

# Characterizing antibody-antigen/superantigen interactions

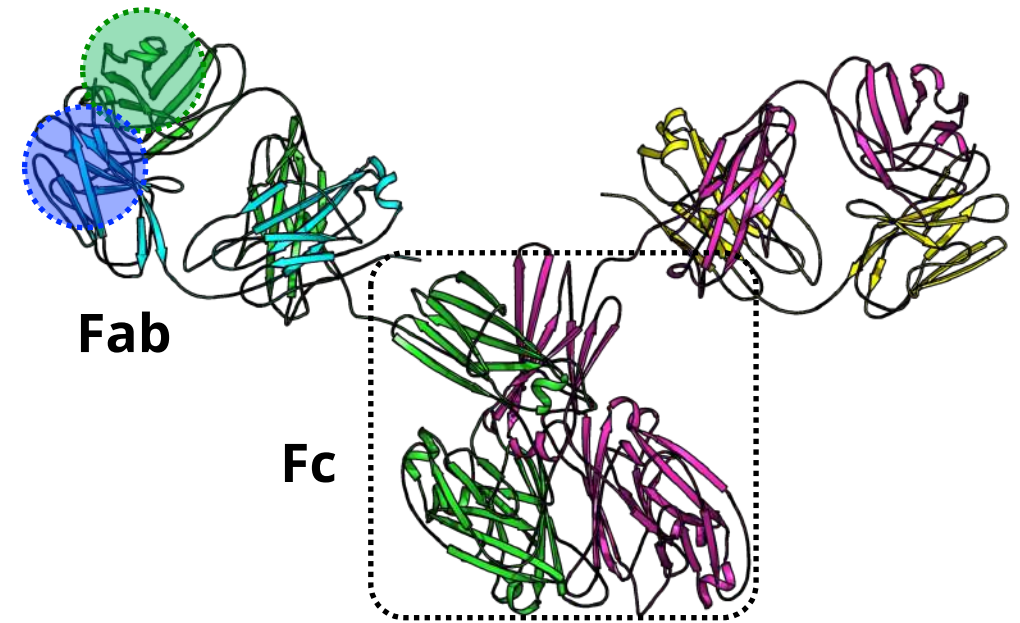
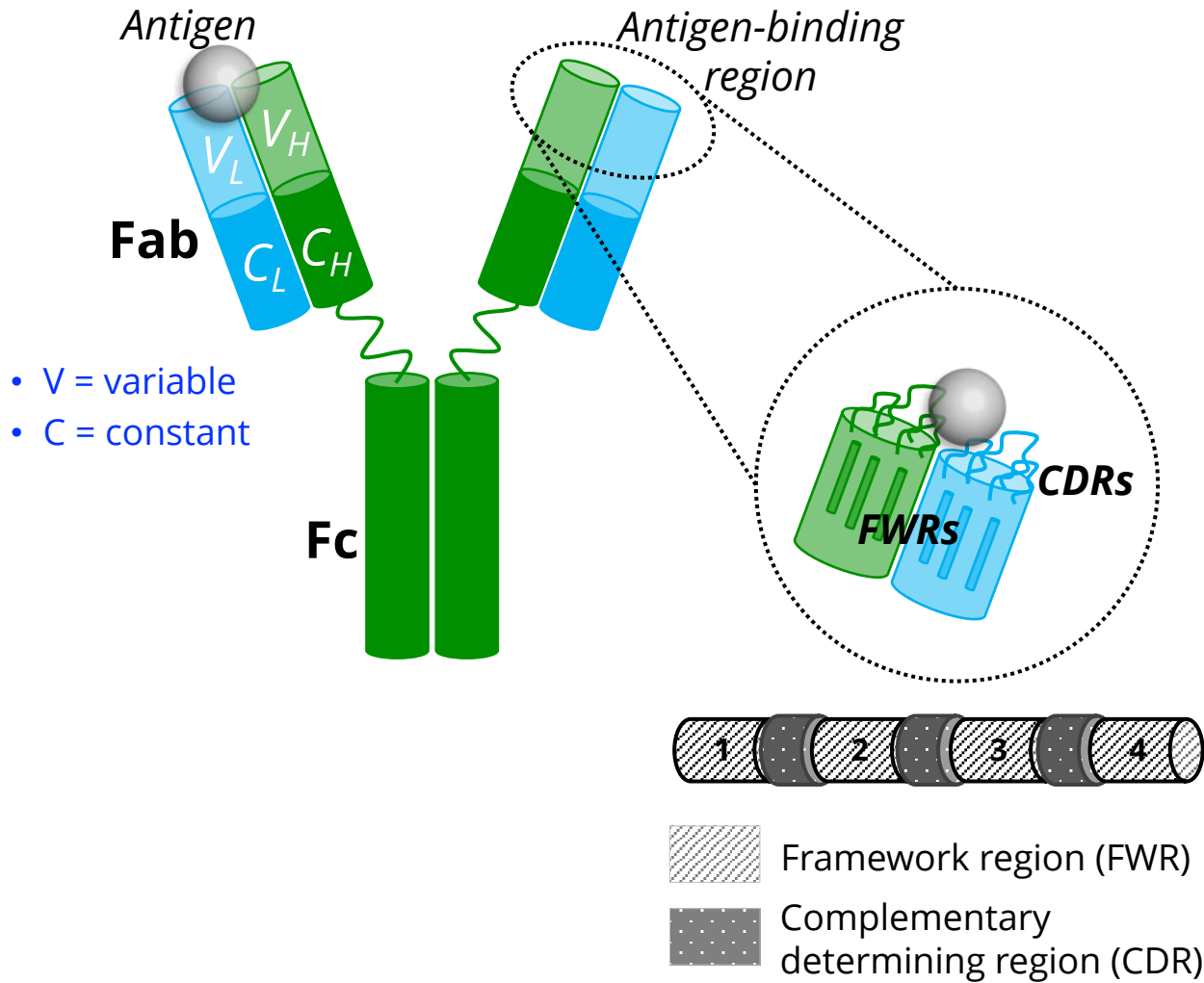
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# Antibody structure



