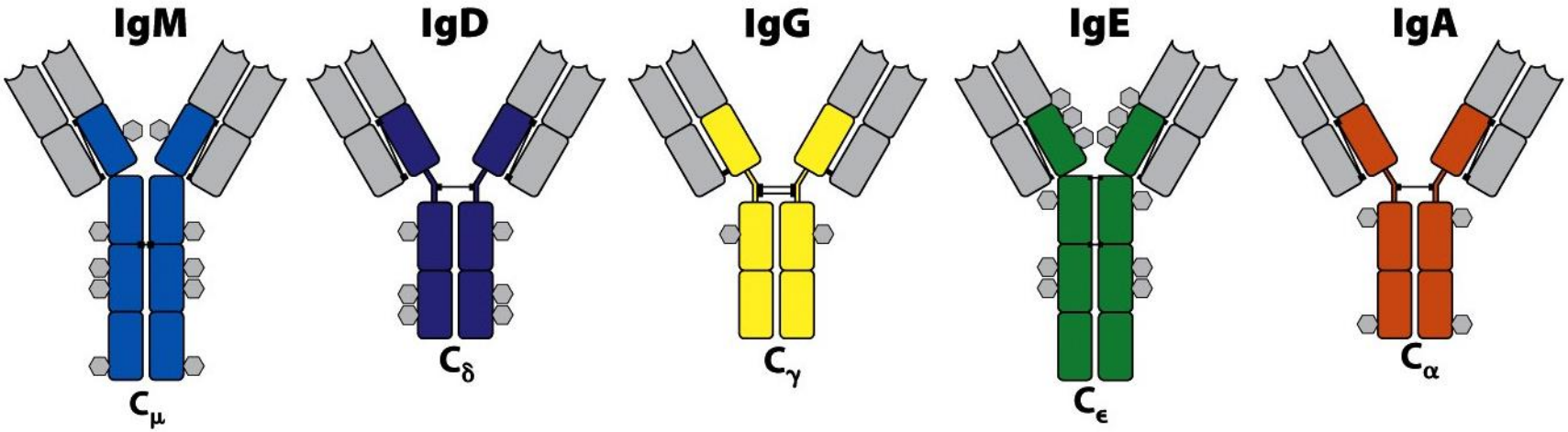
Adaptive antibody diversification through *N*-linked glycosylation of the immunoglobulin variable region

