

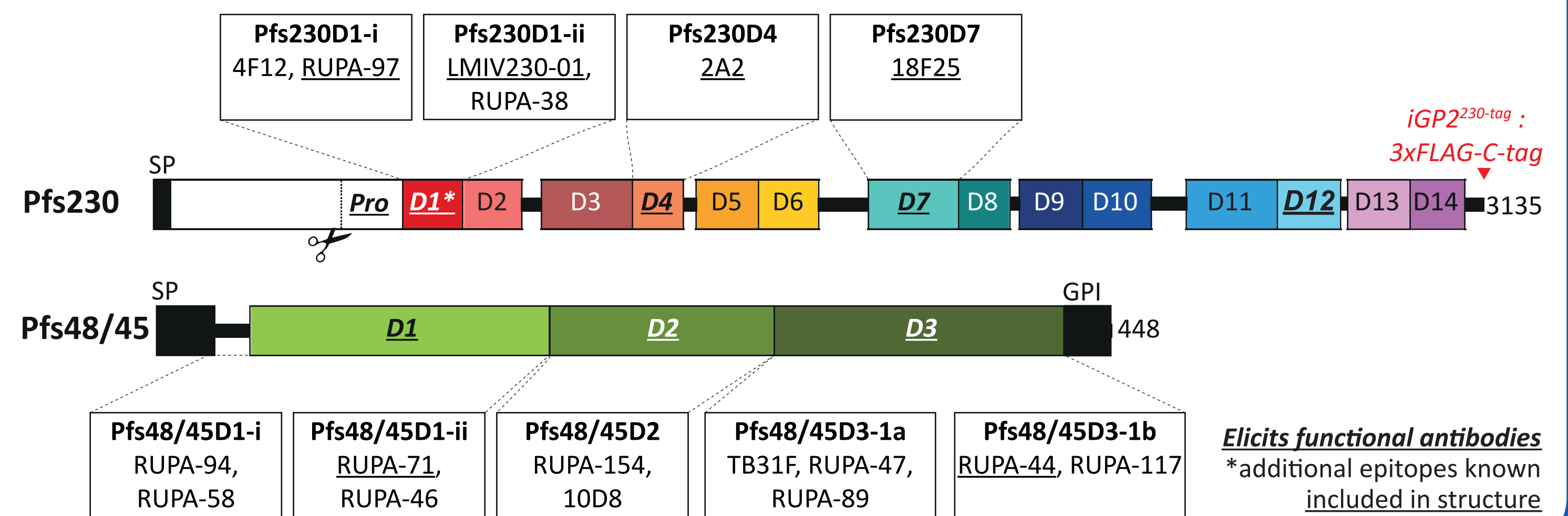
Insights from the cryo-EM structure of the full-length Pfs230:Pfs48/45 complex bound to potent antibodies

