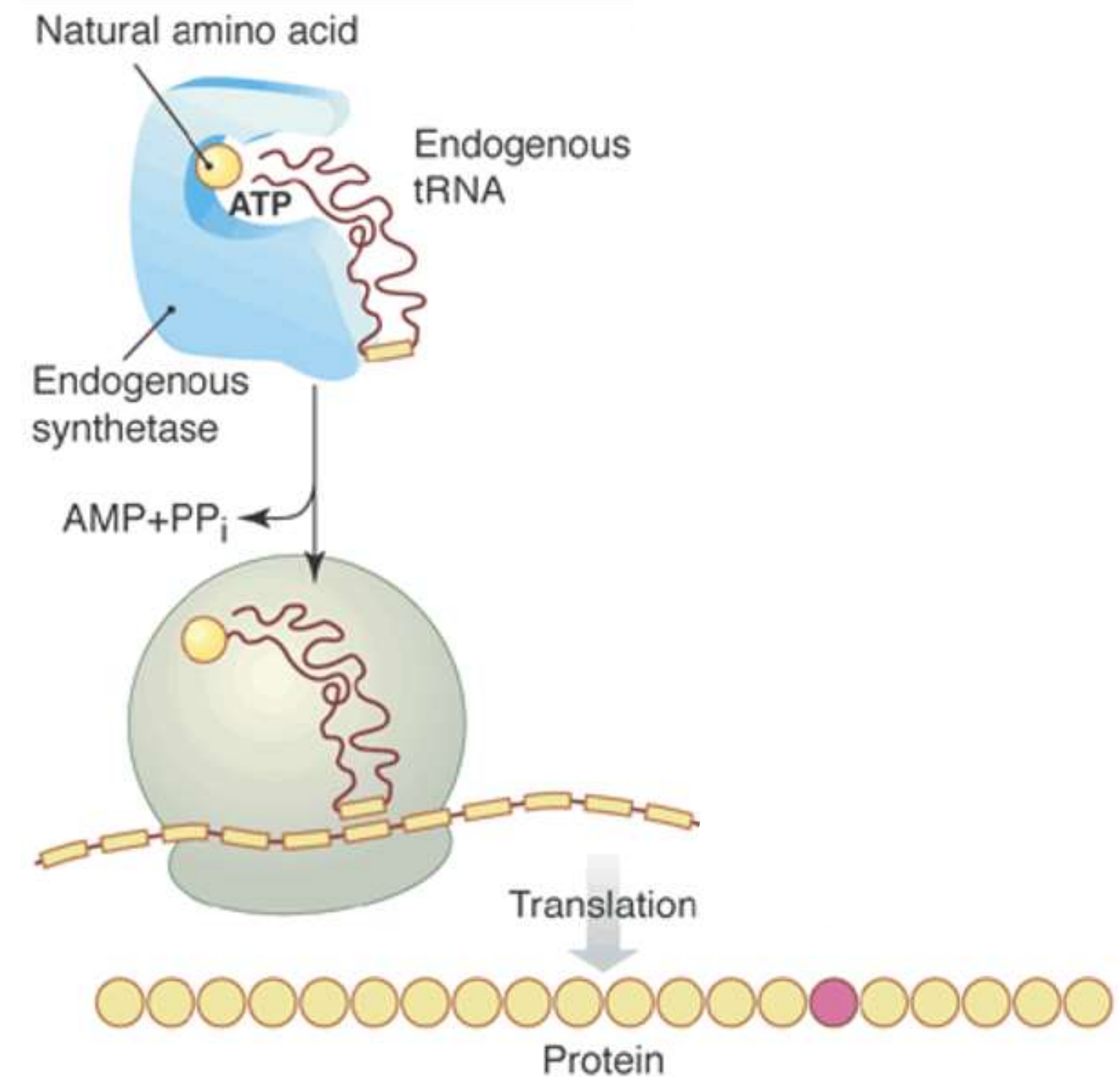
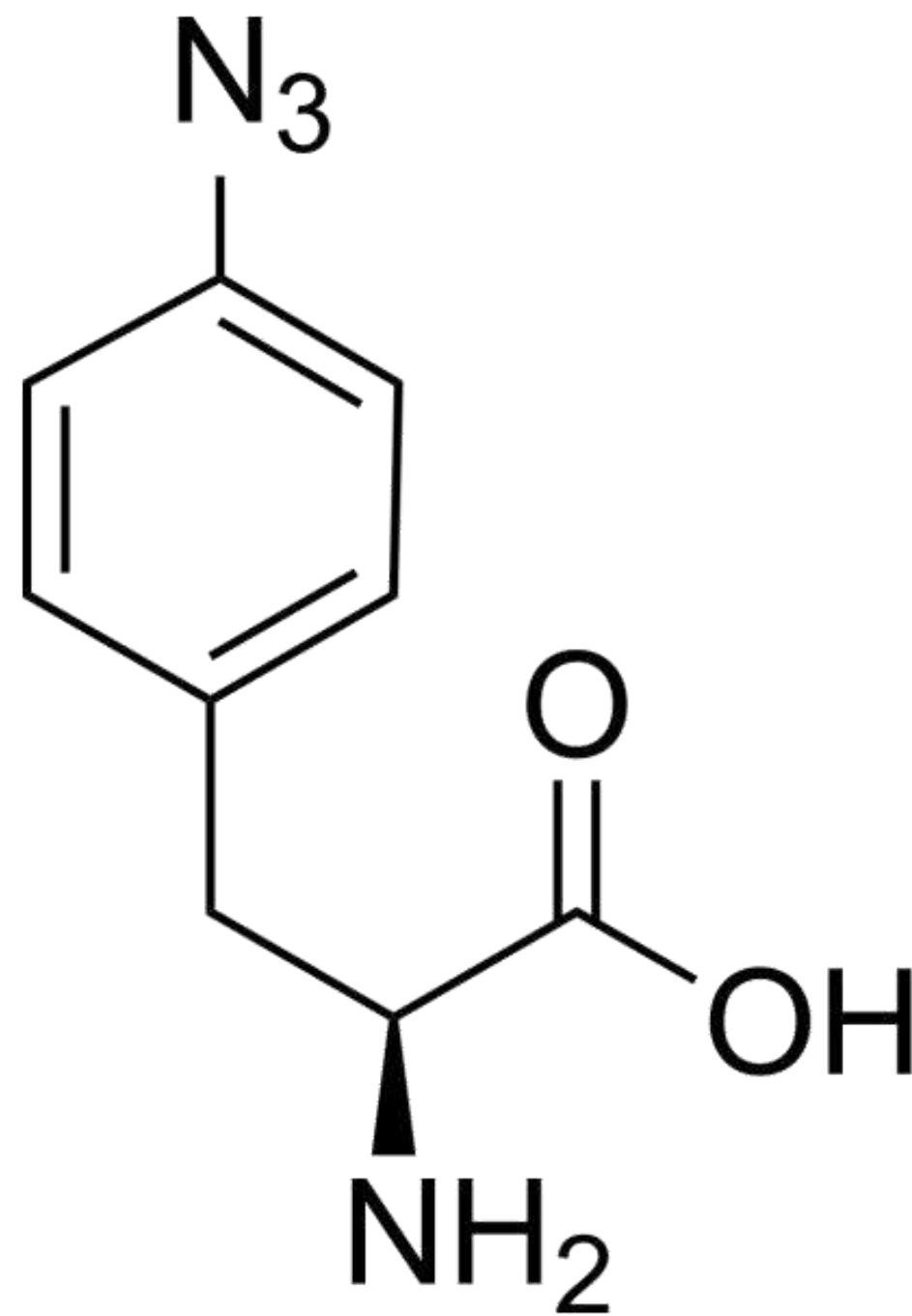


**sdAb**



# Engineering attachment

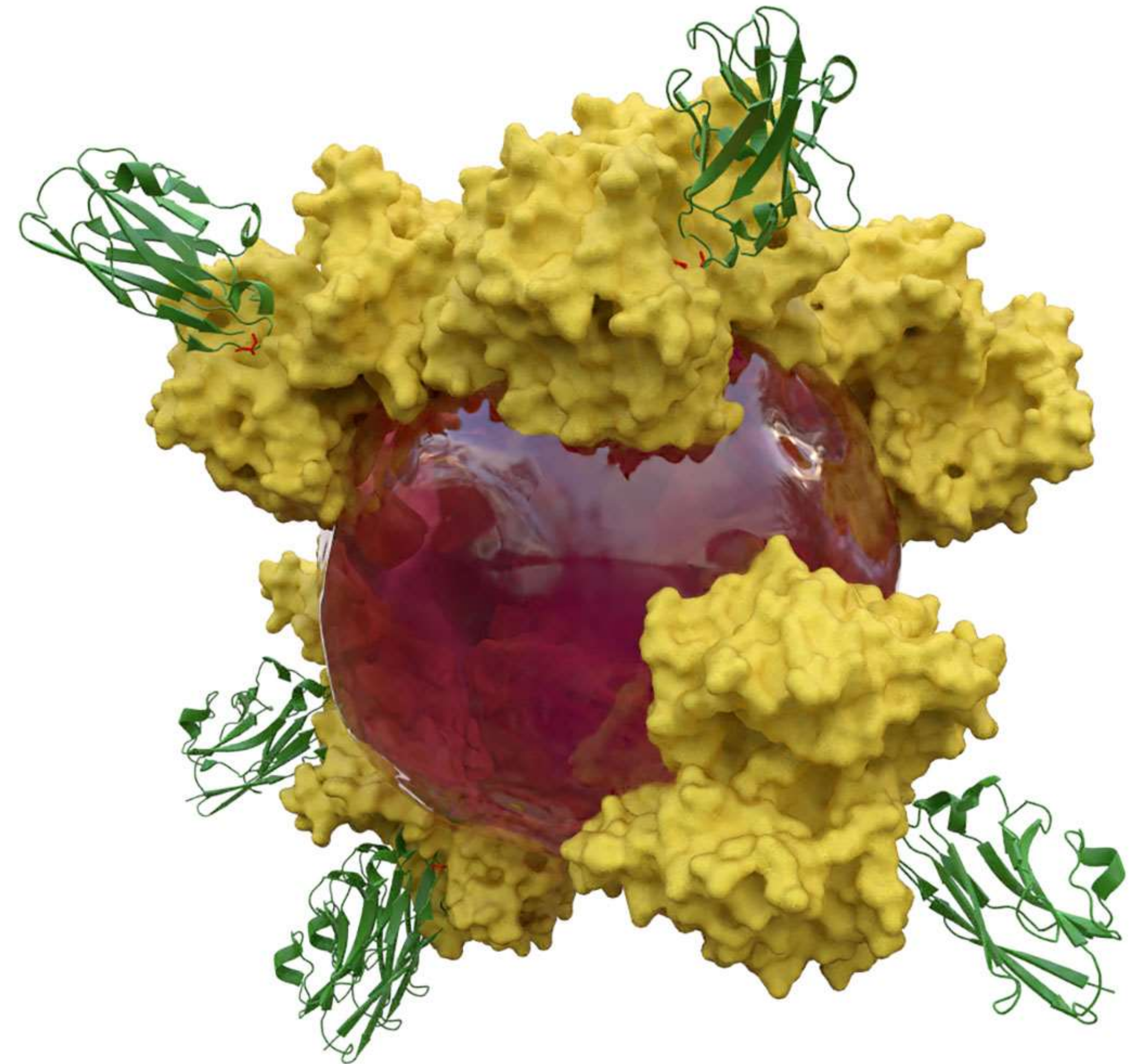
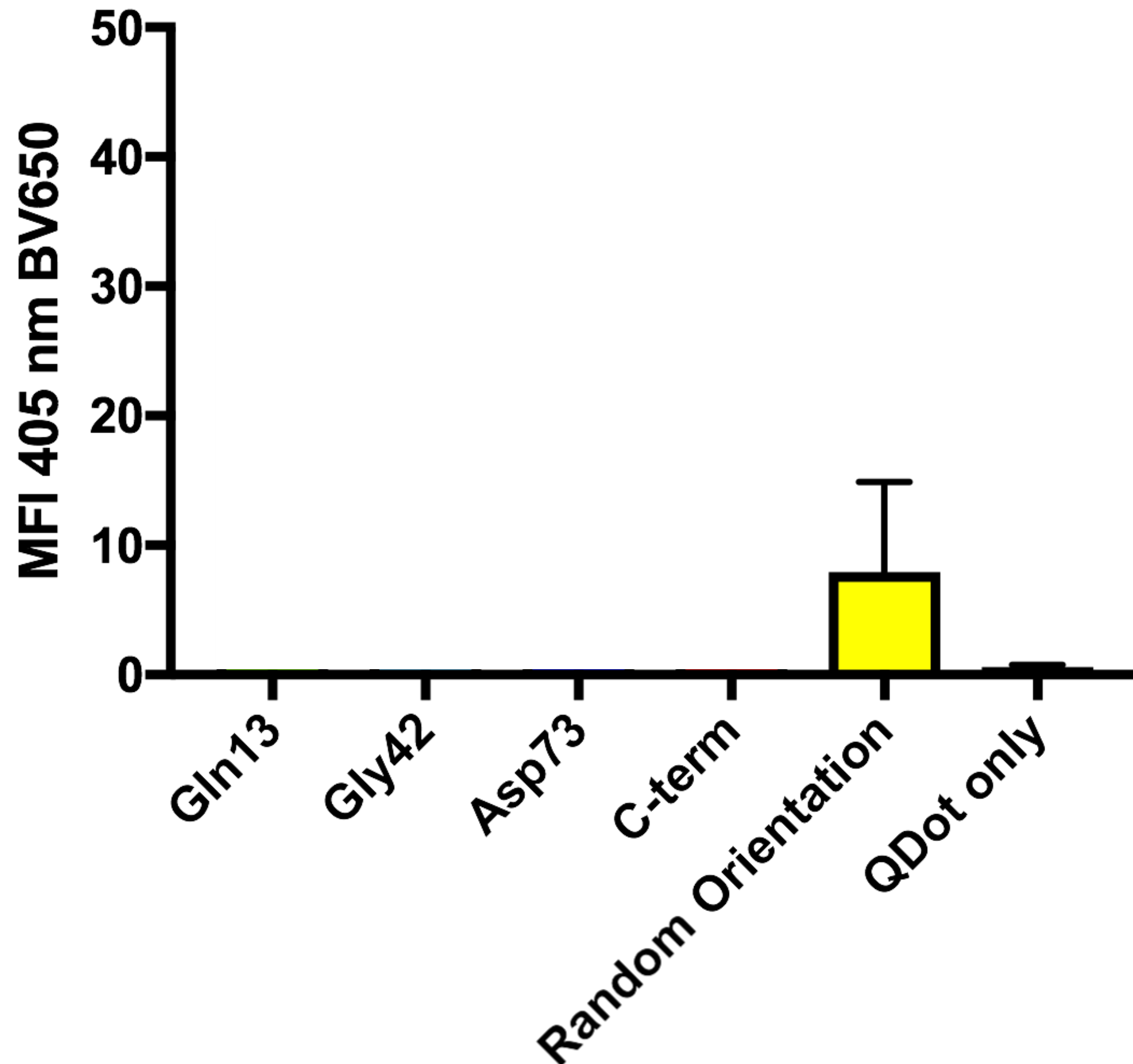
- Protein orientation can be engineered by manipulating the genetic code