# Antibody structure

## VH family (heavy variable FWRs):

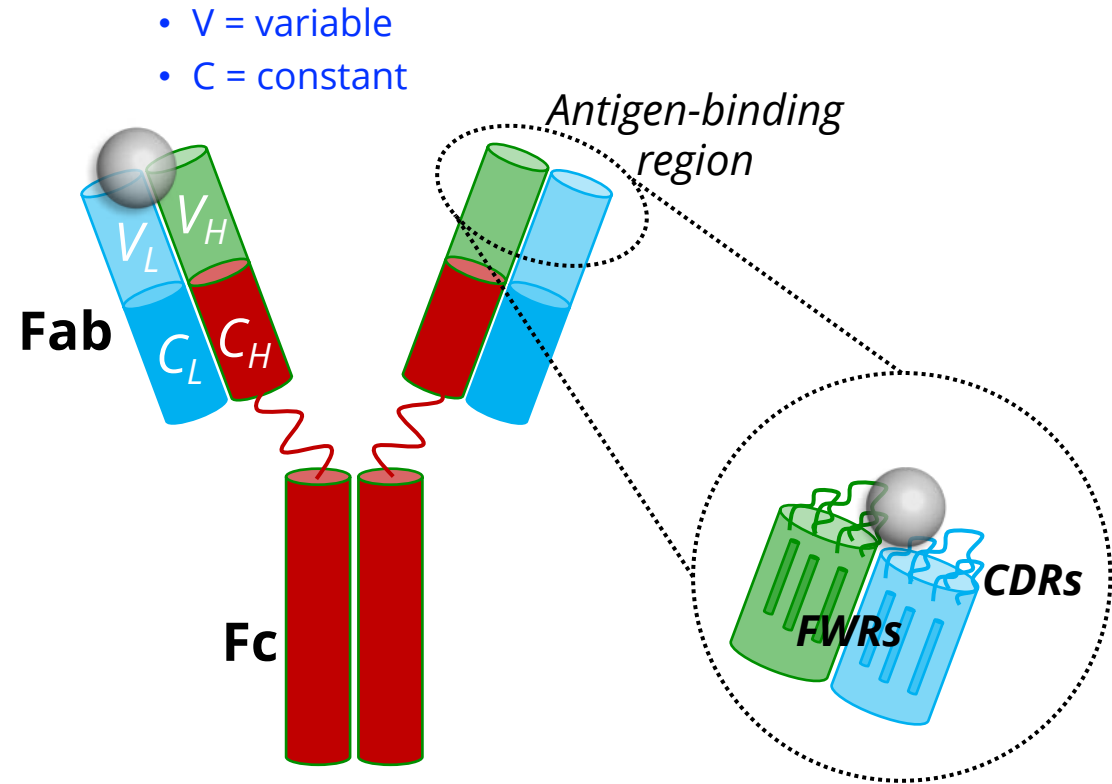
- VH1, VH2, ..., VH7

## VL family (light variable FWRs):

- Vκ1, ..., Vκ6