Sanne van de Bovenkamp
Immunopathology

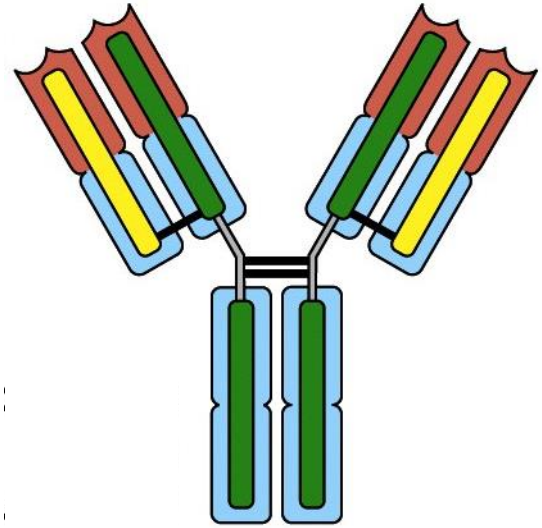
Immunoglobulins



IgG

- Heavy & light chain
- Variable & constant region

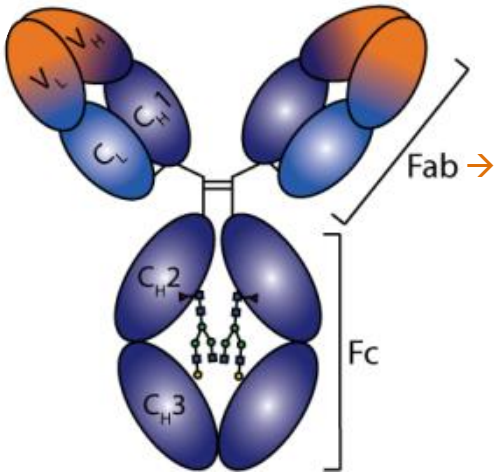
Antigen binding



C1q binding
FcγR binding

IgG glycosylation

15-25%



- Diseases
- Antigen binding
- Anti-inflammatory activity

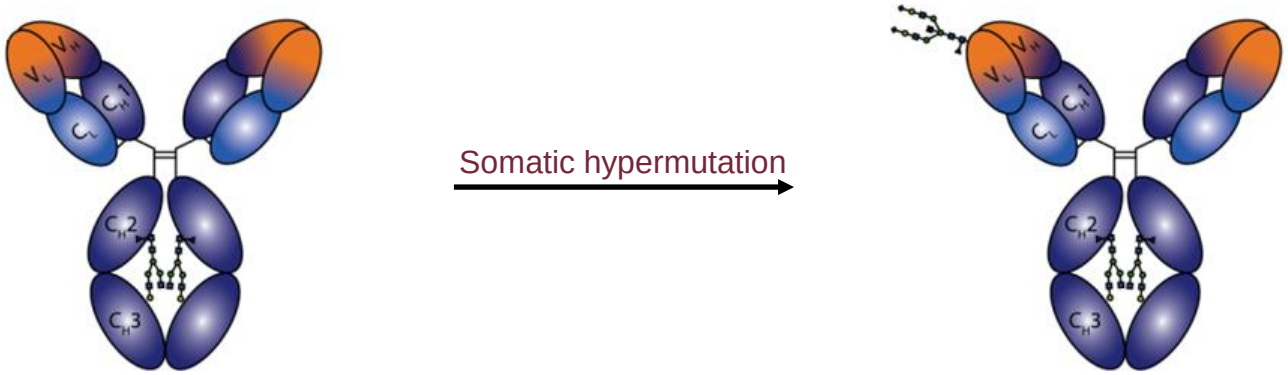
van de Bovenkamp *et al.* 2016 J Immunol

What is the role of Fab glycosylation in immunity?

How do antibodies get Fab glycans?

- *N*-glycosylation sites → asparagine – X (≠ proline) – serine / threonine

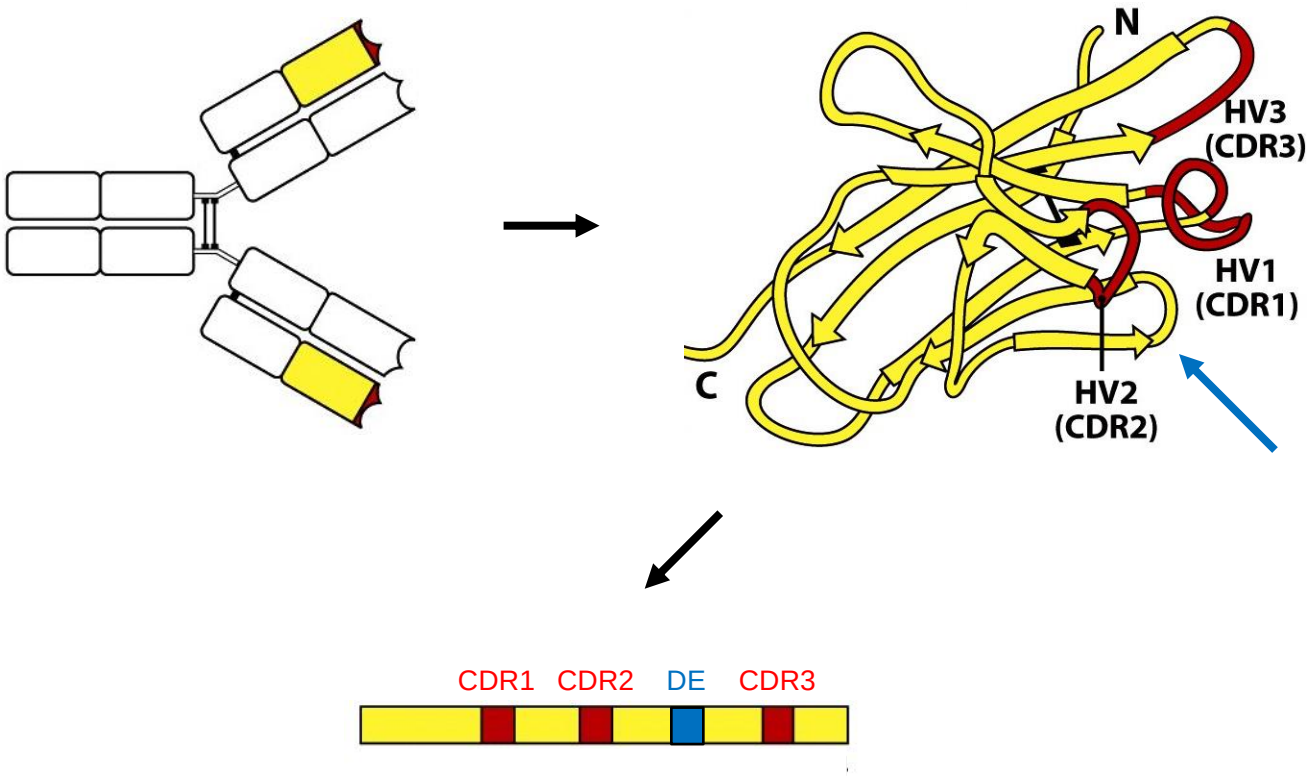
- Germline sequences (naive repertoire) → largely absent
- Rearranged sequences (memory repertoire) → present (10%)