# Engineering nanobody orientation



# Controlling Orientation Improves Cell Binding

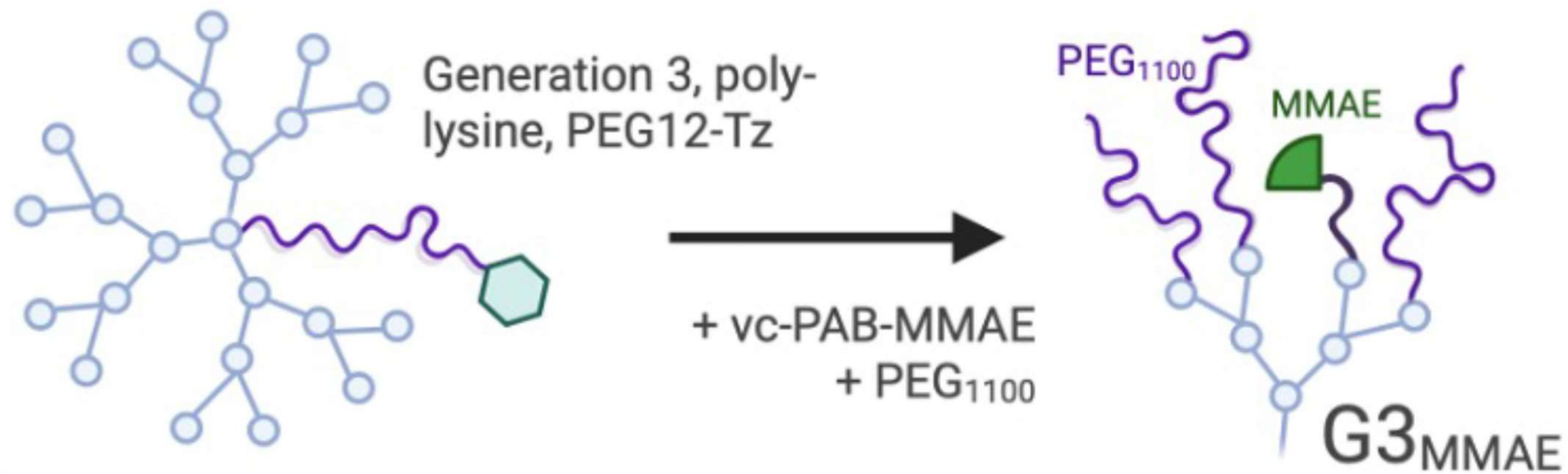


*Nano Letters* 2019, 19, 1827-1831

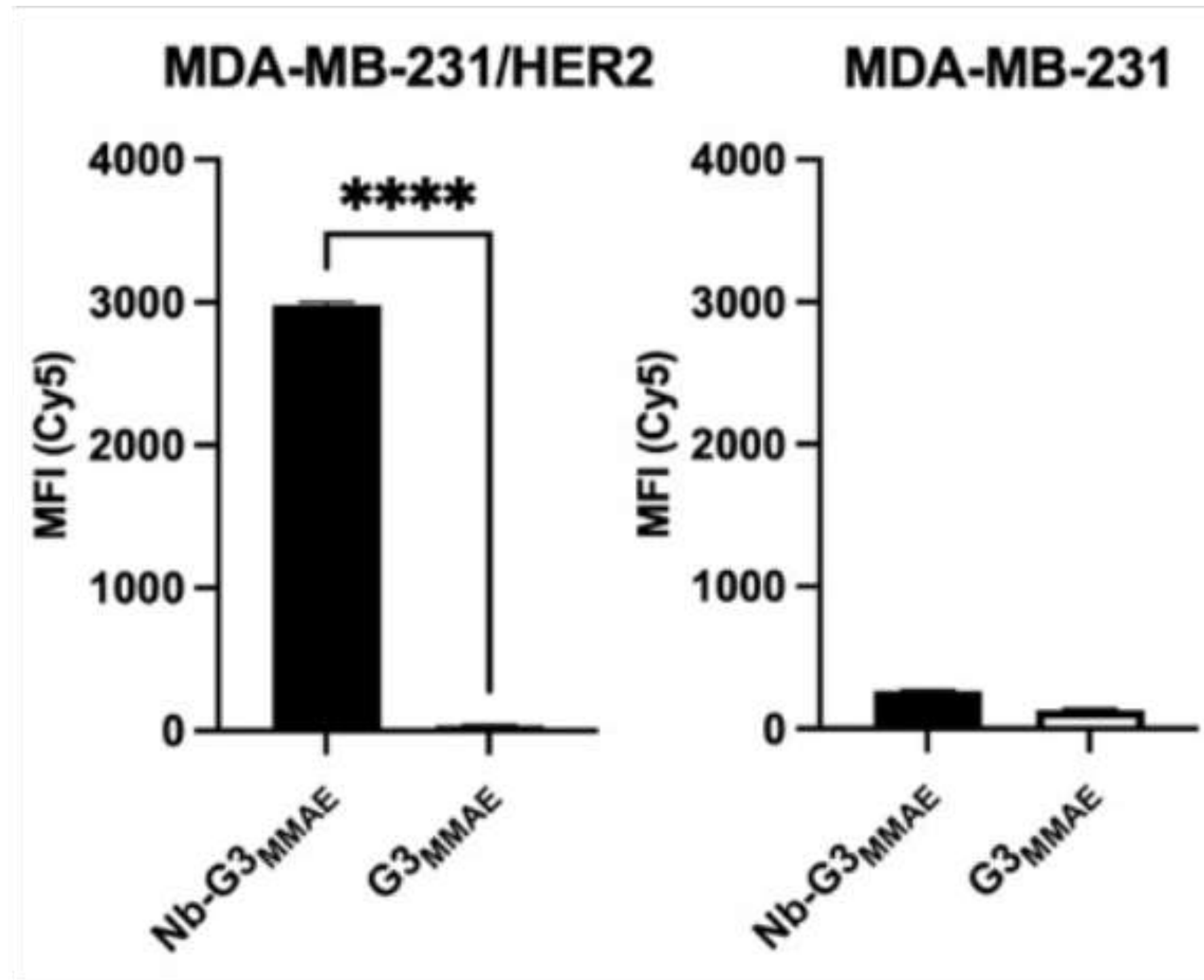
*ACS Applied Materials and Interfaces* **2020**, 12, 5593-5600



