STRUCTURAL INSIGHTS FOR TWO FAB–ANTIGEN COMPLEXES: Platelet glycoprotein VI and SARS-CoV-2 receptor binding domain

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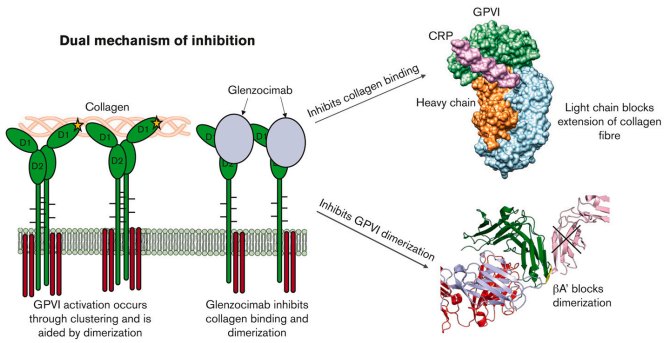
Platelet glycoprotein VI

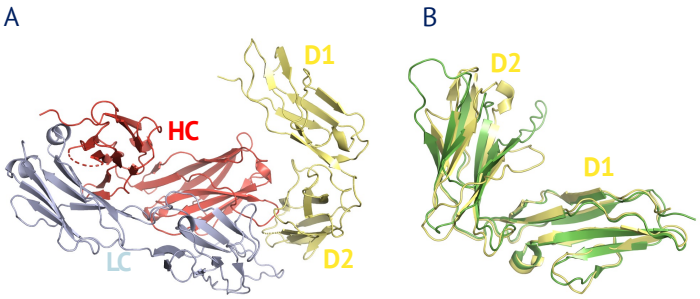
Platelet glycoprotein VI (GPVI) is a potential target for the development of new antiplatelet molecules with low bleeding risk. GPVI binding to vascular collagen initiates thrombus formation and GPVI interactions with fibrin stimulate the growth and stability of the thrombus.
The study demonstrates that Glenzocimab inhibits GPVI interactions with both ligands by loss of dimerization, conformational changes, and steric hindrance.

- The crystal structure of Glenzocimab with the monomeric extracellular domain of GPVI was determined to 1.9 Å.
- The crystal structure shows that Glenzocimab binds to the site of dimerization in the D2 domain of GPVI.
- Glenzocimab inhibits GPIV interaction with CRP, collagen and fibrin by loss of dimerization, conformational changes and steric hindrance.

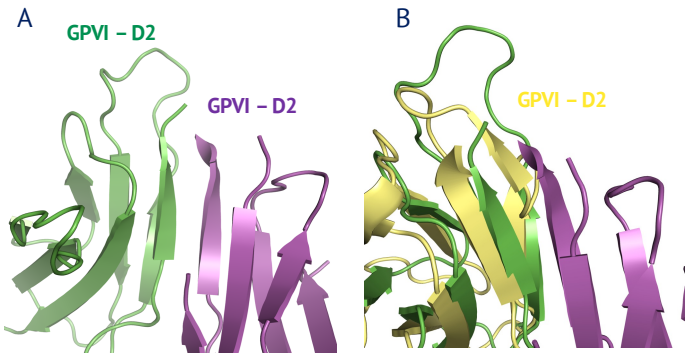


Mode of action

When Glenzocimab binds to domain D2 of GPVI, there is a rearrangement in a loop region. This loop changes conformation and part of the loop forms a β-strand that extends the β-sheet. The extended β-sheet disrupts the formation of a dimer.



A) Complex of Glenzocimab – GPVI. B) Superimpostion of one molecule of dimeric GPVI (PDB ID 2GI7) with GPVI from the Glenzocimab – GPVI complex.