Antibodies get Fab glycans through somatic hypermutation

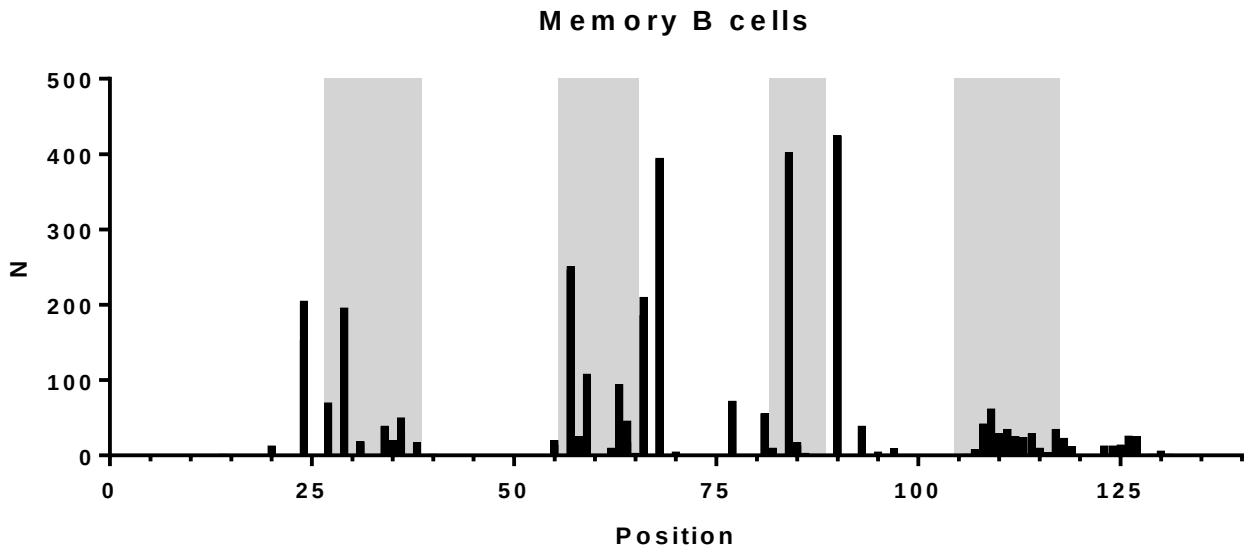
Is Fab glycosylation regulated?

- Random distribution of glycosylation sites?