# Starpharma Dendrimers

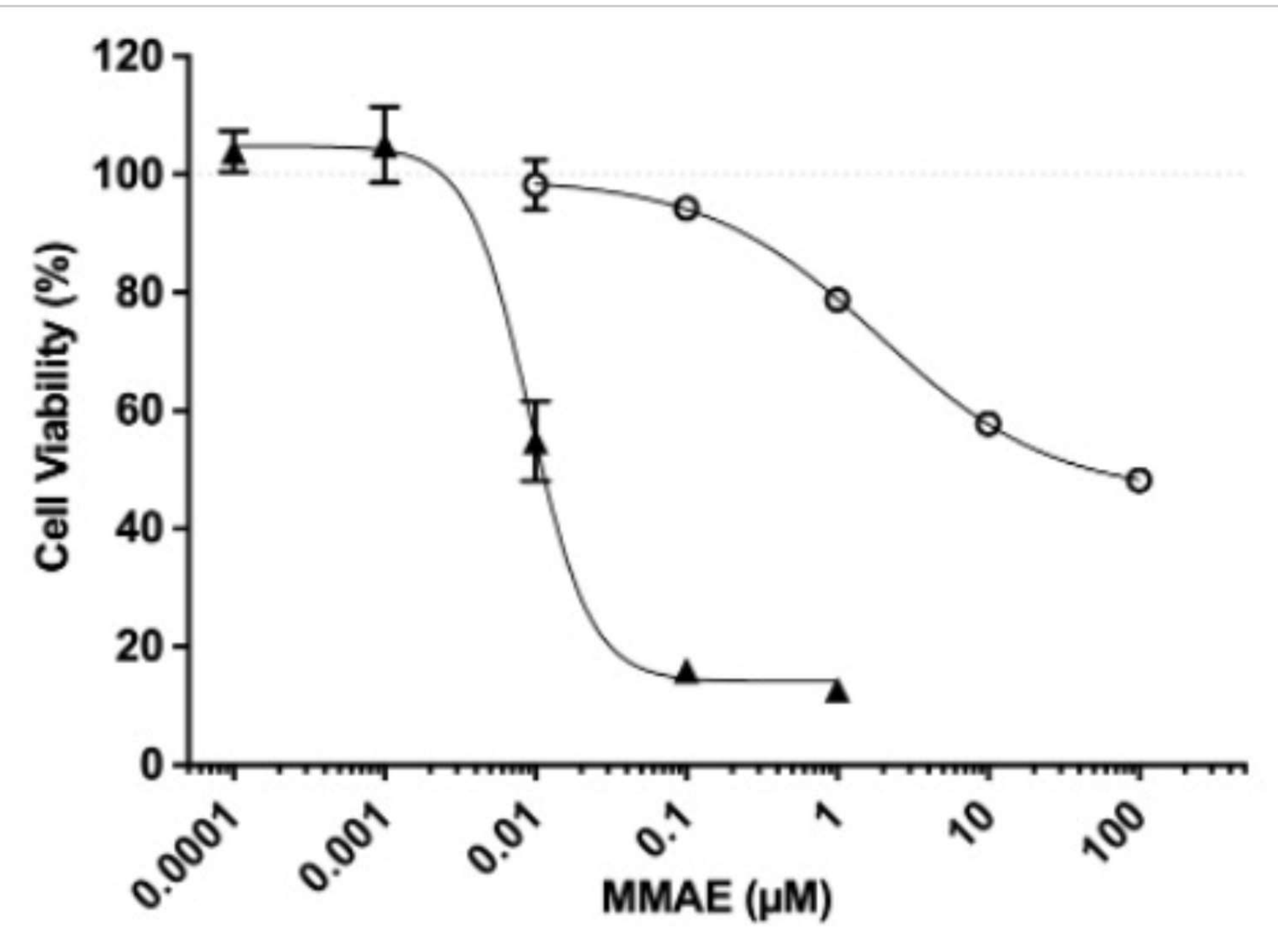


# Targeted Dendrimers Specifically Bind Her2<sup>+</sup> Cells

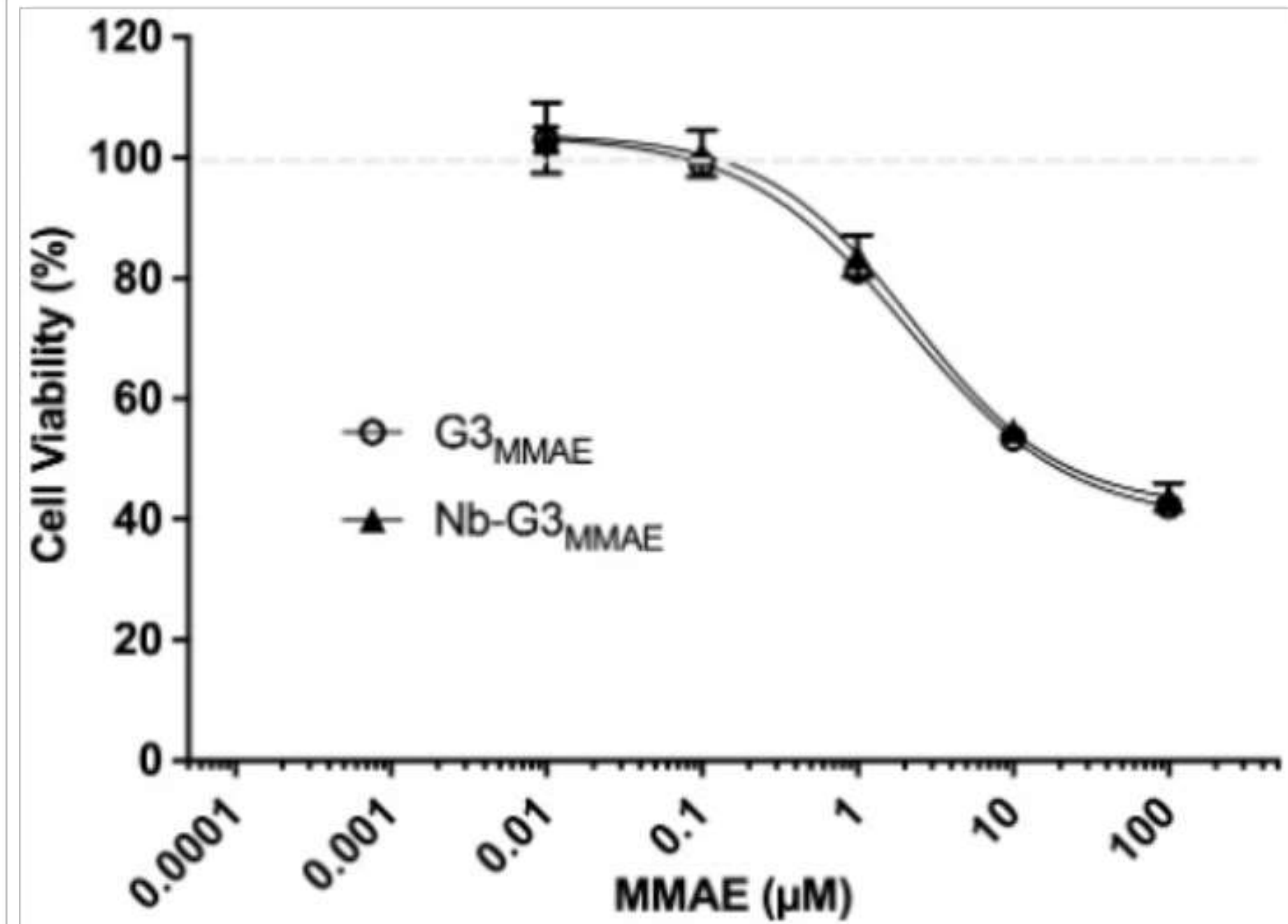


# Her2 Targeted Dendrimers have 100x Activity

MDA-MB-231/HER2

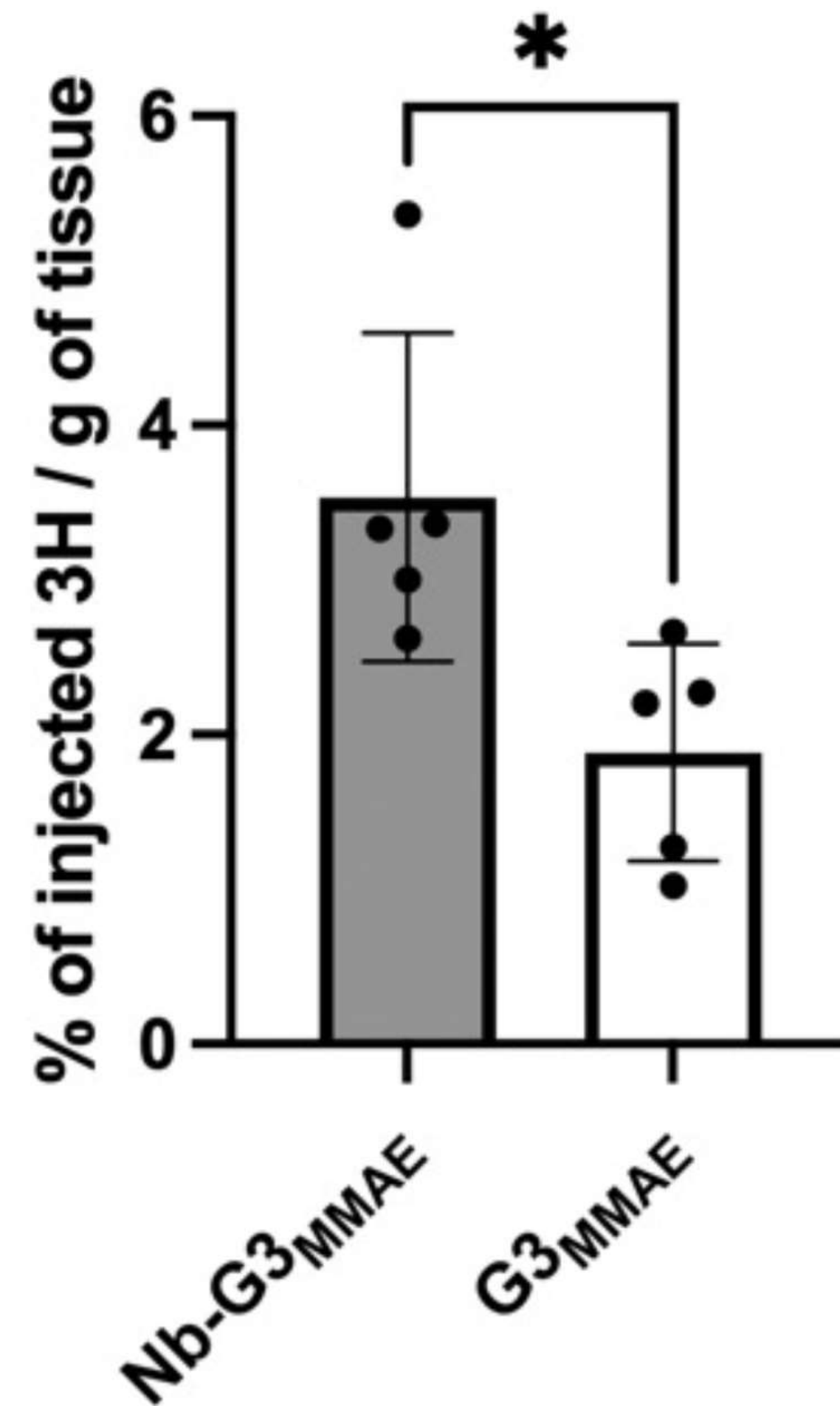


MDA-MB-231

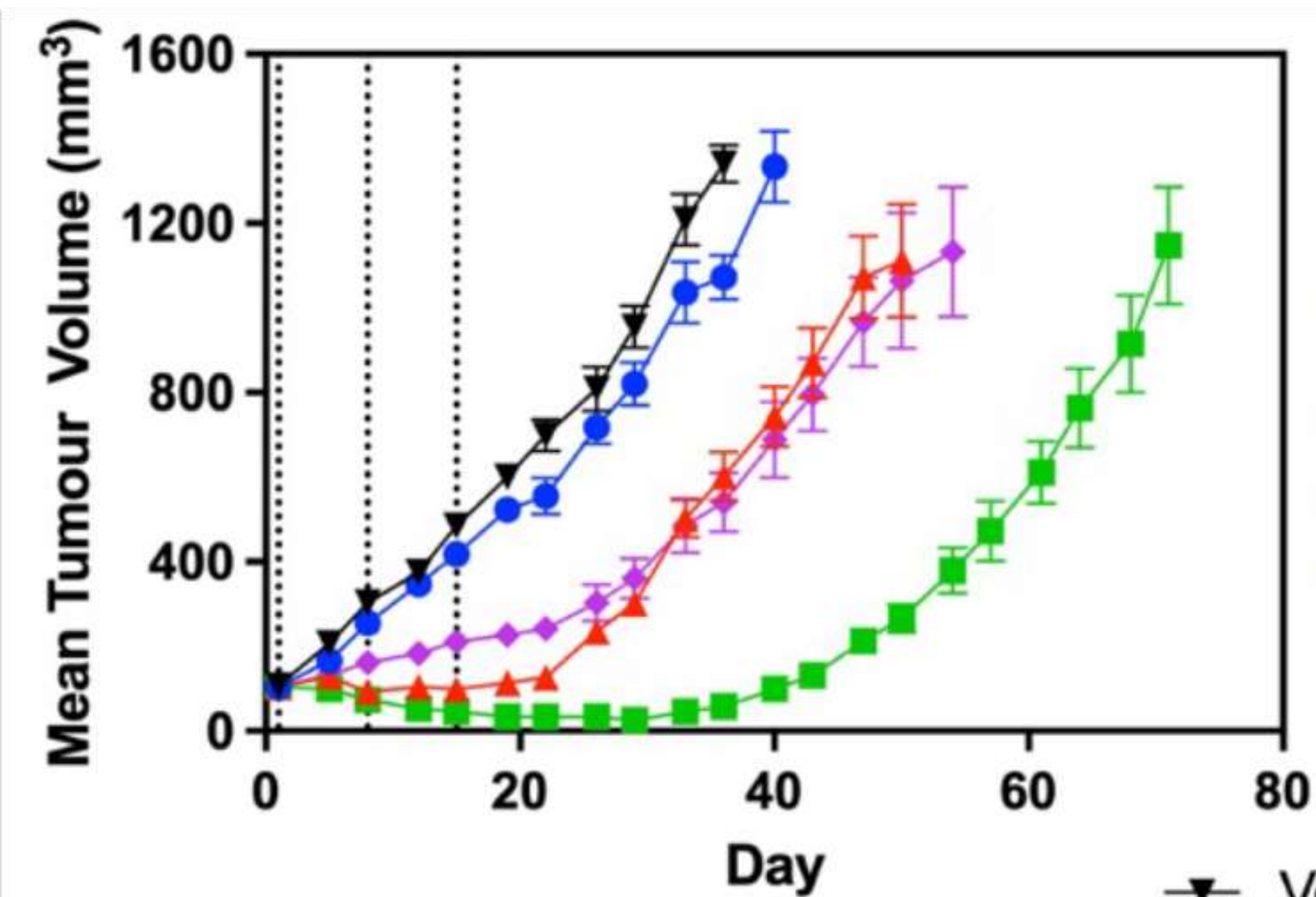
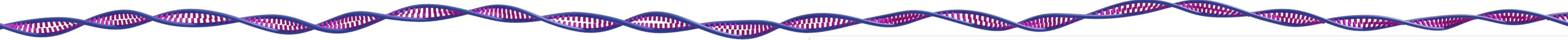


# Her2 Targeted Dendrimers Increase Tumour Accumulation ... just

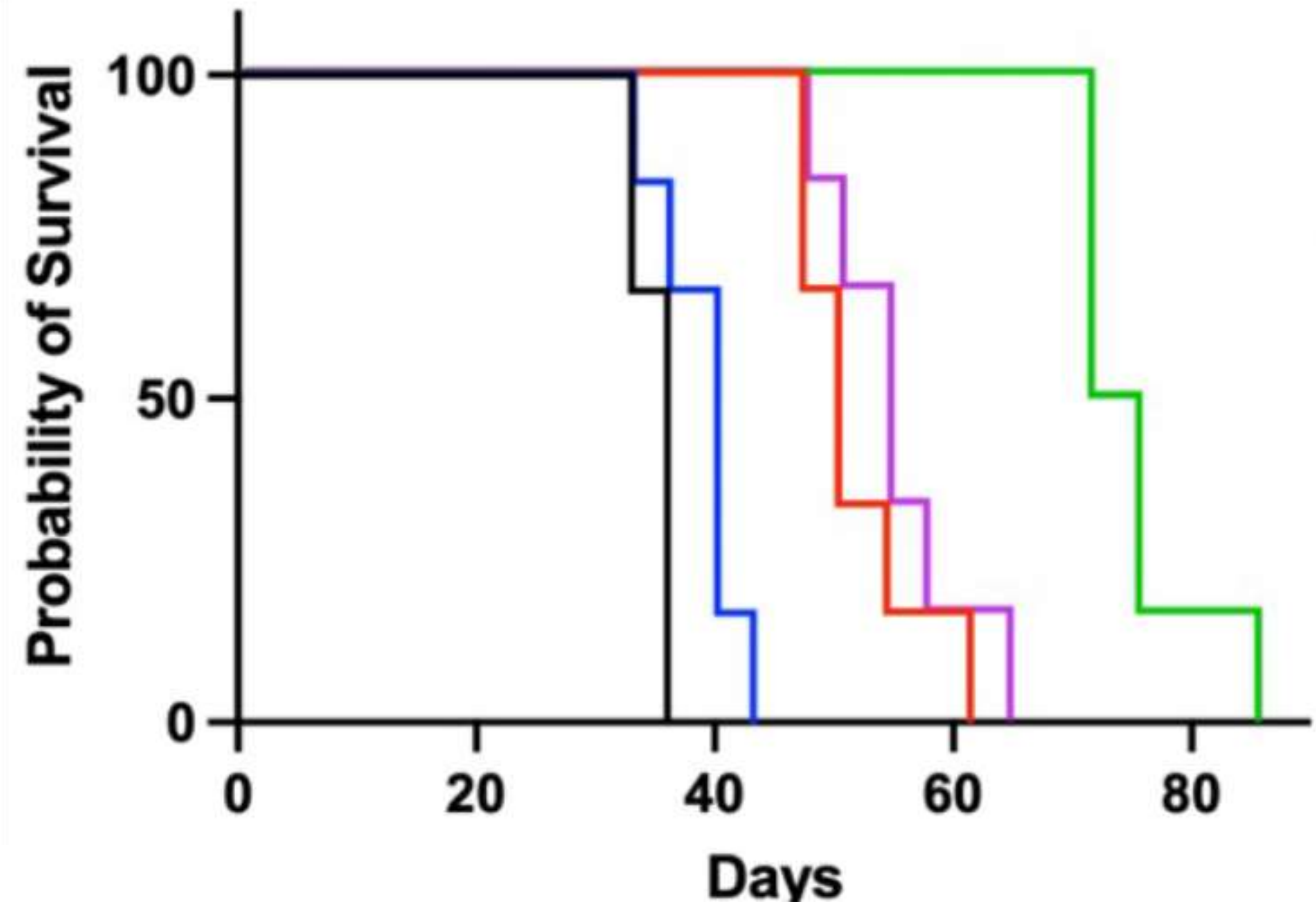
## MDA-MB-231/HER2



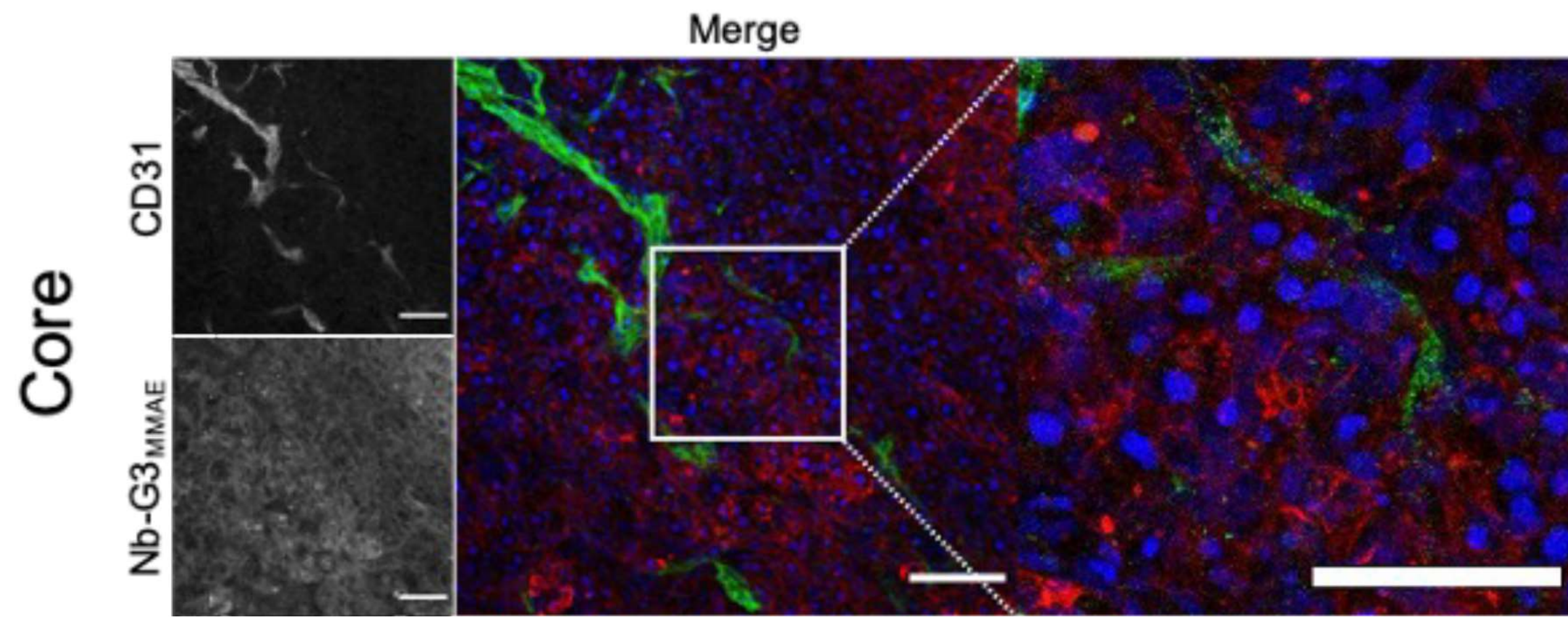
# Her2 Targeted Dendrimers Prolong Survival