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Introduction

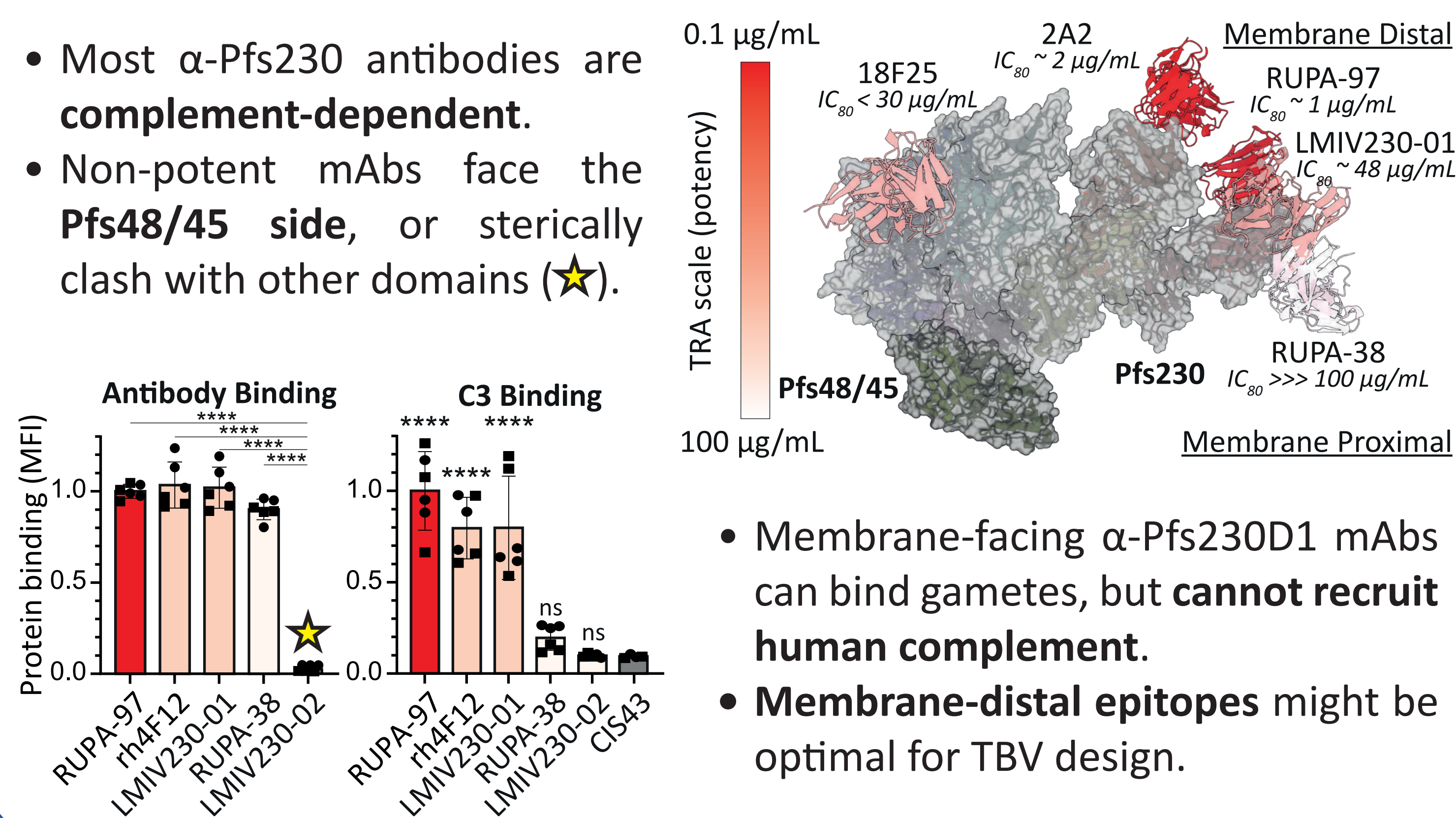
- **Pfs230** and **Pfs48/45** are the targets of the most advanced **Transmission Blocking Vaccine (TBV)** candidates.
- They form a complex on the plasma membrane of gametocytes and gametes, and play an essential role in human-to-mosquito transmission.
- Our **structural understanding of the complex is limited** due to roadblocks in recombinant expression.
- Here, we solved the cryoEM structure of the **endogenous Pfs230:Pfs48/45 complex**, bound to six transmission-blocking antibodies.