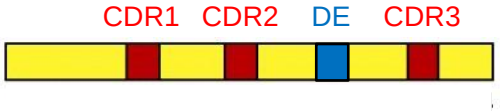


Distribution of glycosylation sites is not random

- Glycosylation sites in memory repertoire

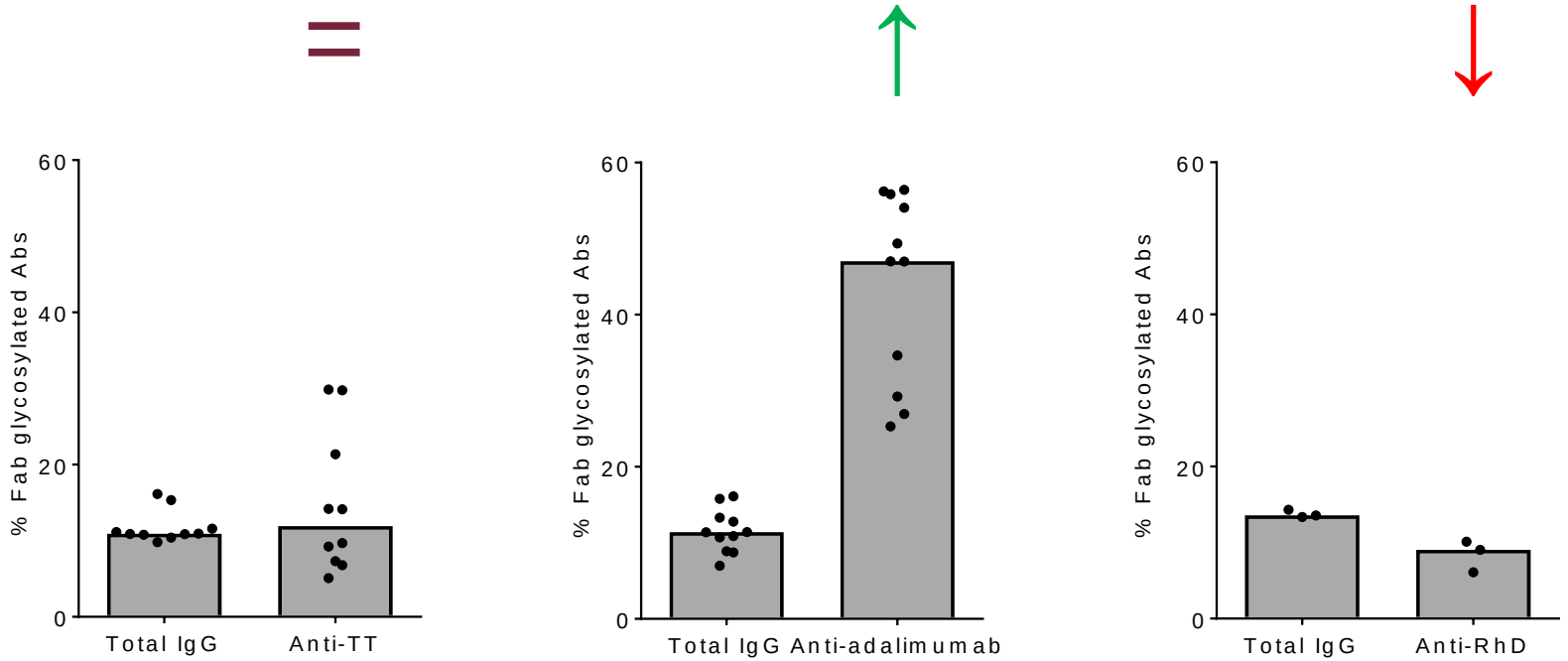


Fab glycosylation sites emerge near antigen-binding regions



van de Bovenkamp *et al.* 2018 Proc Natl Acad Sci U S A

Fab glycosylation levels of antigen-specific IgGs