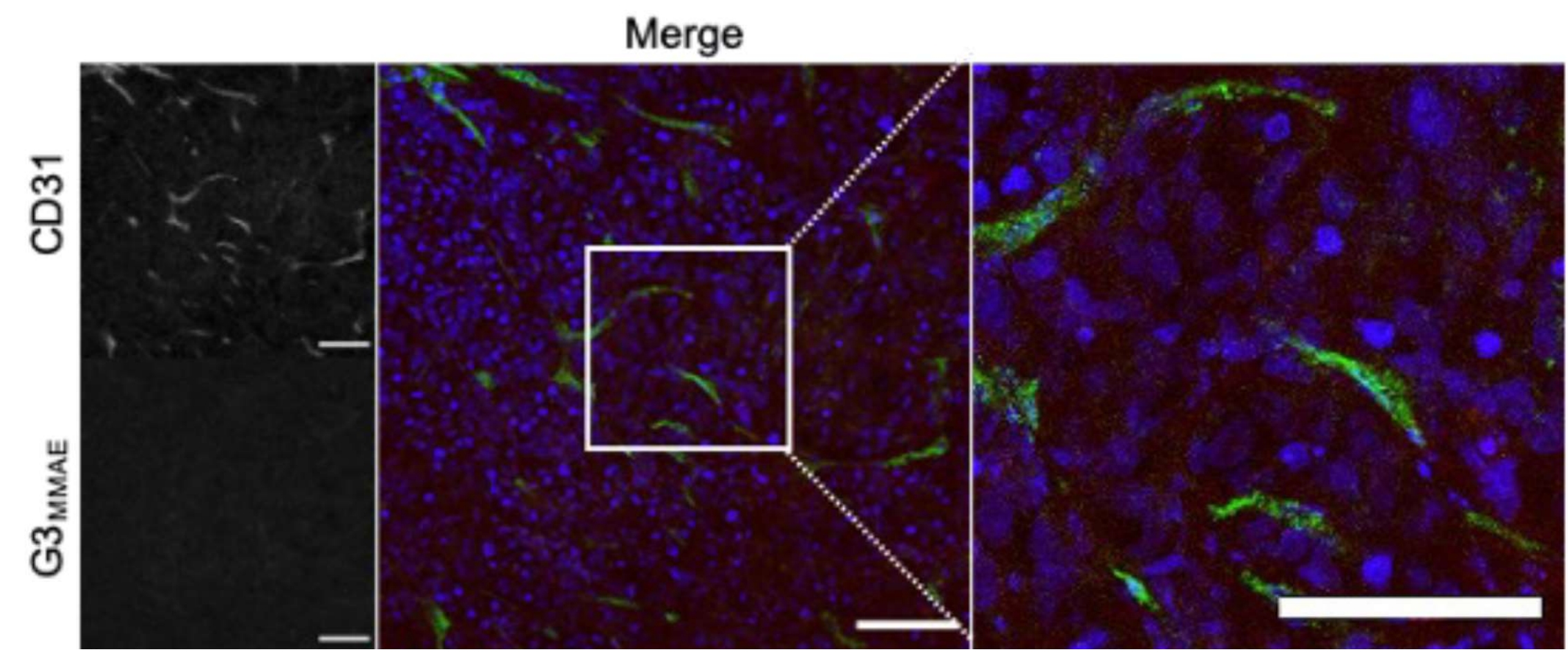
- Vehicle
- Herceptin (40mg/kg)
- Kadcyla (40mg/kg)
- Nb-G3<sub>MMAE</sub>
- G3<sub>MMAE</sub>



# Her2 Targeted Dendrimers Interact Differently

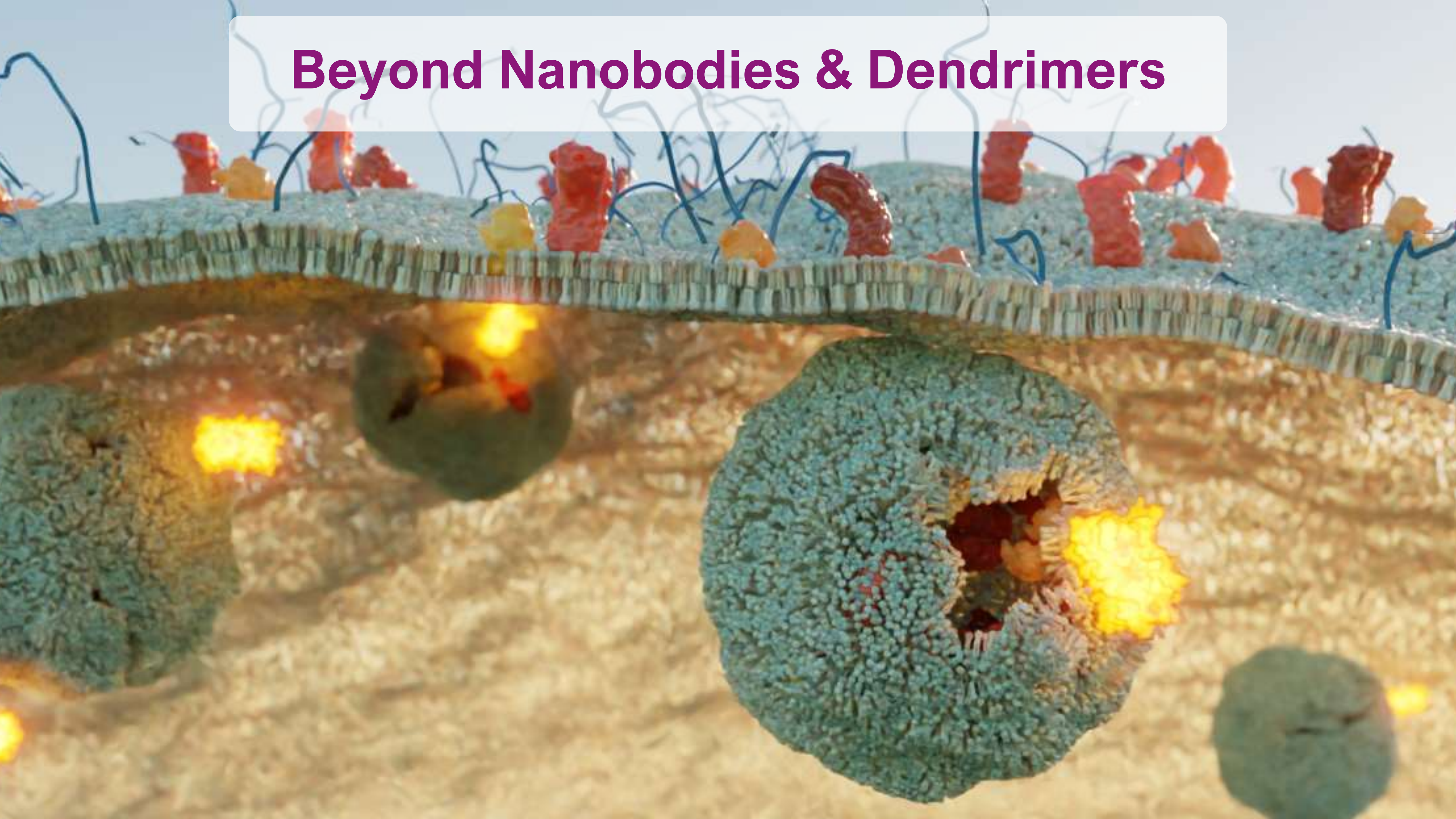


Nb-G3<sub>MMAE</sub>

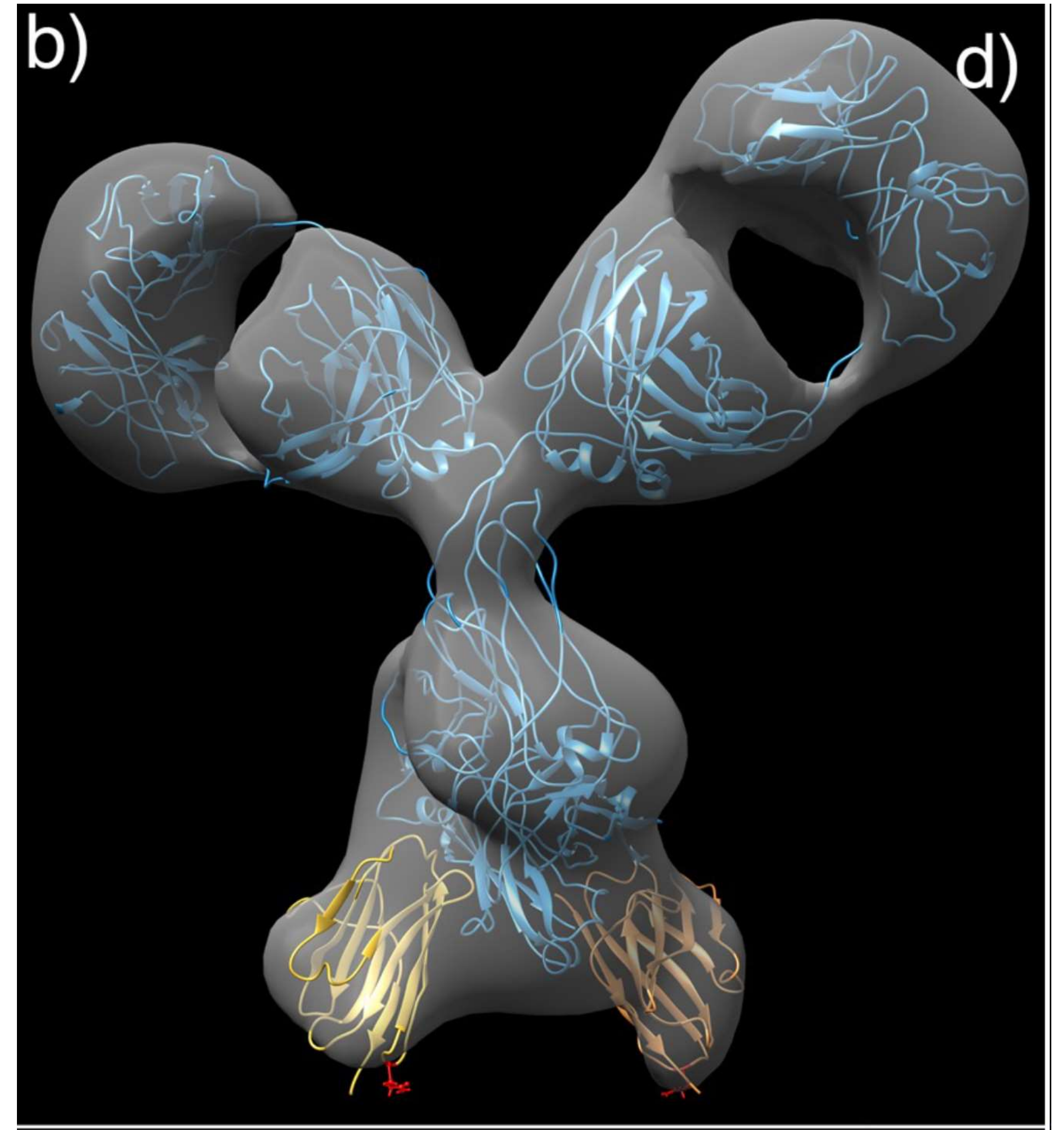
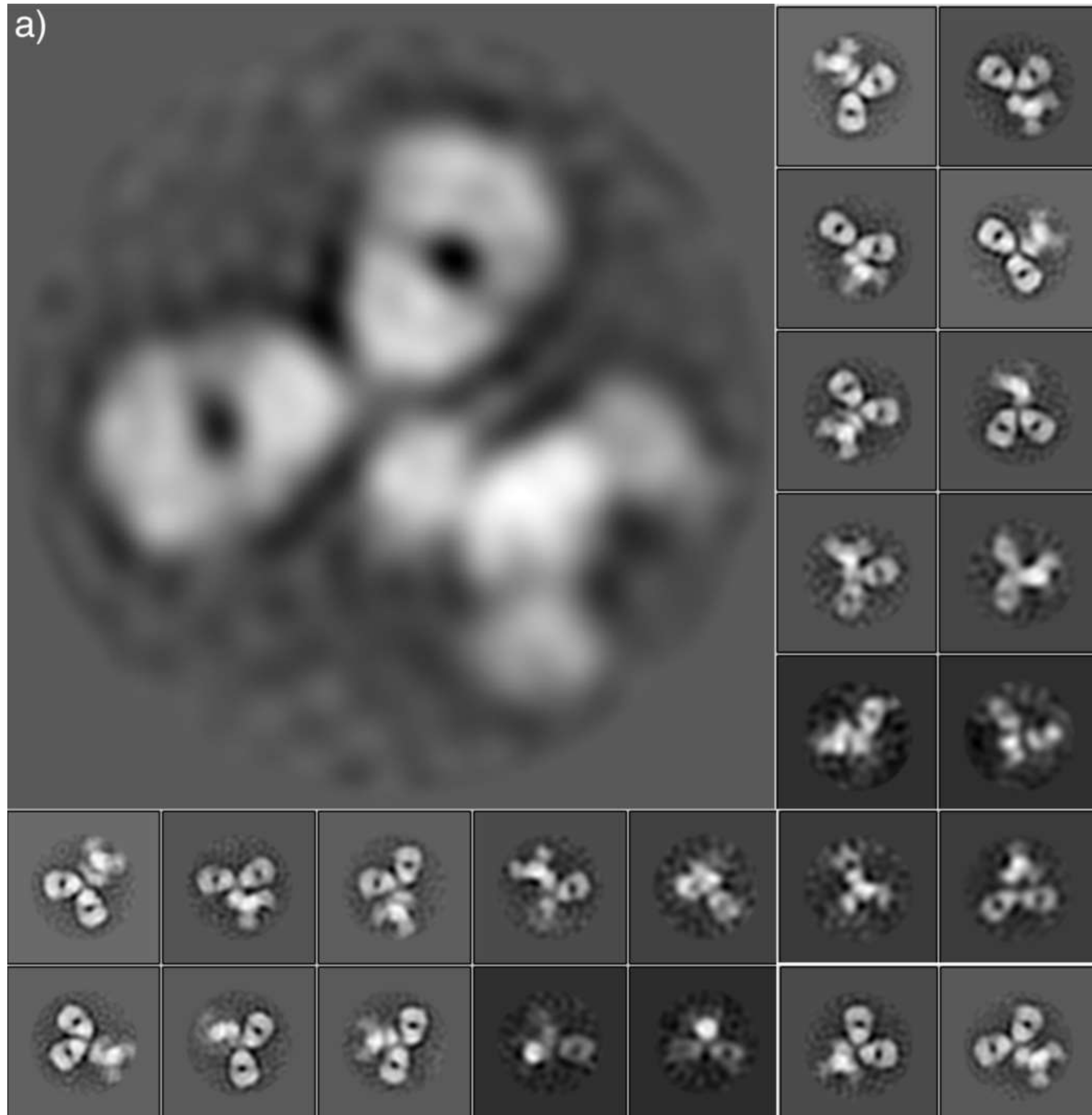