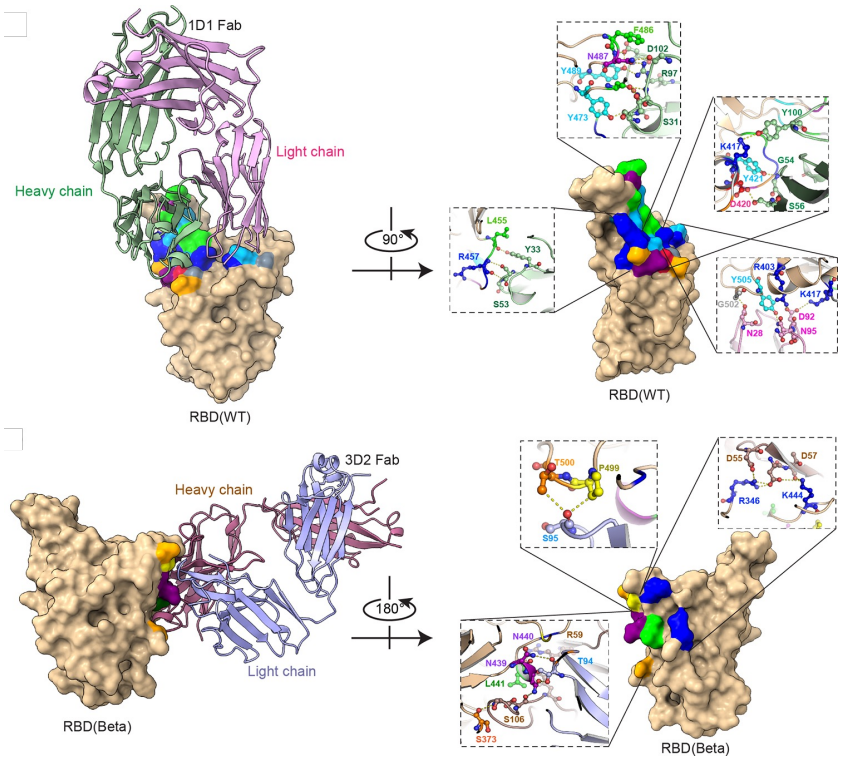
A) Dimerization of GPVI (PDB ID 2GI7) colored in green and magenta. B) Superimposition of monomeric GPVI domain D2 (yellow) revealing conformational changes that disrupt the dimerization. Same color scheme as in A.

Reference: Billiald P, Slater A, Welin M, Clark JC, Loyau S, Pugnière M, Jiacomini IG, Rose N, Lebozec K, Toledano E, François D, Watson SP, Jandrot-Perrus M. *Blood Adv.* 2023 Apr 11;7(7):1258-1268.

SARS-CoV-2 receptor binding domain

The SARS-CoV-2 pandemic has been a major public health issue worldwide. Although the population has widely received vaccination against SARS-CoV-2, immunocompromised patients can still be susceptible to infection.
The study demonstrates how two different hmAbs (1D1 and 3D2) that showed high binding activity to the RBD of SARS-CoV-2 could be used against multiple variants of the virus and provide therapeutic benefits to COVID-19 patients.

- We determined the structures of
  - 1D1 Fab – RBD complex to 1.9 Å
  - 3D2 Fab – RBD (beta variant) complex to 2.2 Å
- Pseudovirion-based neutralization results showed that the antibody cocktail of 1D1 and 3D2 showed high potency in multiple variants of SARS-CoV-2 infection.
- The results illustrate the potential of this cocktail as an intervention against SARS-CoV-2 infection.
- In vivo studies showed the ability of the antibody cocktail treatment to reduce viral load (beta variant) in blood and various tissues.



Reference: Boonkrai C, Cotrone TS, Chaisuriyong W, Tantawichien T, Thisyakorn U, Fernandez S, Hunsawong T, Reed M, Wongtangprasert T, Audomsun T, Phakham T, Attakitbancha C, Saelao P, Focht D, Kimbung R, Welin M, Malik AA, Pisitkun T, Srisawat N. *PLoS One* 2023 May 4;18(5):e0284173.

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