- Vλ

## CL family (light constant):

- Cκ, Cλ



## Isotypes (heavy constant):

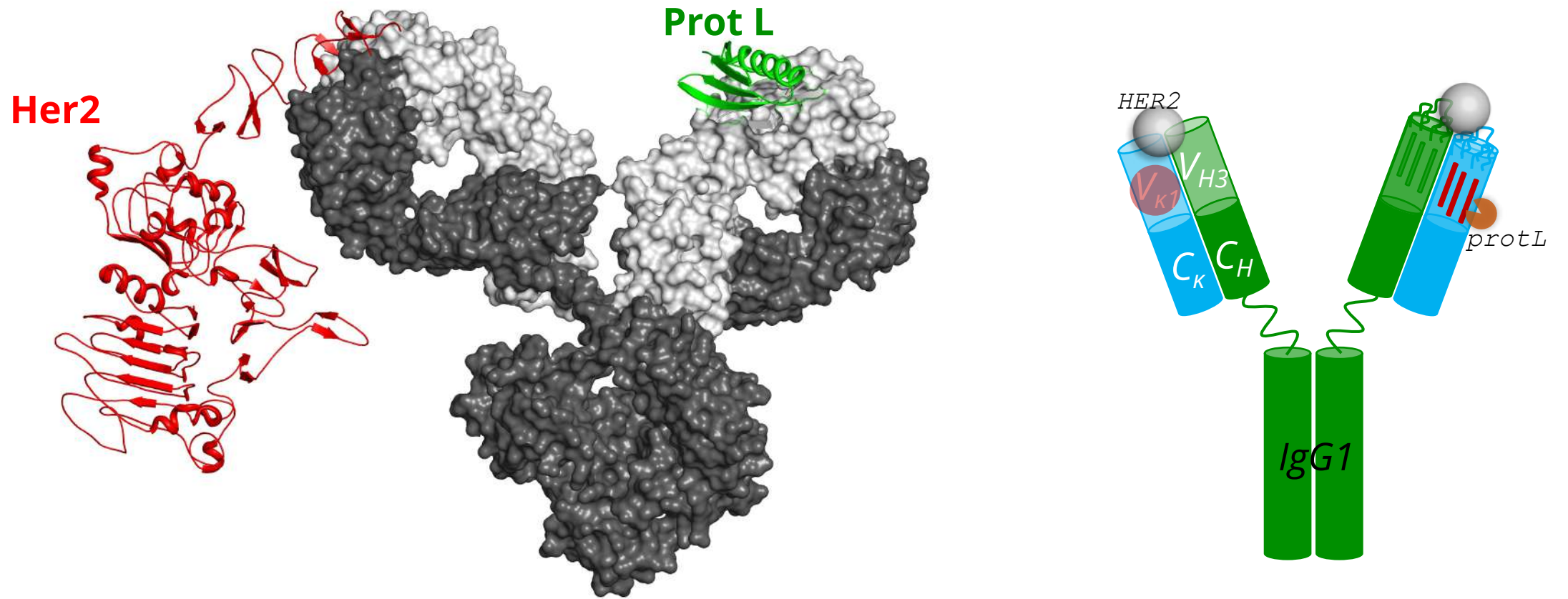
- IgM
- IgA1, IgA2
- IgD
- IgG1, IgG2, IgG3, IgG4
- IgE