G3<sub>MMAE</sub>

# Beyond Nanobodies & Dendrimers



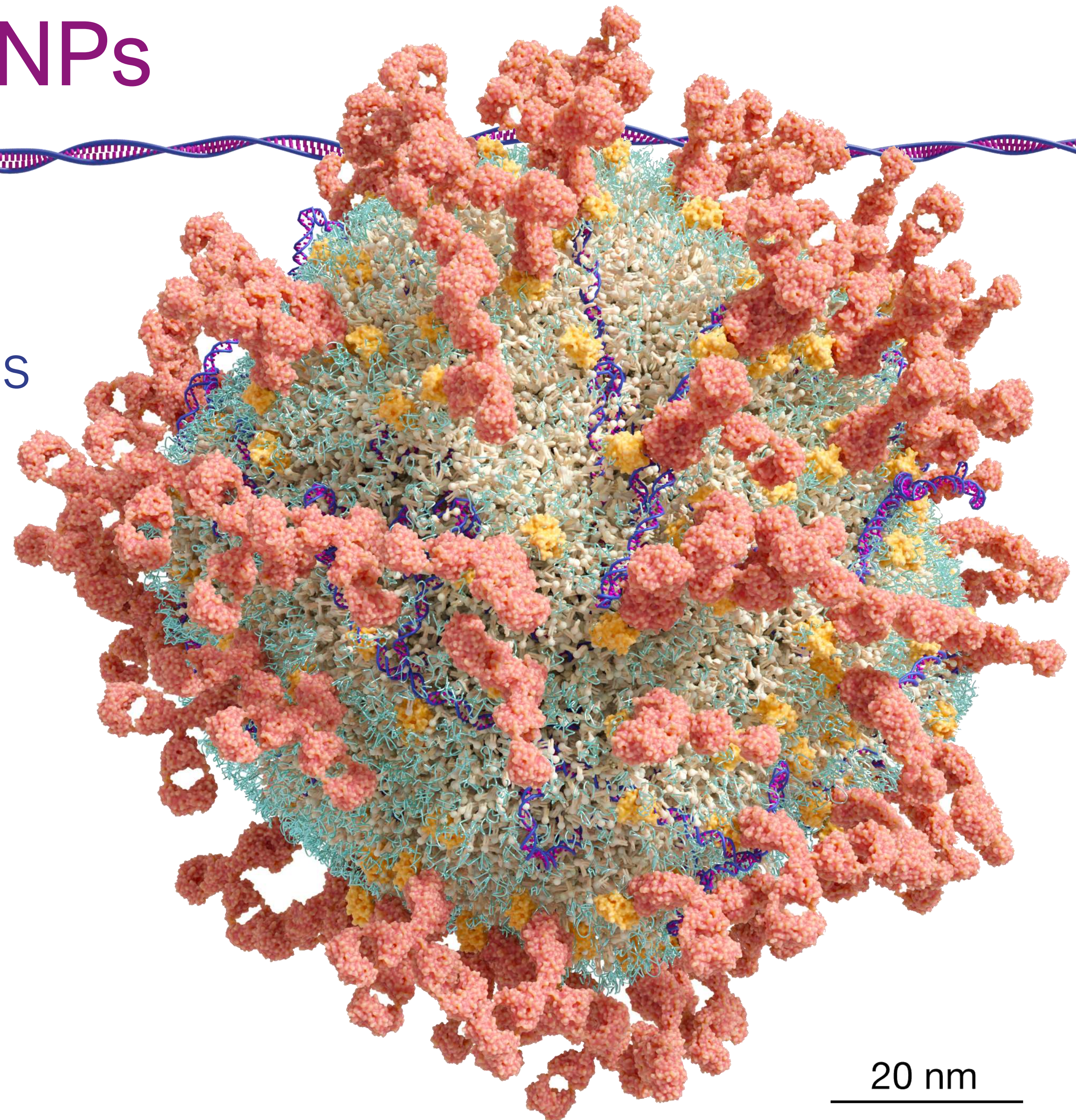
# Capturing Antibodies in their Optimal Orientation





# Precisely Targeted LNPs

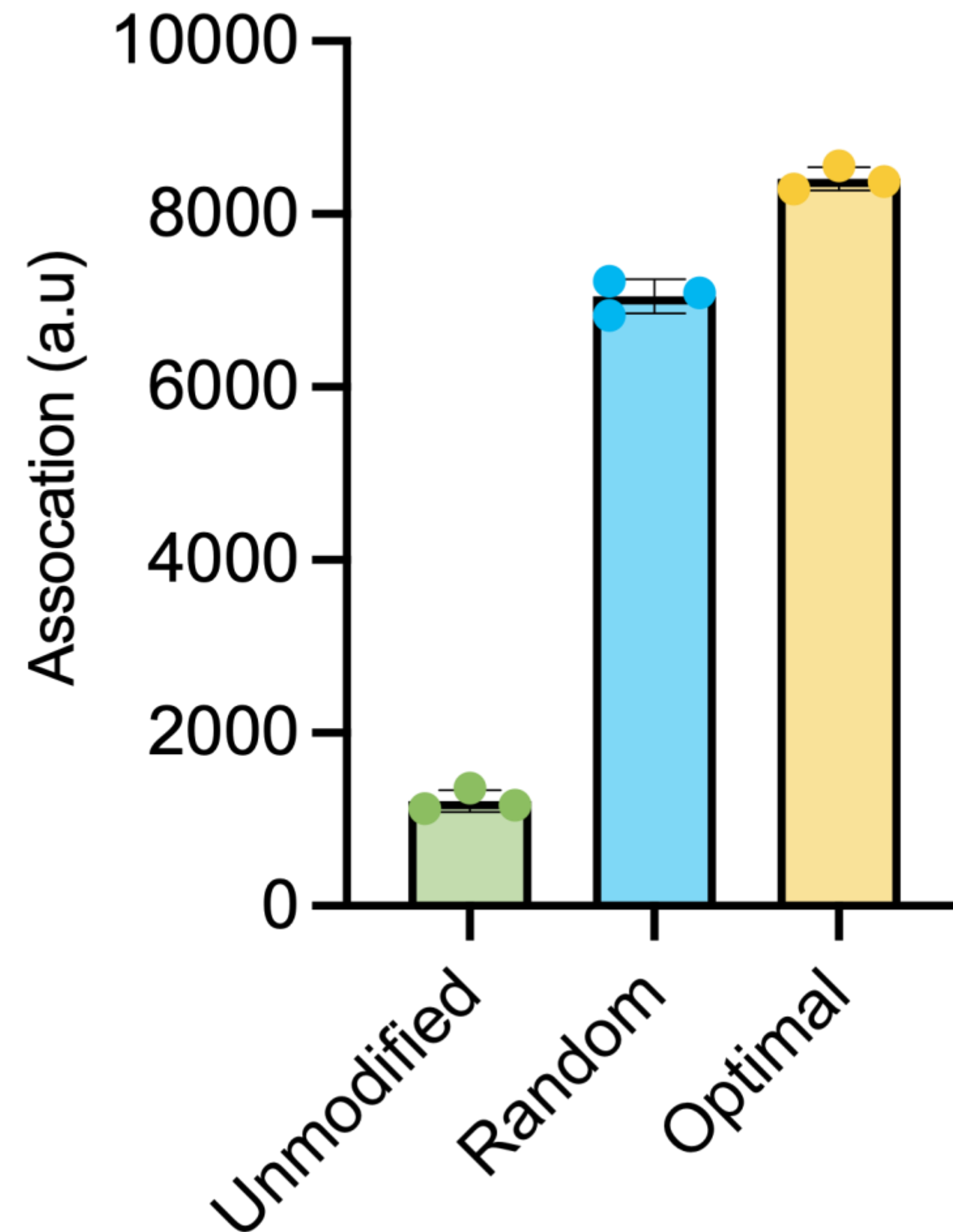
- 100 optimally oriented antibodies per particle
- Simple purification
- No aggregation



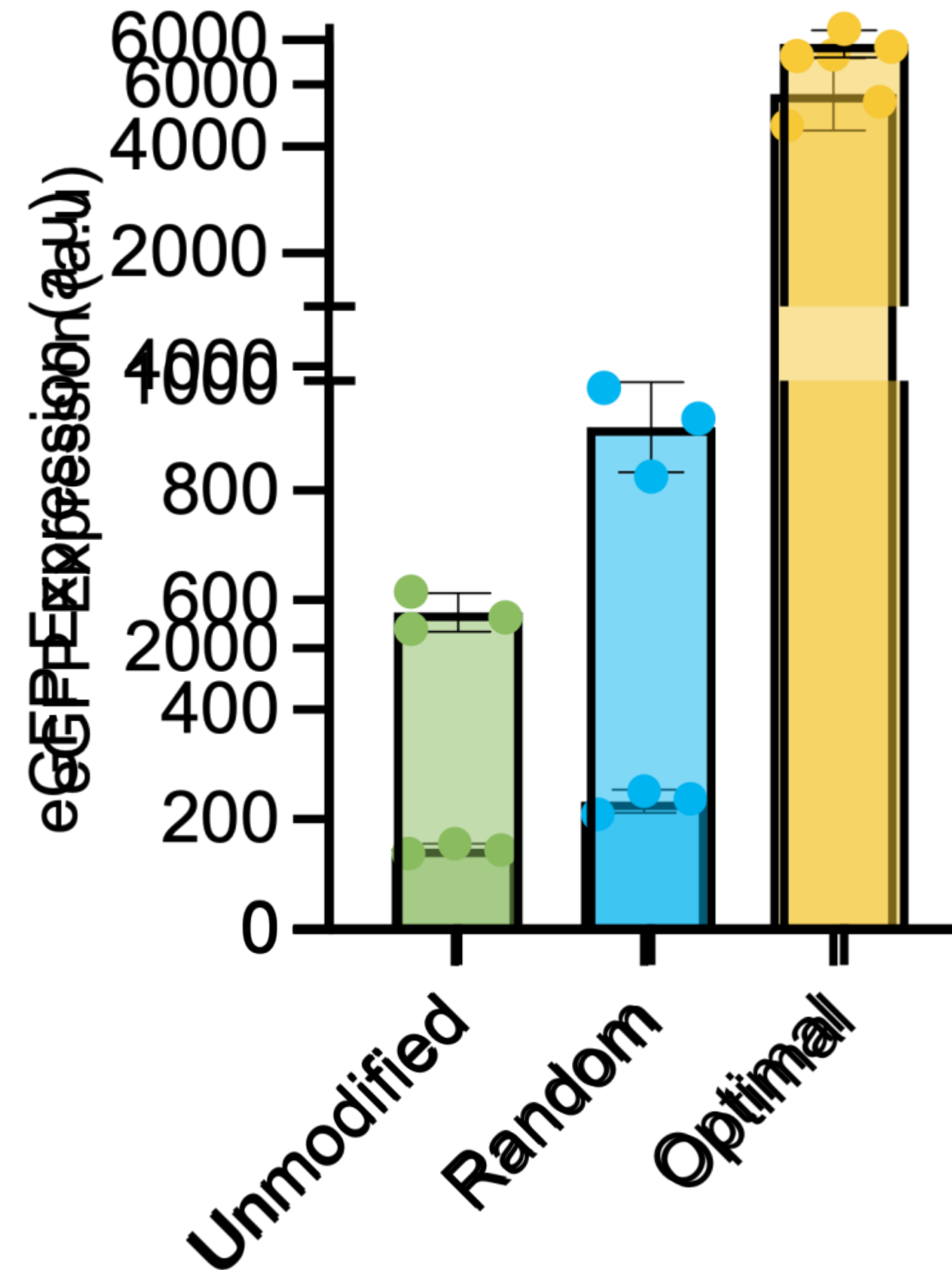
# Orientation control improves protein expression