Pfs230 and Pfs48/45 domain organization



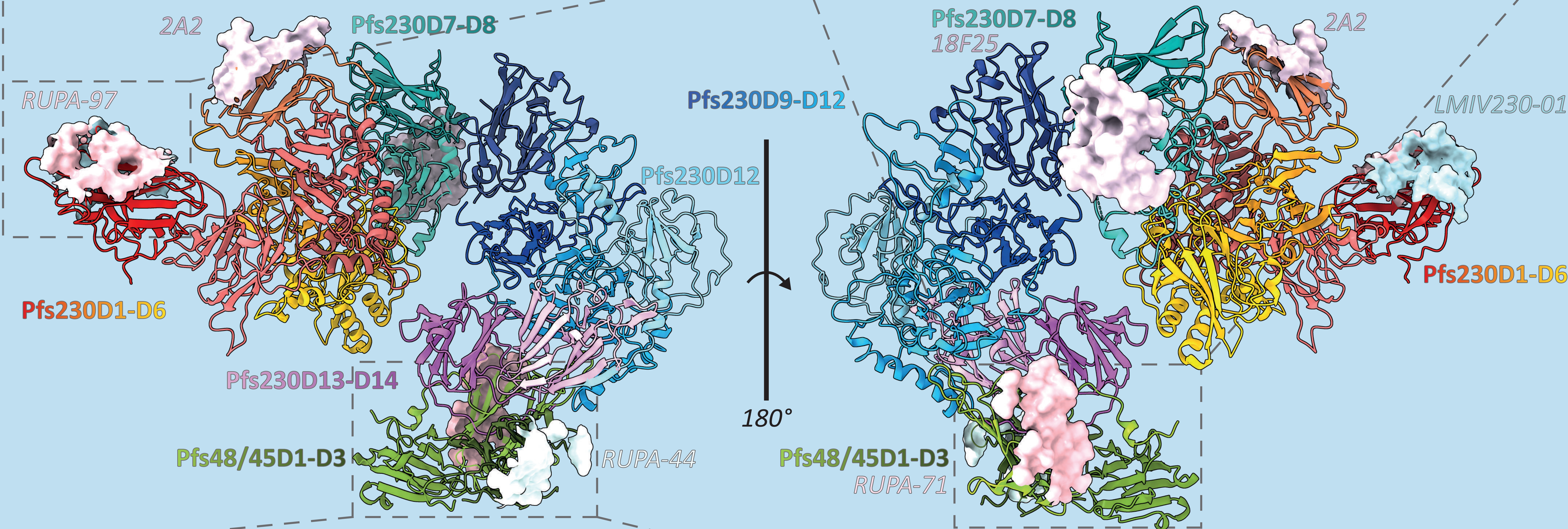
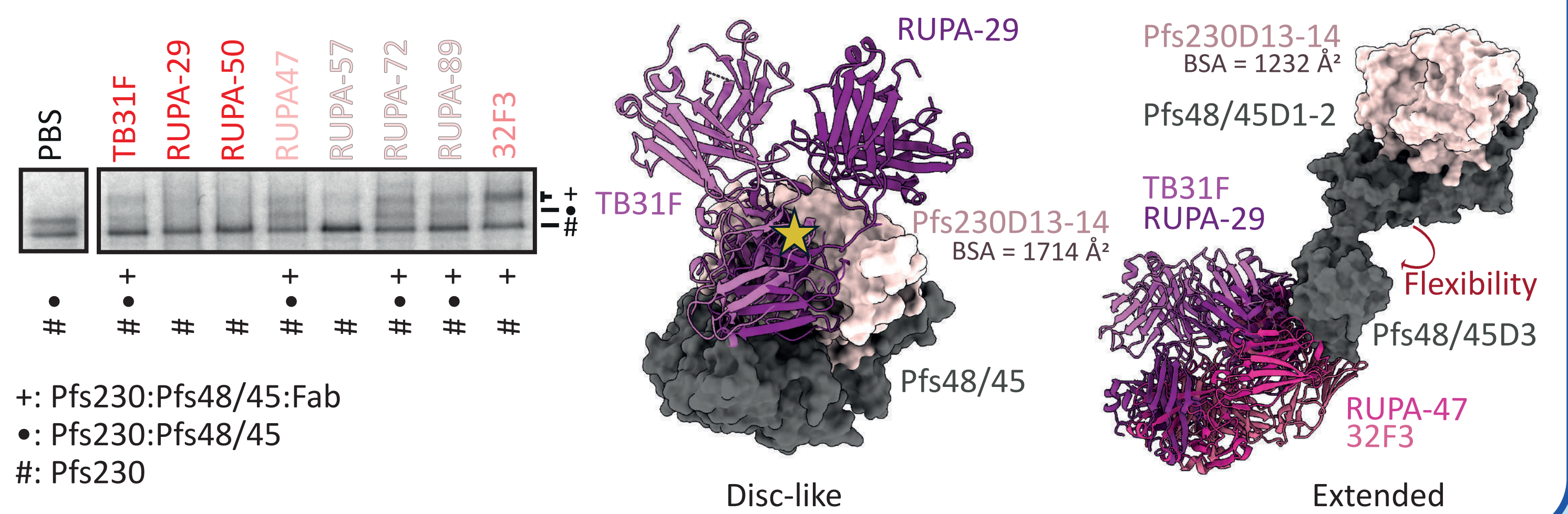
Potent Pfs230 epitopes are membrane-distal

- Most α -Pfs230 antibodies are **complement-dependent**.
- Non-potent mAbs face the **Pfs48/45 side**, or sterically clash with other domains (★).