## **What we could:**

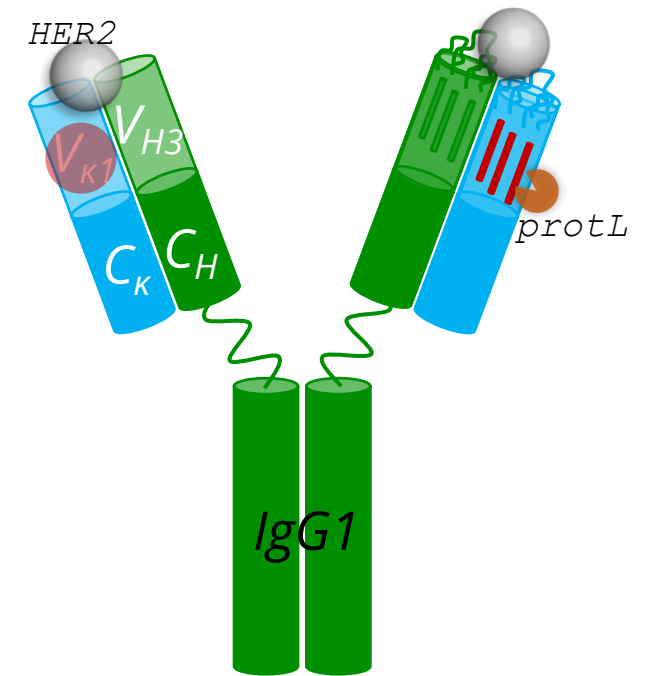
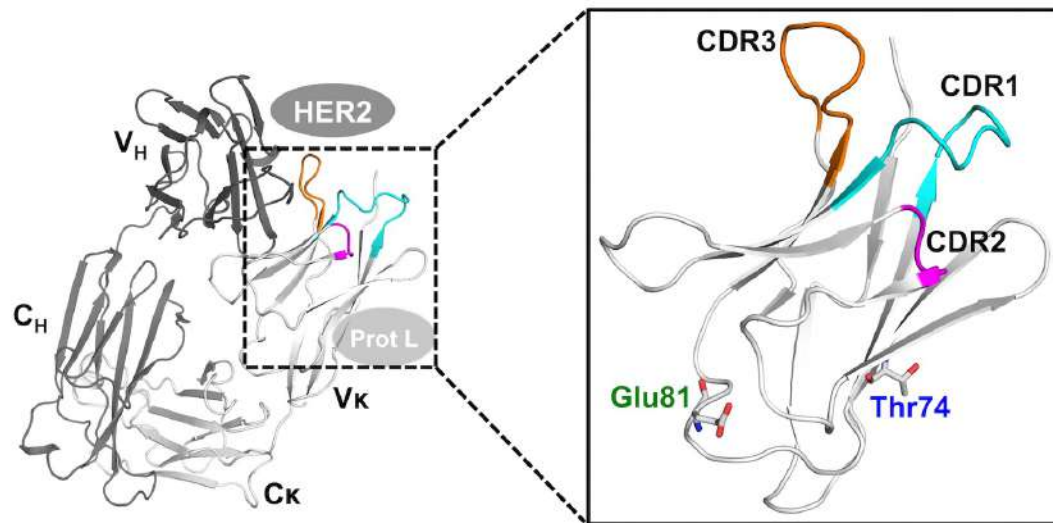
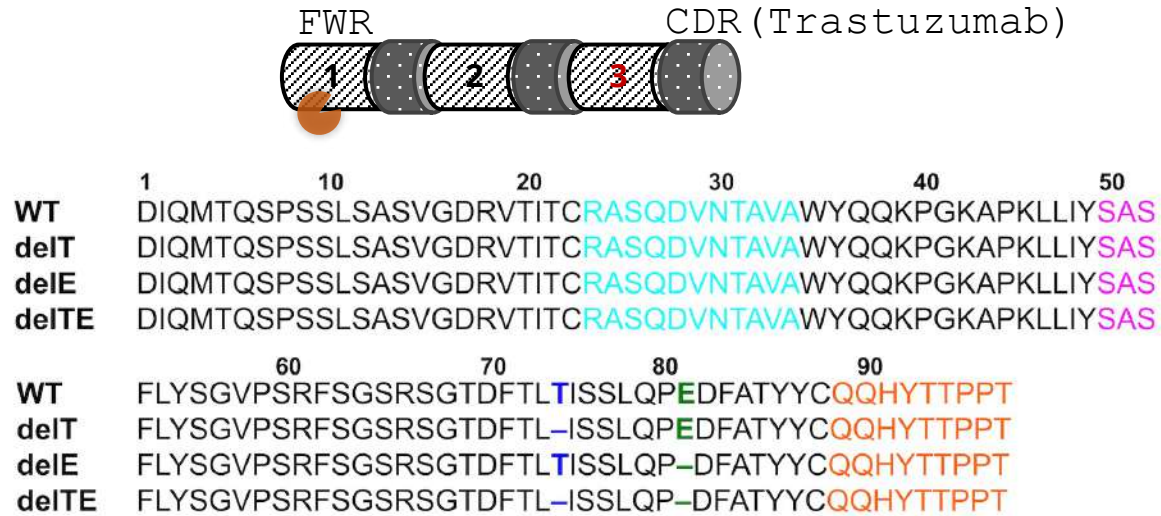
Manipulate interactions of Ab to antigen and/or superantigens via mutagenesis