## LNP Binding



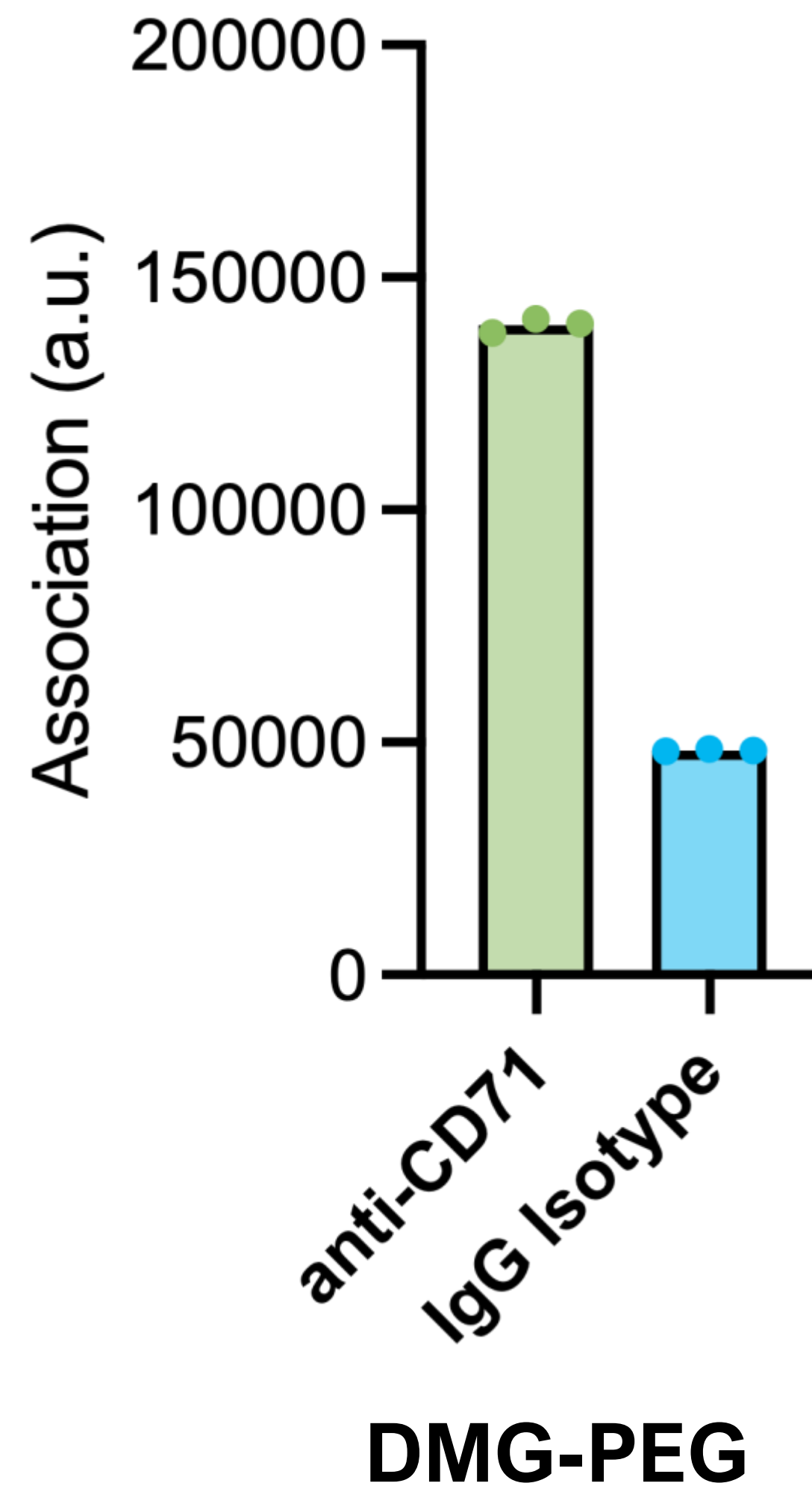
## Protein Expression



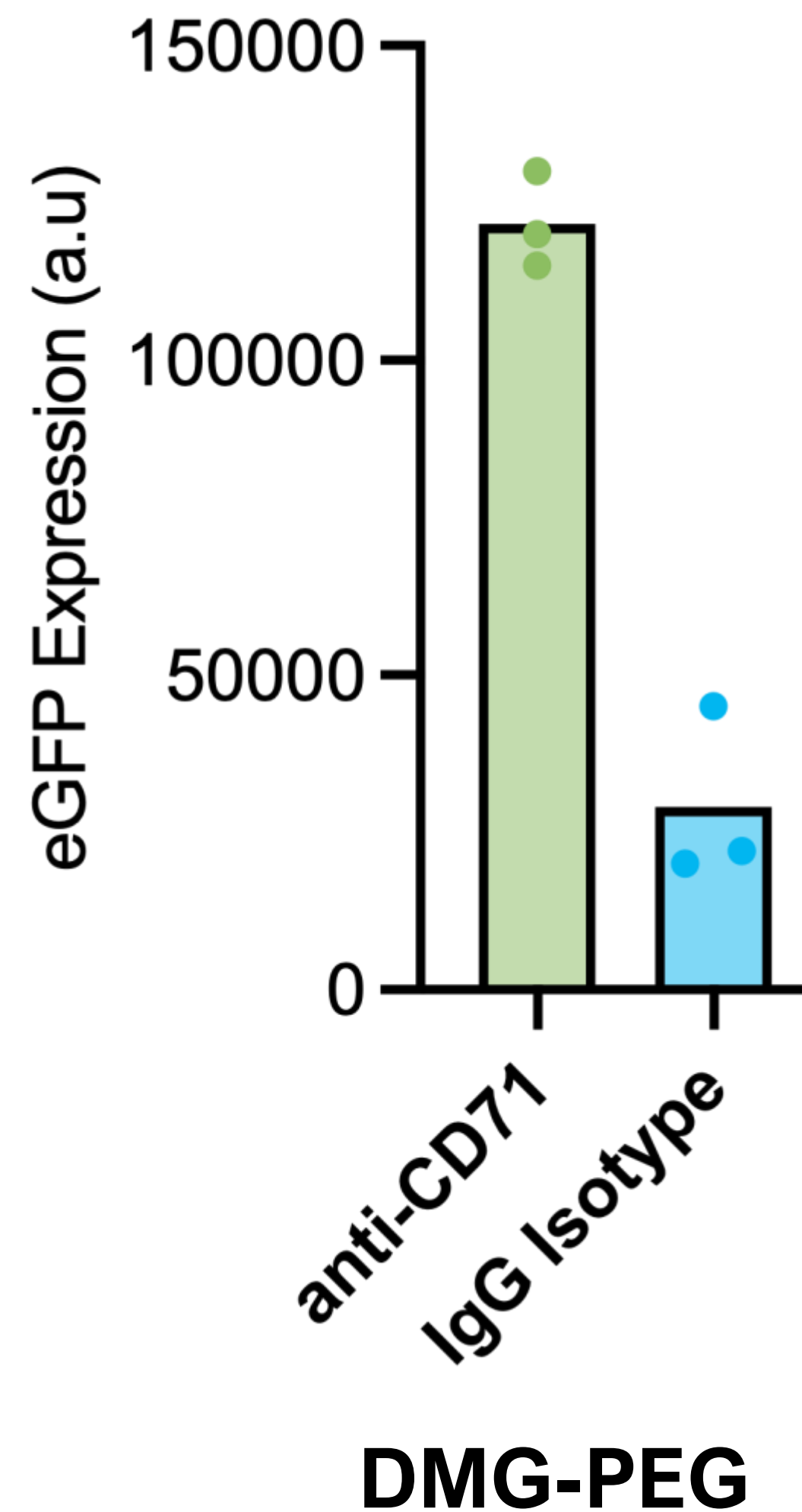
# Existing LNPs are a poor starting point