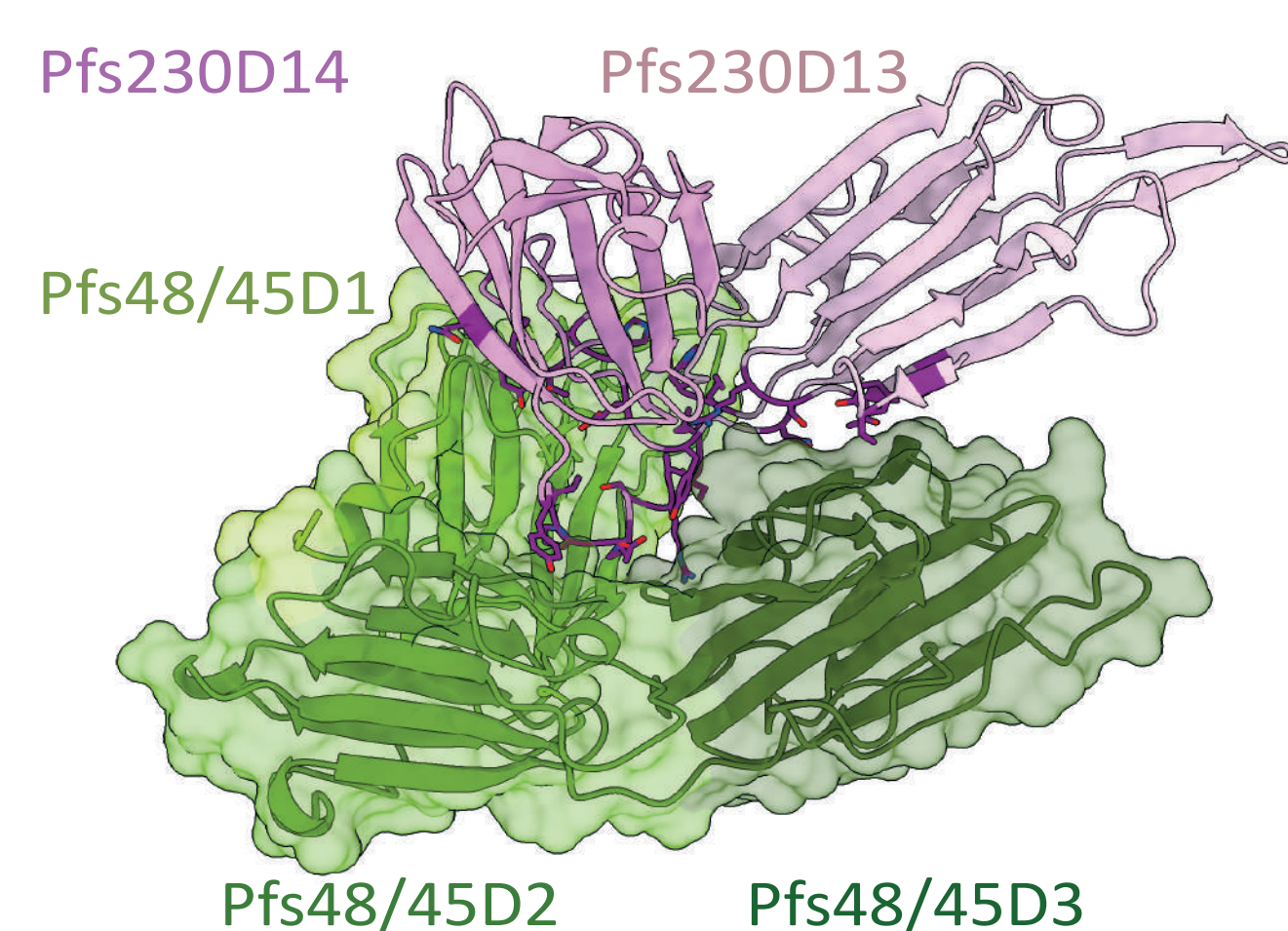
Pfs48/45 might exist in two conformations