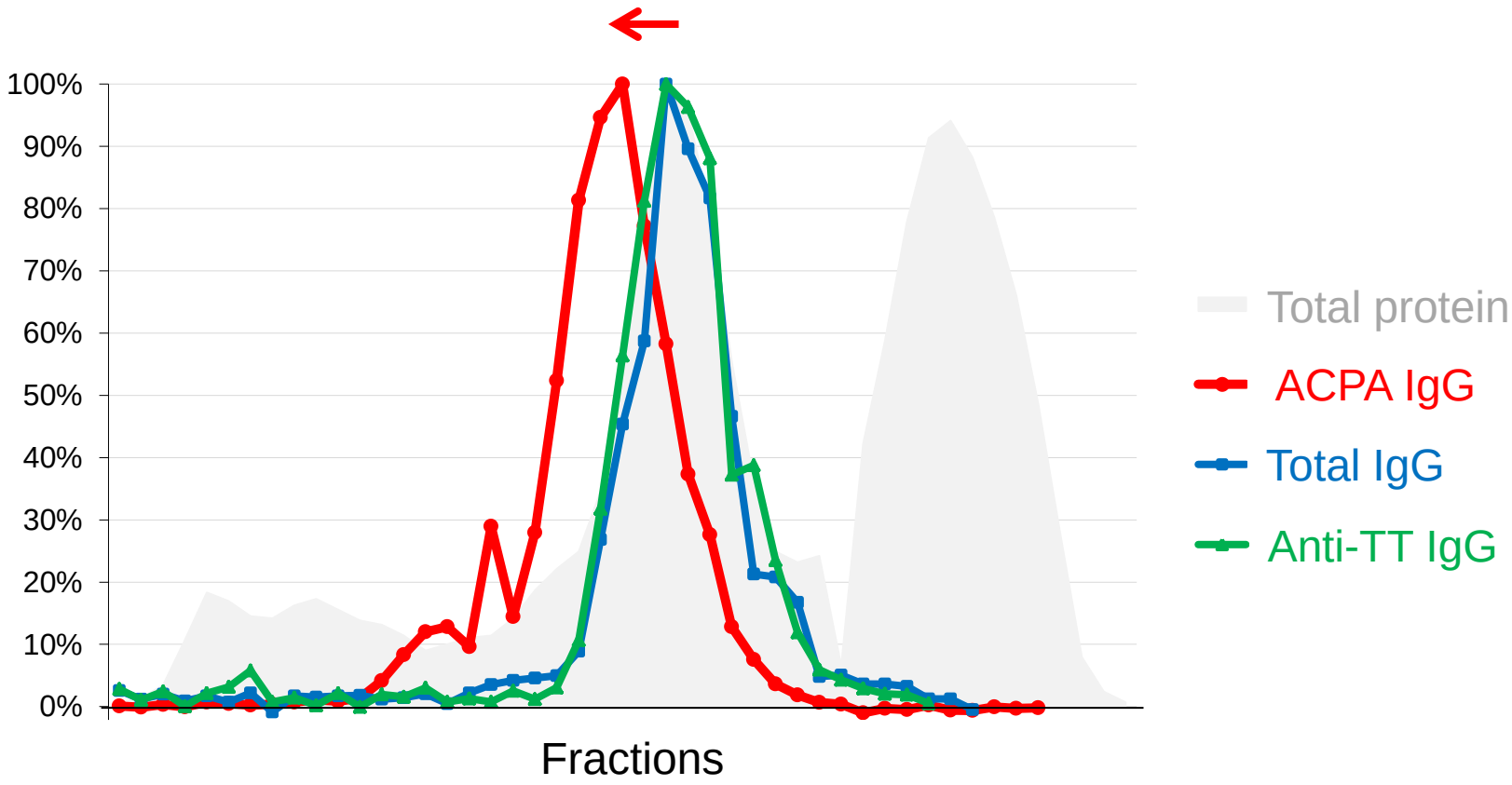


Anti-natalizumab

Anti-PLA2
Anti-infliximab
Anti-CCP
Anti-hinge

Fab glycosylation levels differ between different antigen-specific IgGs

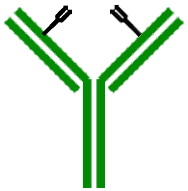
ACPA IgGs are highly Fab glycosylated



Rombouts *et al.* 2015 Ann Rheum Dis

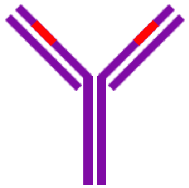
Effect of Fab glycosylation on antigen binding