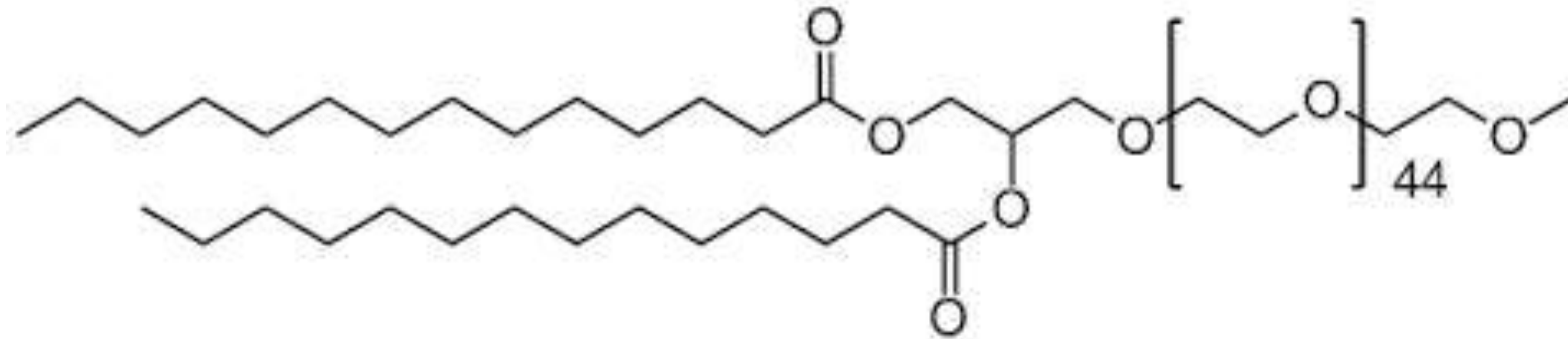
## LNP Binding



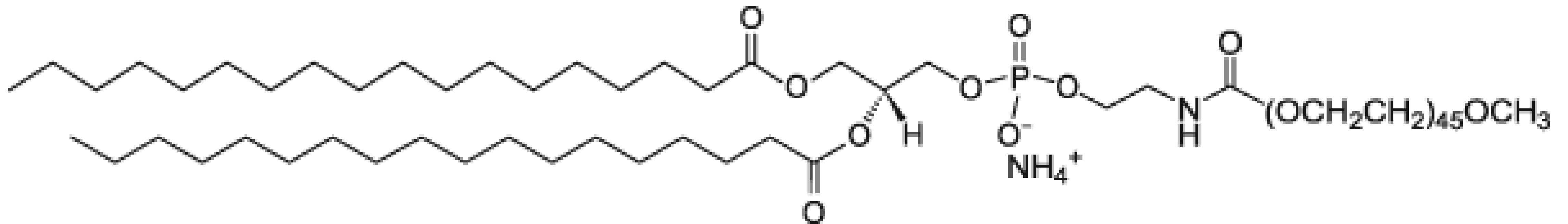
## Protein Expression



# Keeping PEG Attached



**DMG-PEG2000**

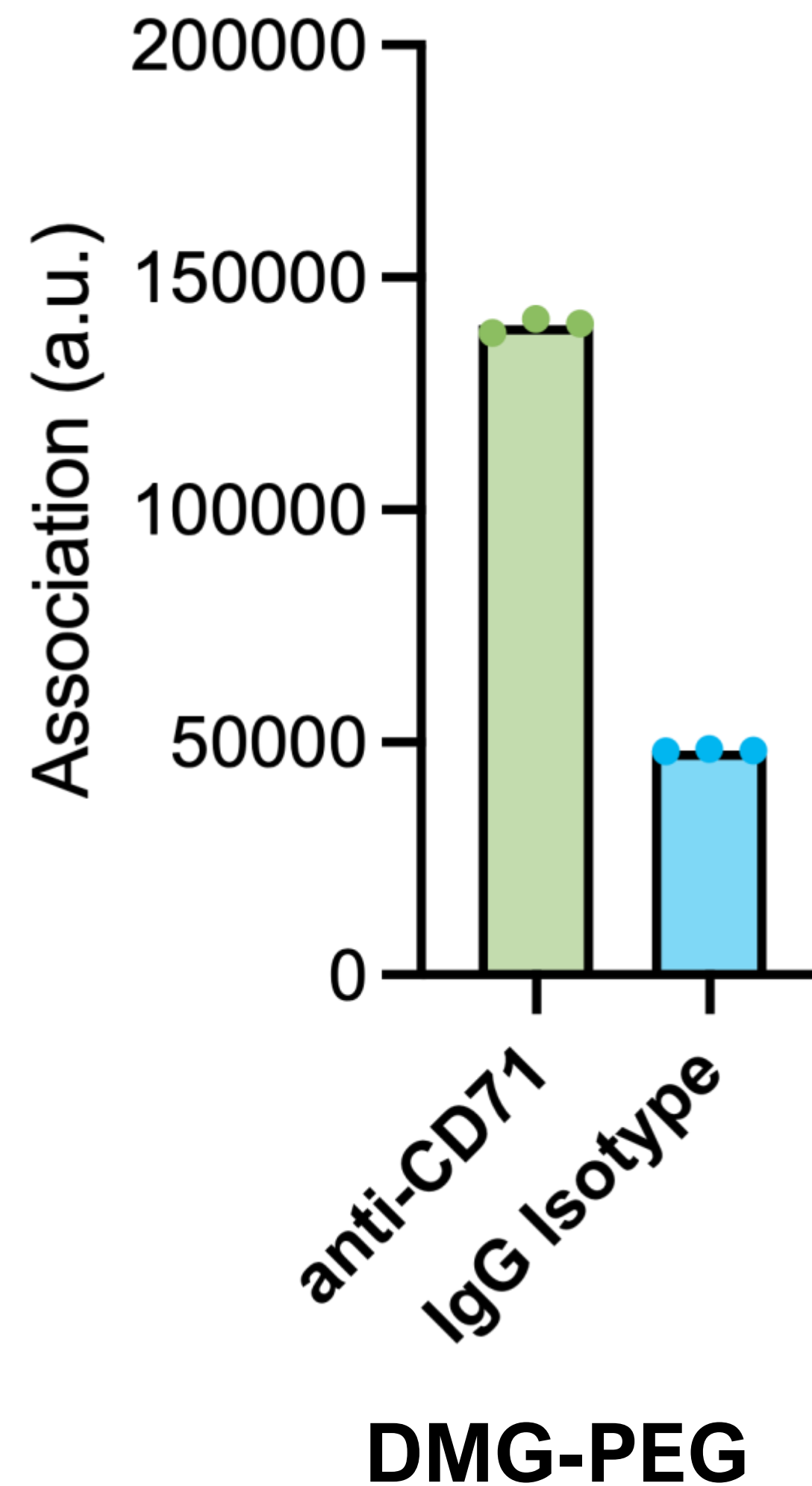


**DSPE-PEG2000**

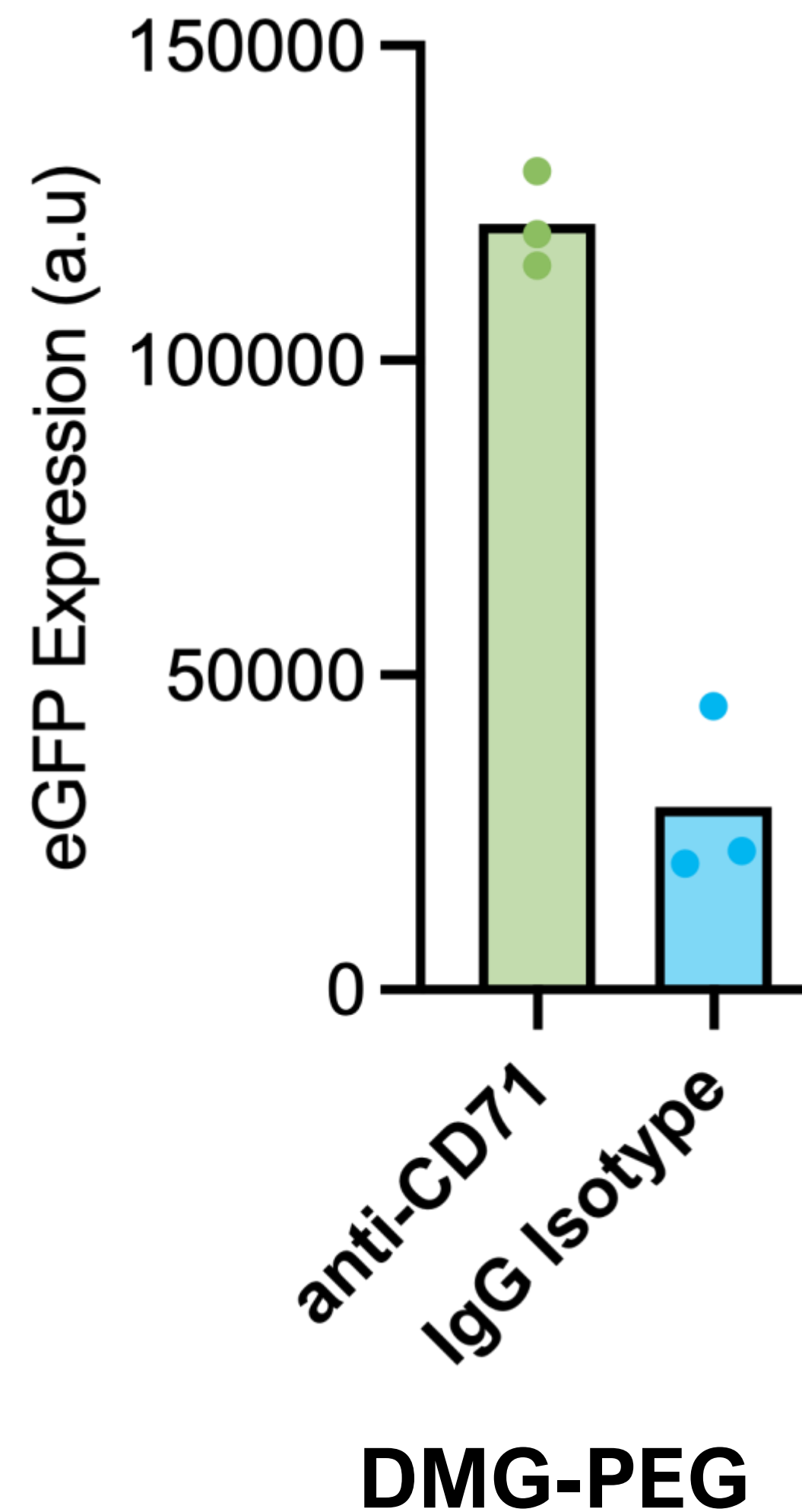
# Existing LNPs are a poor starting point