- Pfs48/45 has been described in a **disc-like** and **extended** conformation.
- Superposition of α -Pfs48/45 antibodies suggest that the **D3-1a epitope is inaccessible** in the disc-like Pfs230-bound Pfs48/45.
- Binding assays suggest that **D3-1a targeting antibodies can still bind** the Pfs230:Pfs48/45 complex.
 - D3-1a would be accessible in the **extended conformation**.

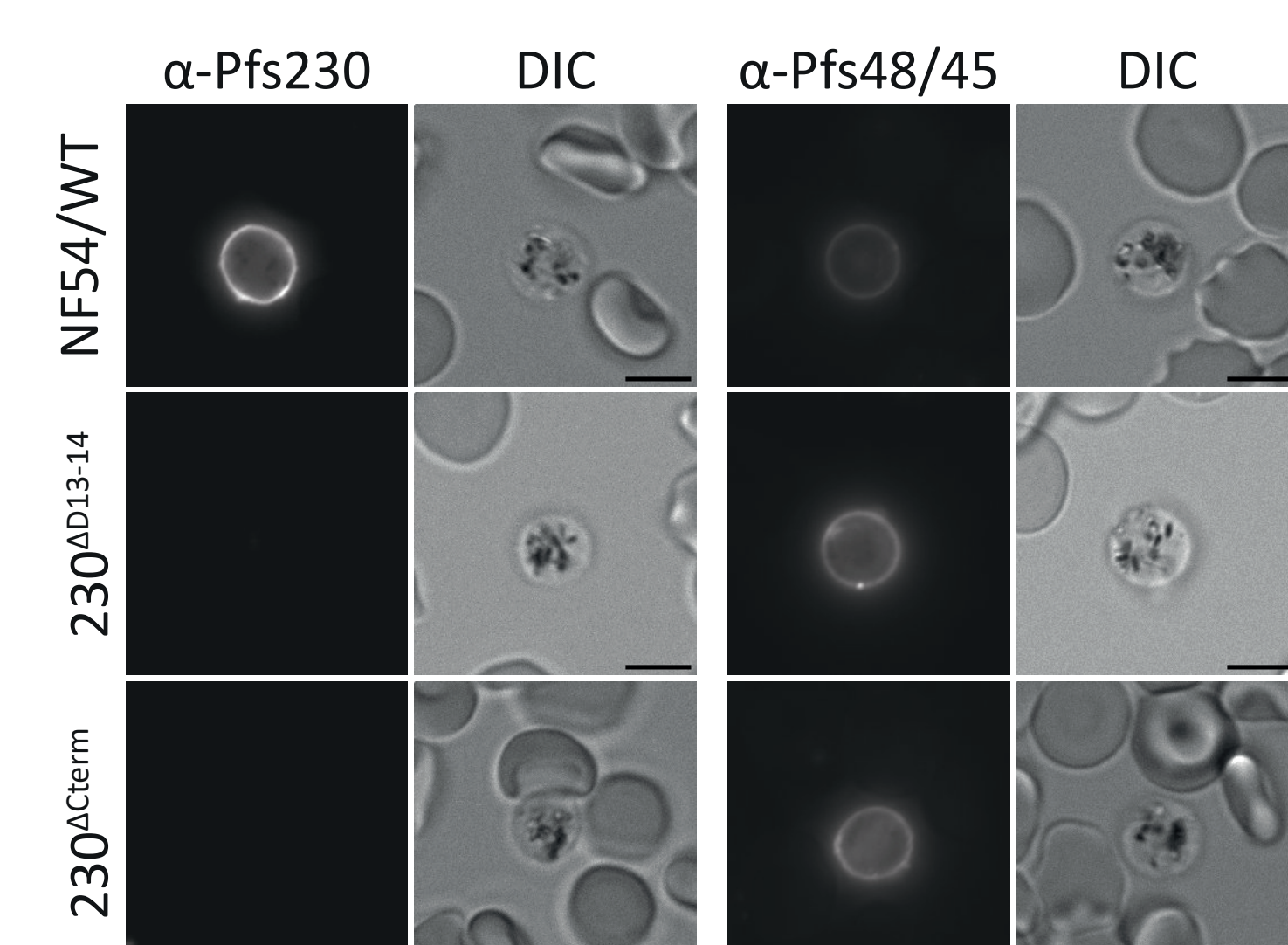


Pfs230D13-D14 interacts with Pfs48/45...