Adalimumab Fab/
infliximab Fab



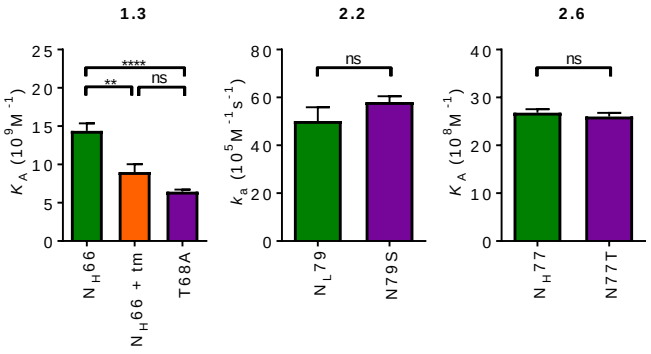
Anti-adalimumab/
anti-infliximab

+ tunicamycin

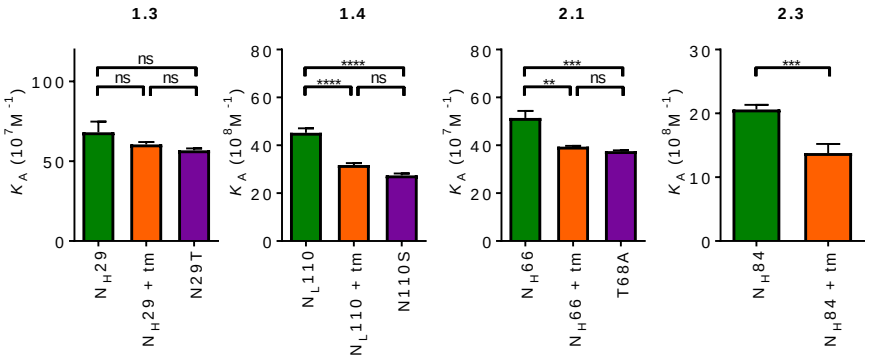


+ mutation

Anti-adalimumab

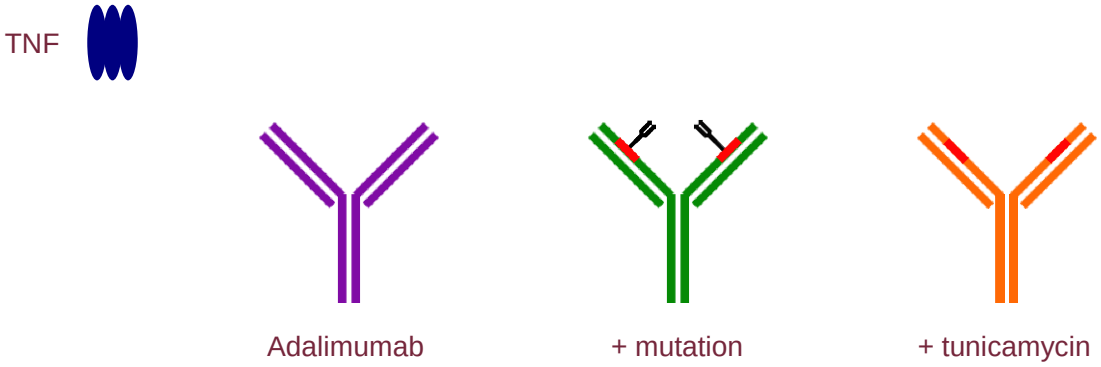


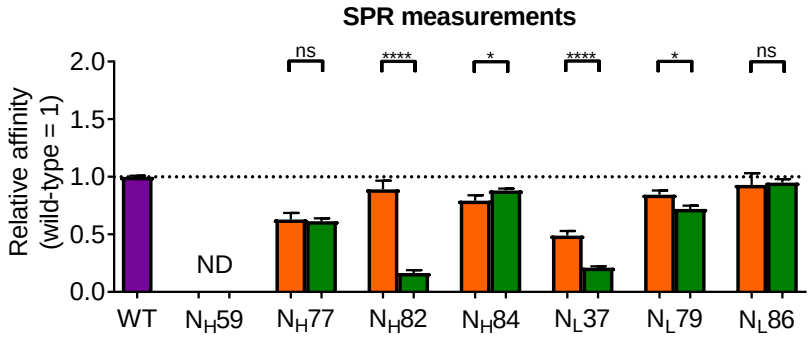
Anti-infliximab



Fab glycans introduced during an *in vivo* immune response can positively affect antigen binding

Effect of Fab glycosylation on antigen binding





Fab glycans randomly introduced at predicted sites can negatively affect antigen binding