Observe allosteric communications between distal regions of Ab

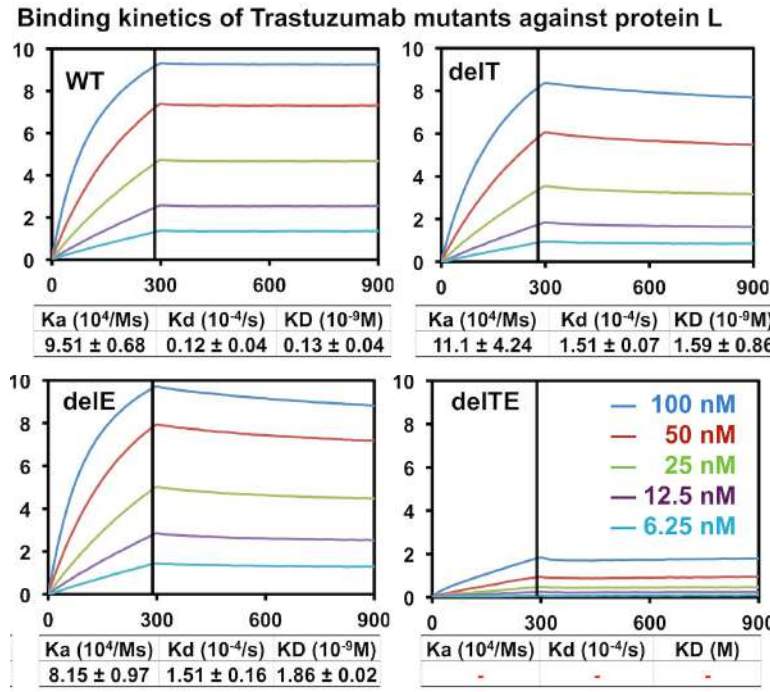
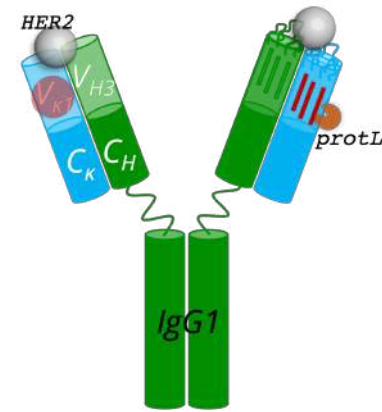
# I. Manipulate interactions: Ab - antigen/superantigen



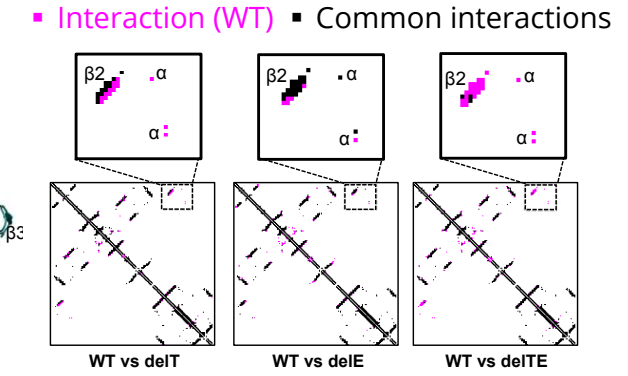
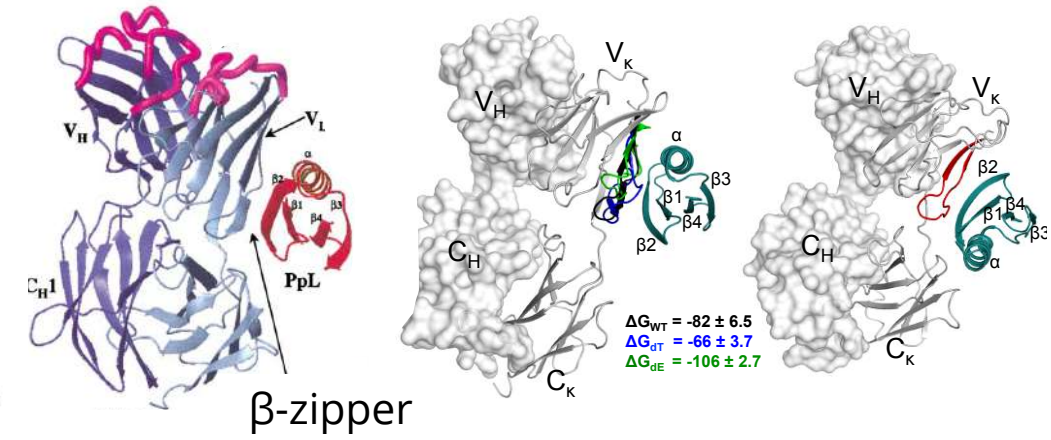
# Mutations disrupted superantigen protL binding on IgG1