- **Pfs230D13-D14** interacts with Pfs48/45, mostly mediated by a **short C-terminal peptide**, outside of the canonical 6-cysteine fold.

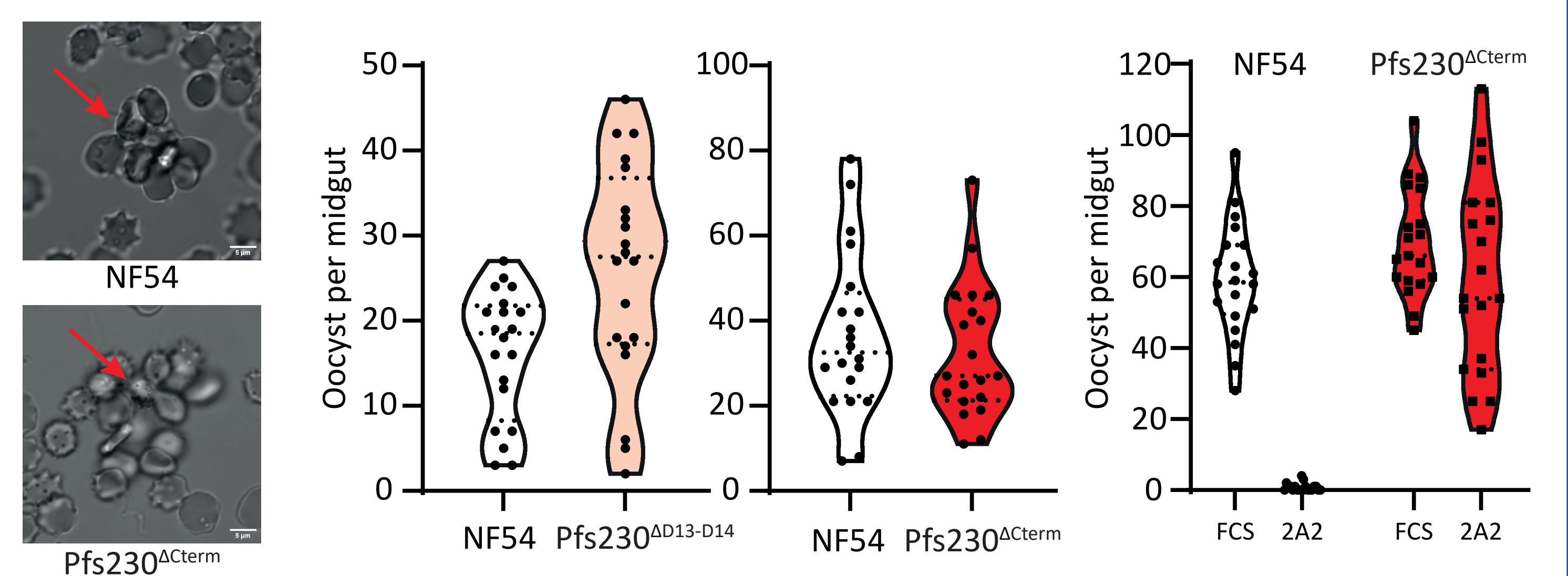


- **Truncated Pfs230** is **not retained** on the parasite plasma membrane, due to the loss of Pfs48/45 anchoring.



... but this is not essential for transmission

- **Pfs230^{ΔD13-D14}** and **Pfs230^{ΔCterm}** gametes do form **exflagellation centers**.
- Both lines transmit normally to *Anopheles* mosquitoes.
- α -Pfs230 mAbs do not block transmission of Pfs230^{ΔCterm}.



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