## LNP Binding

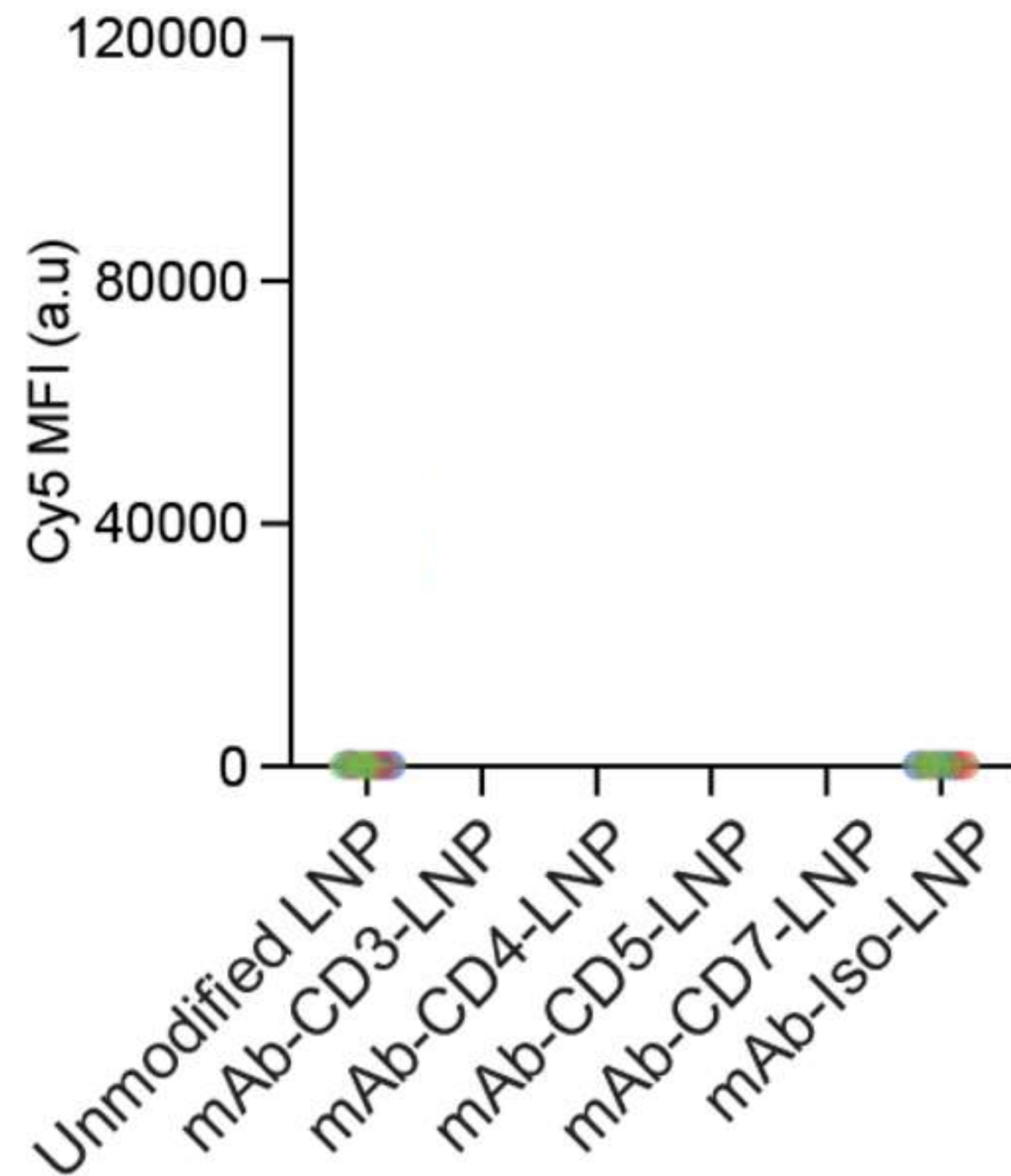


## Protein Expression

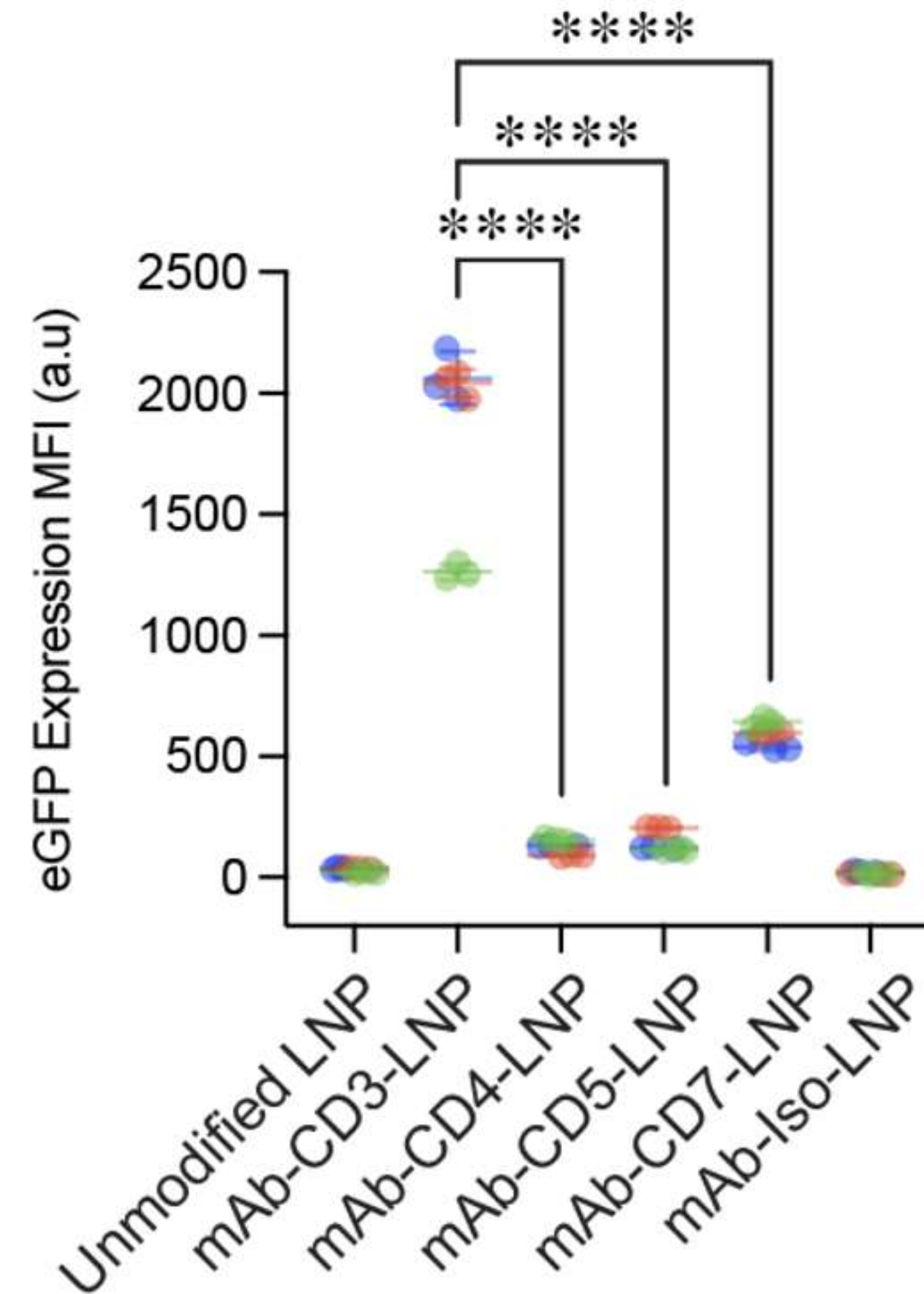


# Screening for the Optimal T cell Target Receptor

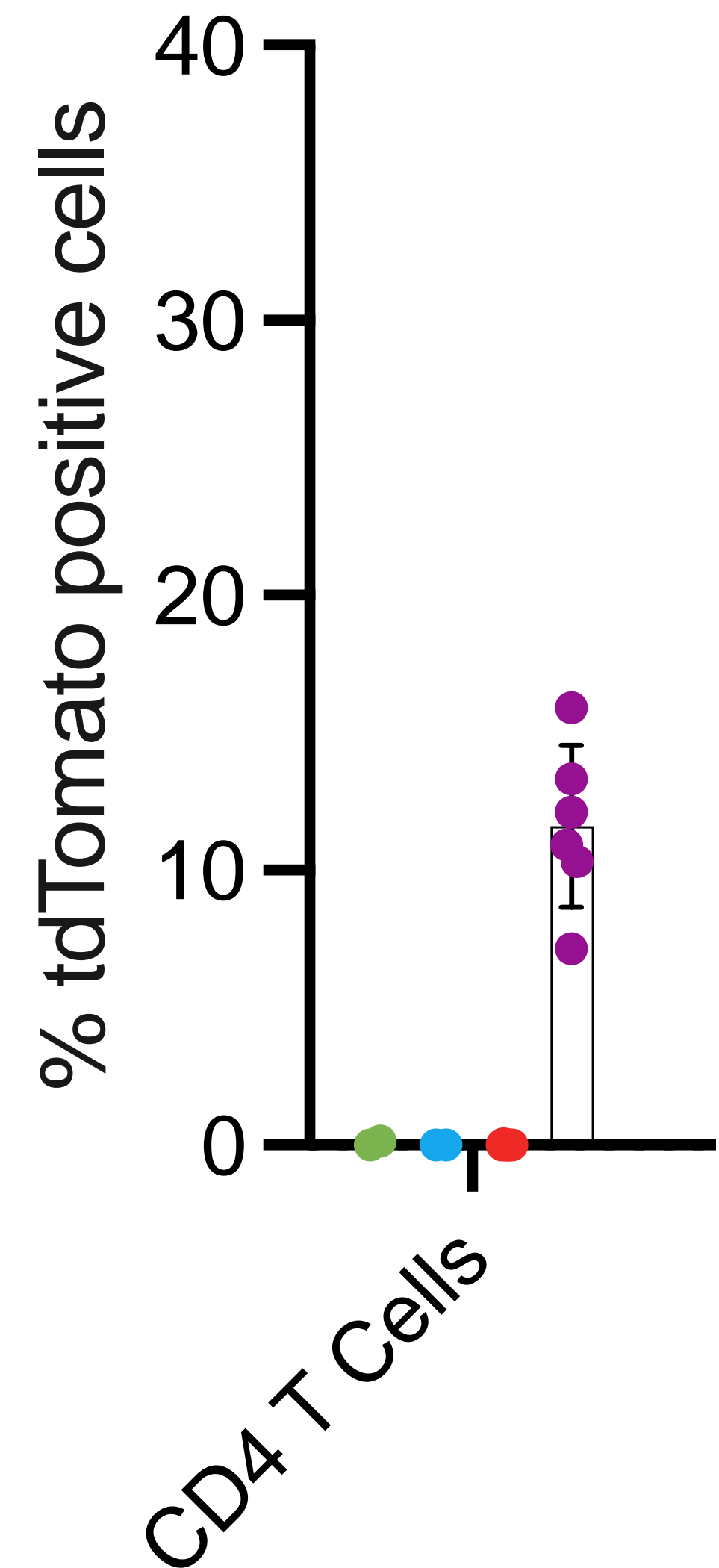
## LNP Binding



## Protein Expression

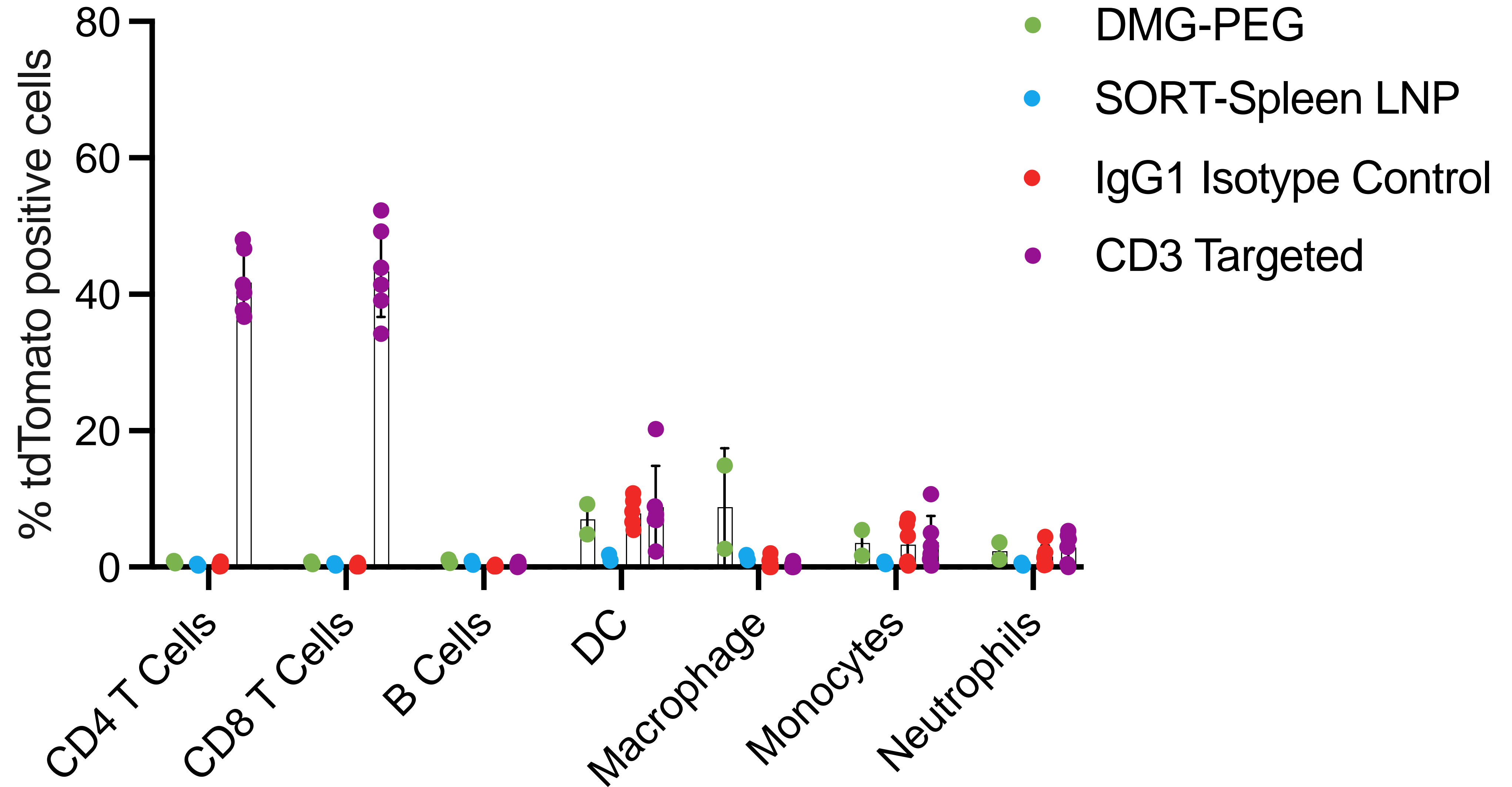


# Targeting Circulating Blood Cells



- DMG-PEG
- SORT-Spleen LNP
- IgG1 LNP
- CD3 targeted

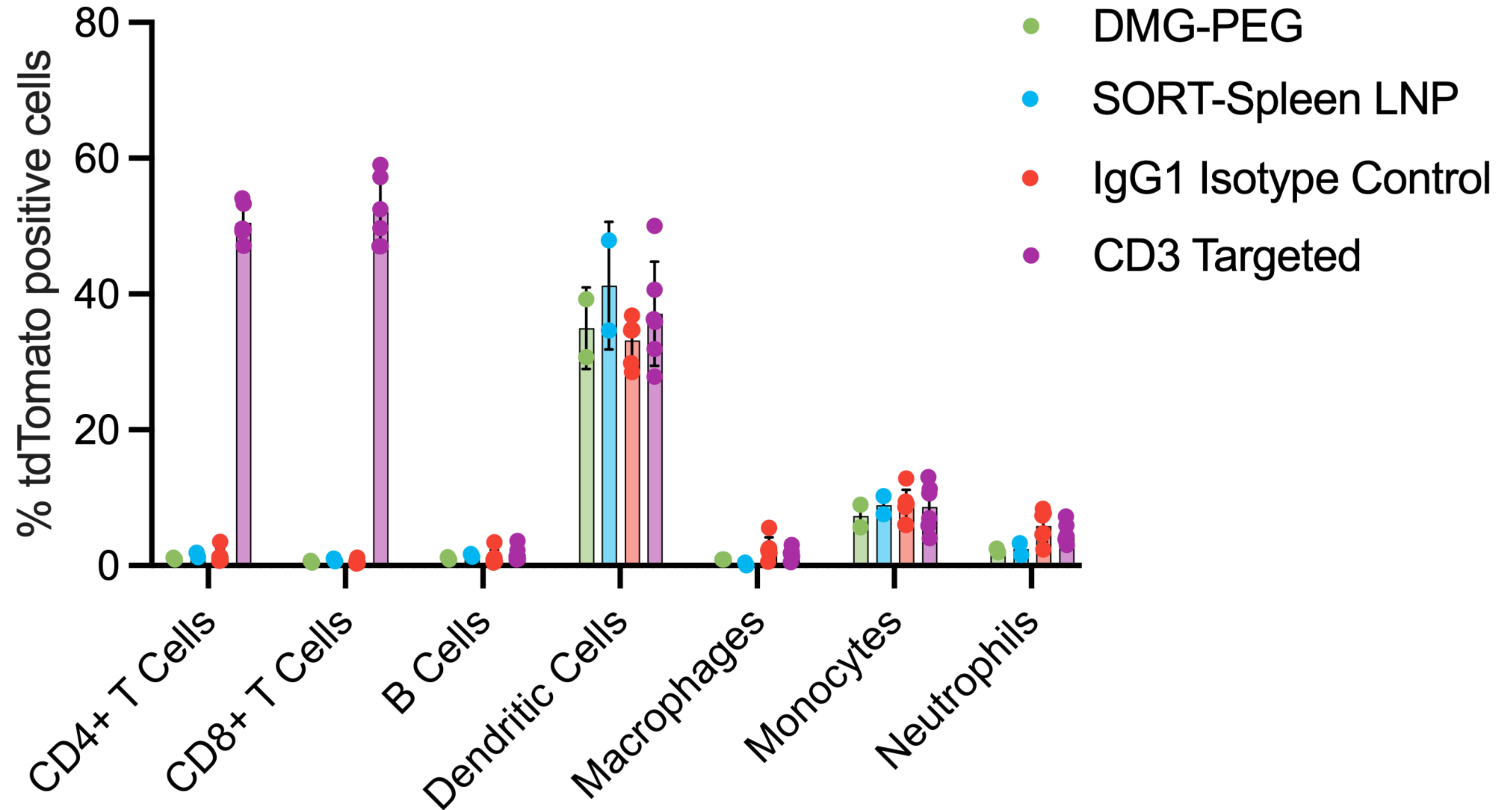
# Liver Targeting



2 $\mu$ g mRNA per mouse (100 $\mu$ g per kg)



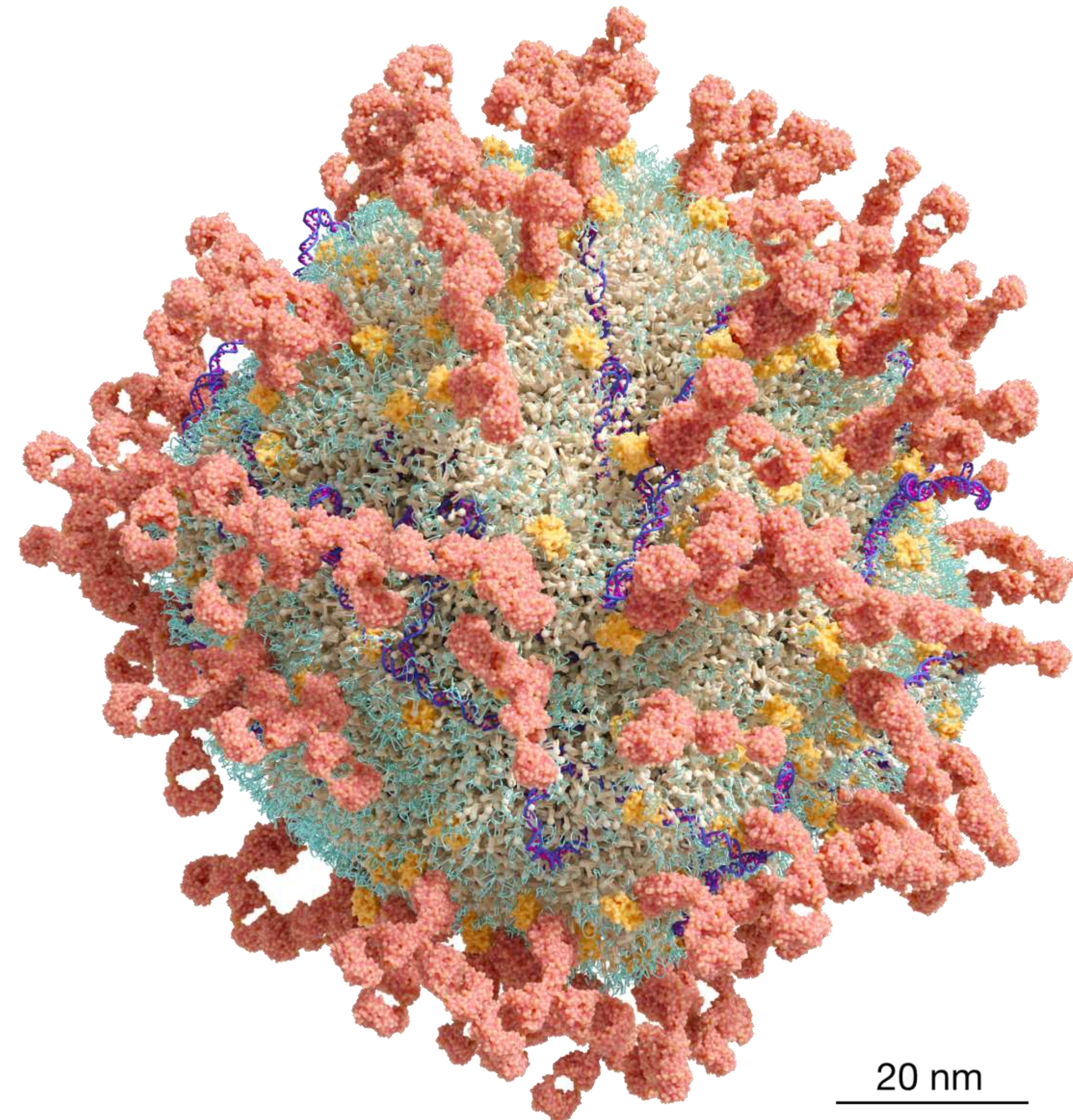
# Delivery to Specific Cells in the Spleen



2 $\mu$ g mRNA per mouse (100 $\mu$ g per kg)

# Summary

- Pointing in the Right Direction
  - Controlling antibody orientation improves target cell binding
- Not just about accumulation
  - Activity is about where the drug is delivered
- Universal Antibody Capture
  - No chemical modifications of the antibody
  - Optimal orientation gives 10x improved expression
  - Not all target receptors are equal



# Acknowledgements



**Chris Porter**  
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