# Mutations disrupted protL binding



Graille et al., Structure (2001)

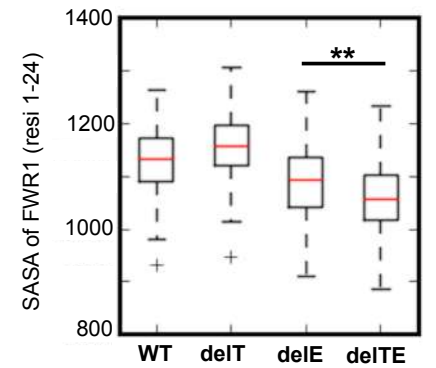


Single del (T74/E81):

- binds protL, but faster dissociates

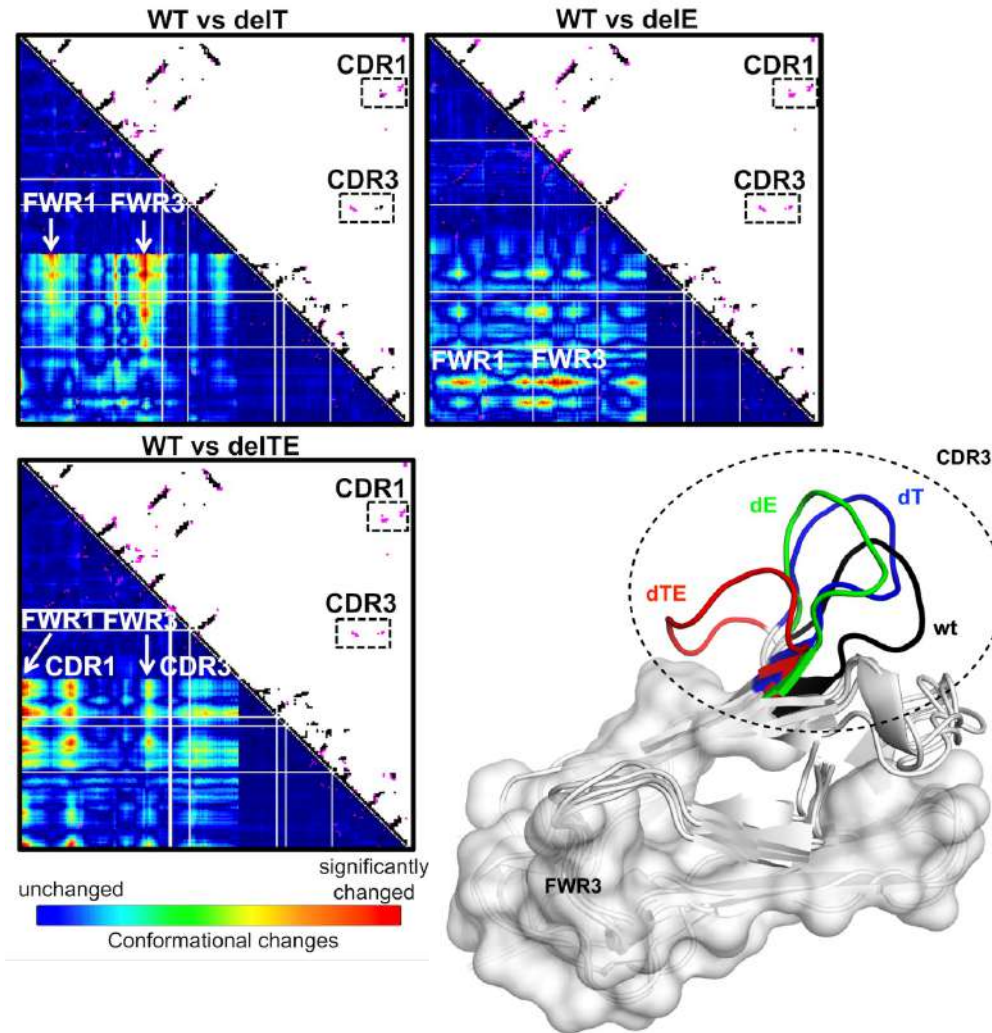
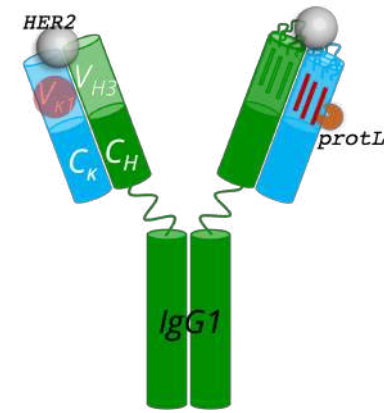
Double dels:

- abolishes protL binding



- The dels damaged the FWR1  $\beta$ -strands, which interact with protL ( $\beta$ 2-strand,  $\alpha$ -helix)
- The **double dels** caused synergistic burying of the anti-parallel  $\beta$ -strands

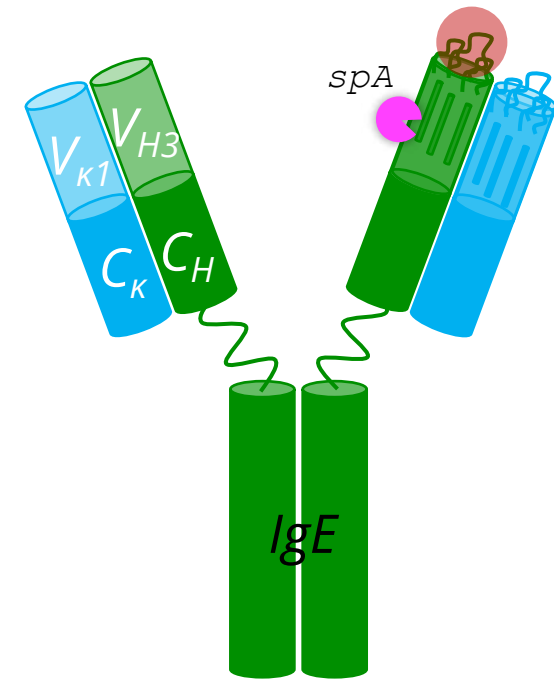
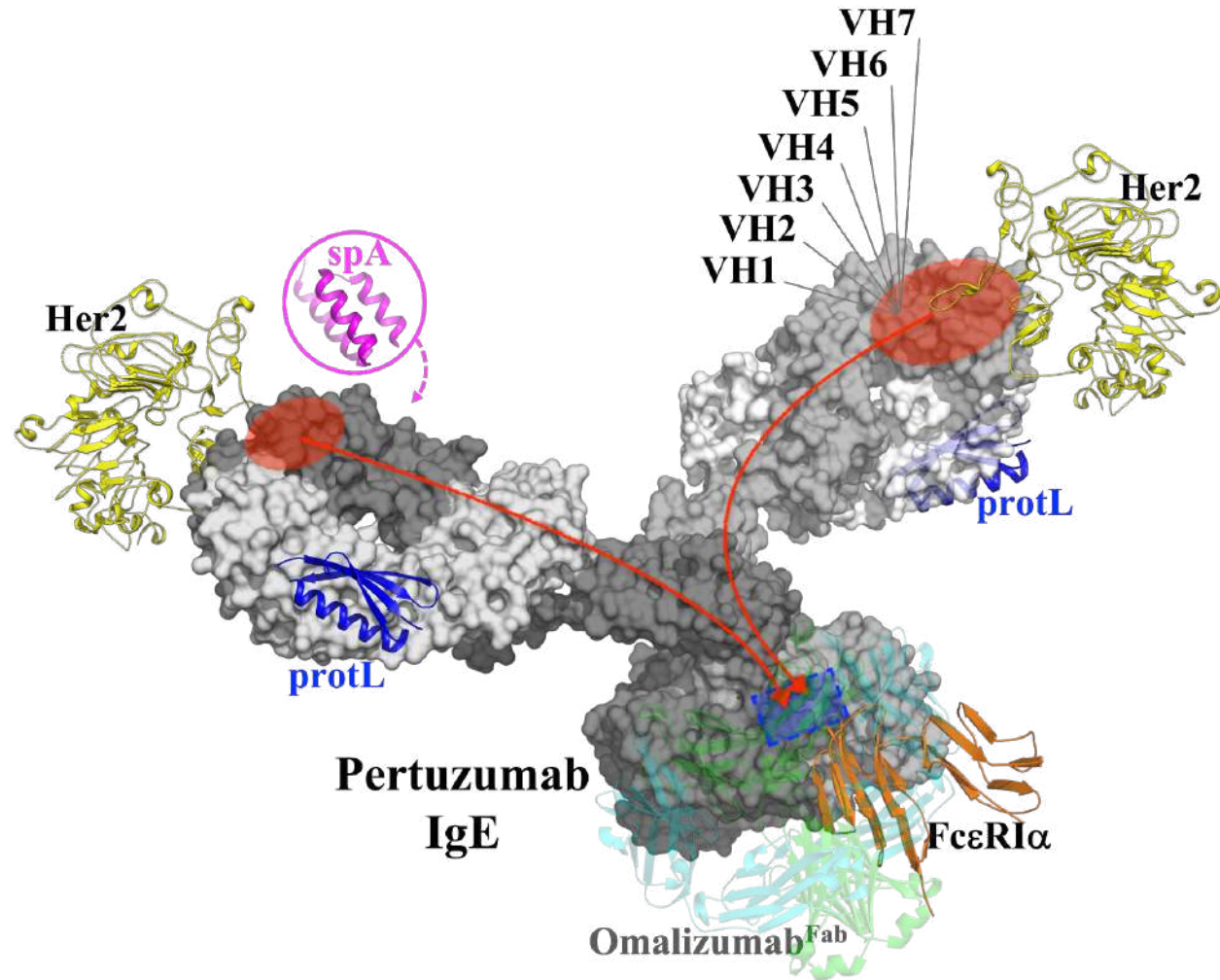
# Mutations disrupted HER2 binding



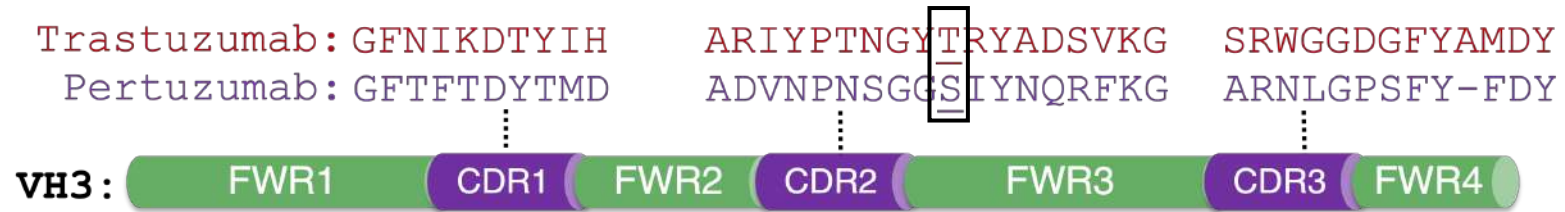
- Several key contacts between CDRs and HER2 were lost due to FWR3 conformational changes
- Buried CDR3 loop in delTE might've diminished binding to HER2
- Allosteric effect on FWR1 conformation



# Mutations disrupted superantigen spA binding on IgE



# A single mutation on VH-CDR2 affected spA binding



The spA binds specifically only to VH3 family antibodies;  
while having similar VH3 FWRs and sharing the same Cε:

- Our **pertuzumab VH3 IgE** did not bind the spA,
- But **trastuzumab VH3 IgE** interacted strongly with spA