van de Bovenkamp *et al.* 2018 Proc Natl Acad Sci U S A

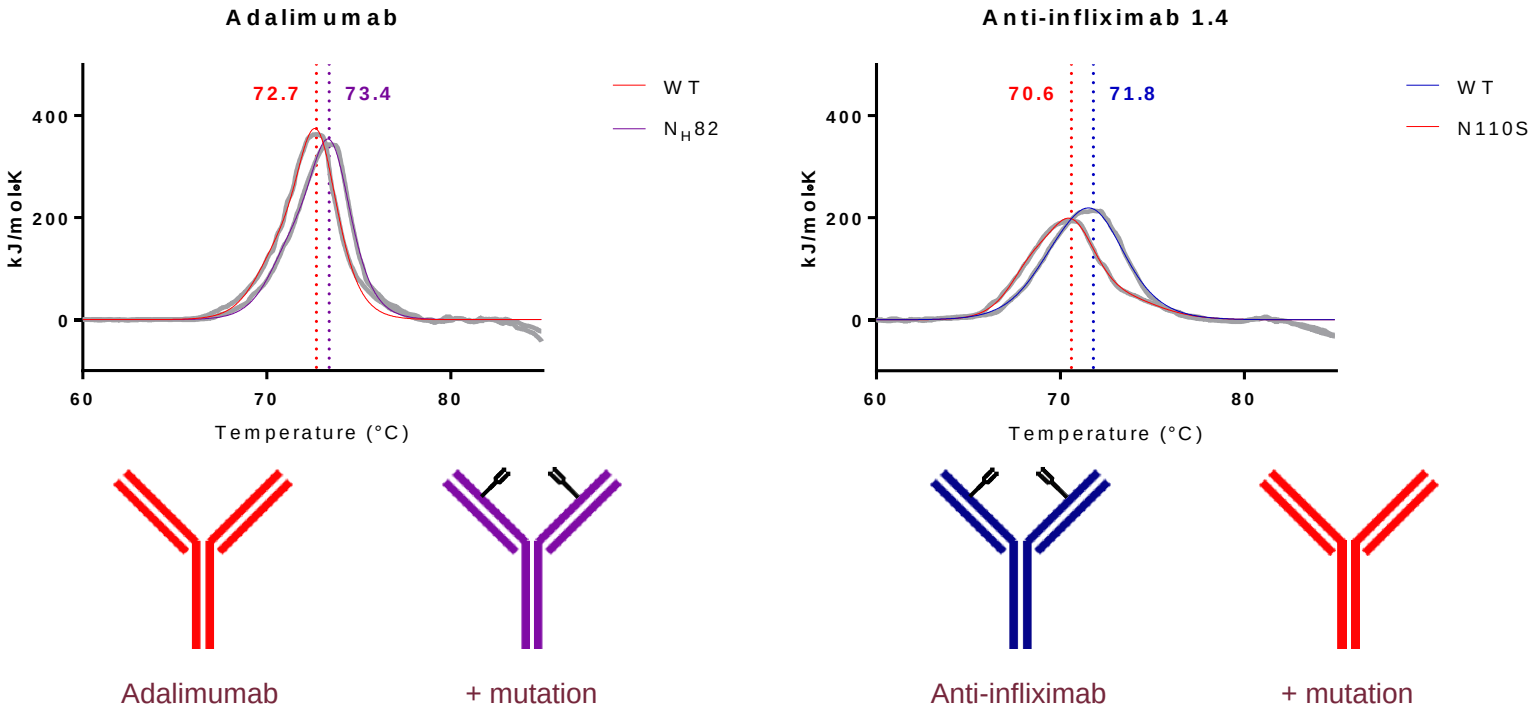
Is Fab glycosylation regulated?

- Fab glycosylation sites emerge near antigen-binding regions
- Fab glycosylation levels differ between different antigen-specific IgGs
- Fab glycans can modulate antigen binding

Antigen-associated selection of Fab glycosylated antibodies

Are there other functions?

- Effect on antibody stability?

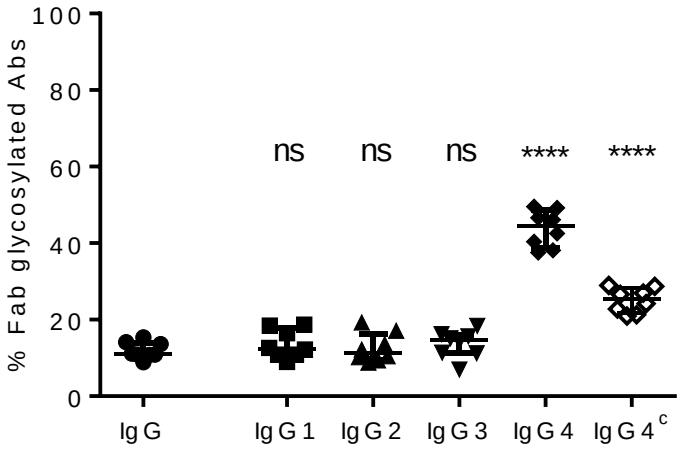


Fab glycans can contribute to antibody stability

van de Bovenkamp *et al.* 2018 Front Immunol

Are there other functions?

- Fab glycosylation levels differ between IgG subclasses
- IgG4 → tolerance
- Anti-inflammatory activity of IVIg
- Immune modulation (CD22)?



Fab glycans might have an immunomodulatory role

van de Bovenkamp *et al.* 2018 Proc Natl Acad Sci U S A

Model

Emergence
Somatic hypermutation

Role of Fab glycosylation in immunity

Regulation
Antigen-associated selection
Antigen-independent factors?

Function
Modulates antigen binding
Contributes to antibody stability
Immune modulation?

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