

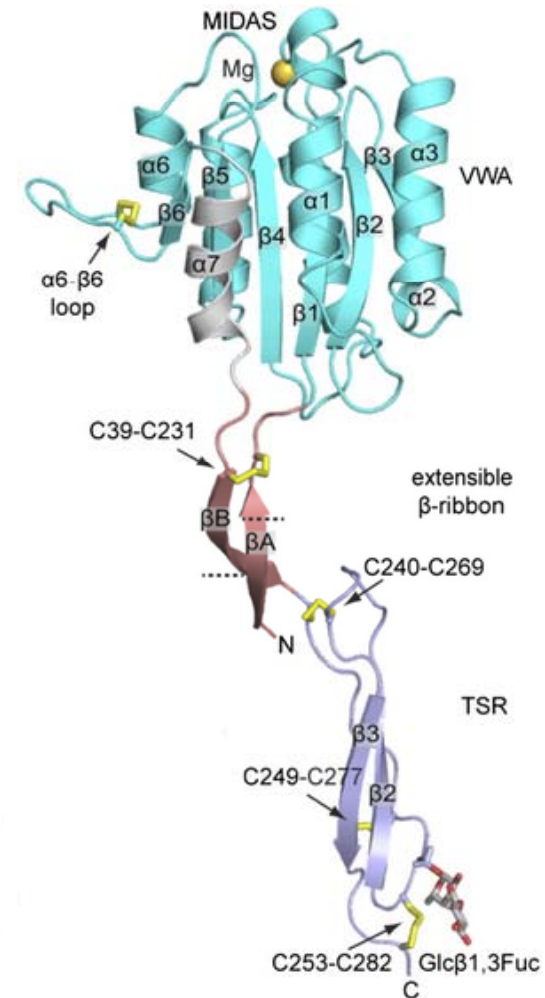
Human PDGFR- β is a host receptor for *Plasmodium falciparum* protein PfTRAP

Noah Sather, Ph.D.

Associate Professor

PfTRAP (Thrombospondin Related Anonymous Protein)

- Remains an attractive vaccine target
- Critical gene in the PE stages
- Role in parasite motility and invasion
- Knock down impairs invasion
- Complex, multi-domain protein
- Partial structure is known
- Clinical trials with rec protein PfTRAP have failed to achieve protection
- Vectored PfTRAP shown some promise



$\alpha V\beta 3$ integrin is a host receptor for PfTRAP

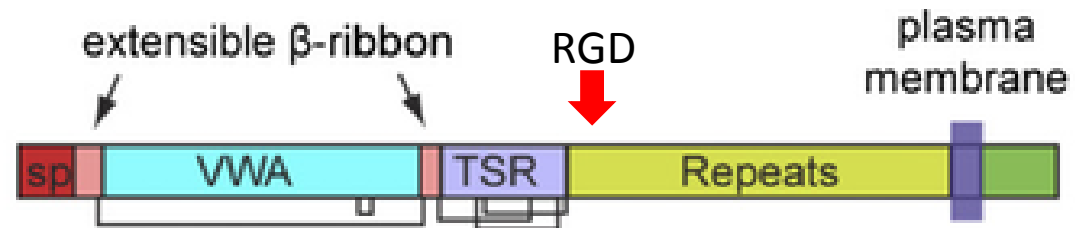
PNAS

Alpha-v-containing integrins are host receptors for the *Plasmodium falciparum* sporozoite surface protein, TRAP

Kirsten Dundas^{a,b}, Melanie J. Shears^c, Yi Sun^{a,1}, Christine S. Hopp^{c,2}, Cecile Crosnier^{a,b}, Tom Metcalf^b, Gareth Girling^b, Photini Sinnis^c, Oliver Billker^b, and Gavin J. Wright^{a,b,3}

^aCell Surface Signalling Laboratory, Wellcome Trust Sanger Institute, CB10 1SA Cambridge, United Kingdom; ^bMalaria Programme, Wellcome Trust Sanger Institute, CB10 1SA Cambridge, United Kingdom; and ^cW. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205

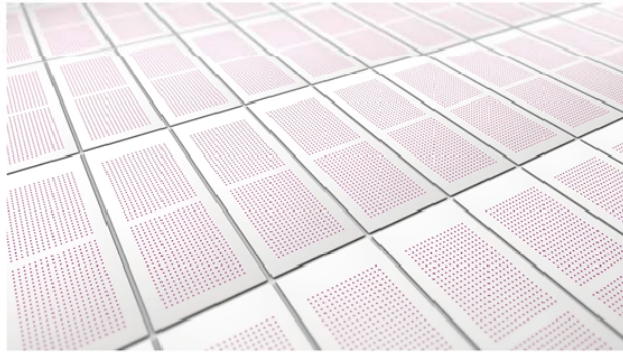
- Identified $\alpha V\beta 3$ integrin as a host receptor for PfTRAP
- Binding is dependent on RGD motif in the proximal repeat region and vWA
- Binding is metal dependent (MIDAS domain)
- Blocking $\alpha V\beta 3$ altered motility in the skin, but interaction appears to not be critical for invasion
- Redundancy?



Screening the human surface proteome



Array based screen (~4000 surface proteins)



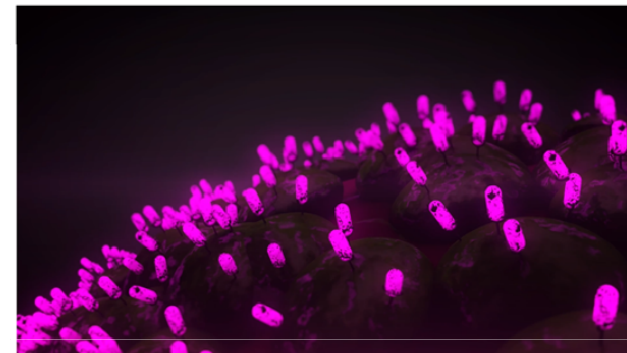
Reverse transfection of HEK293



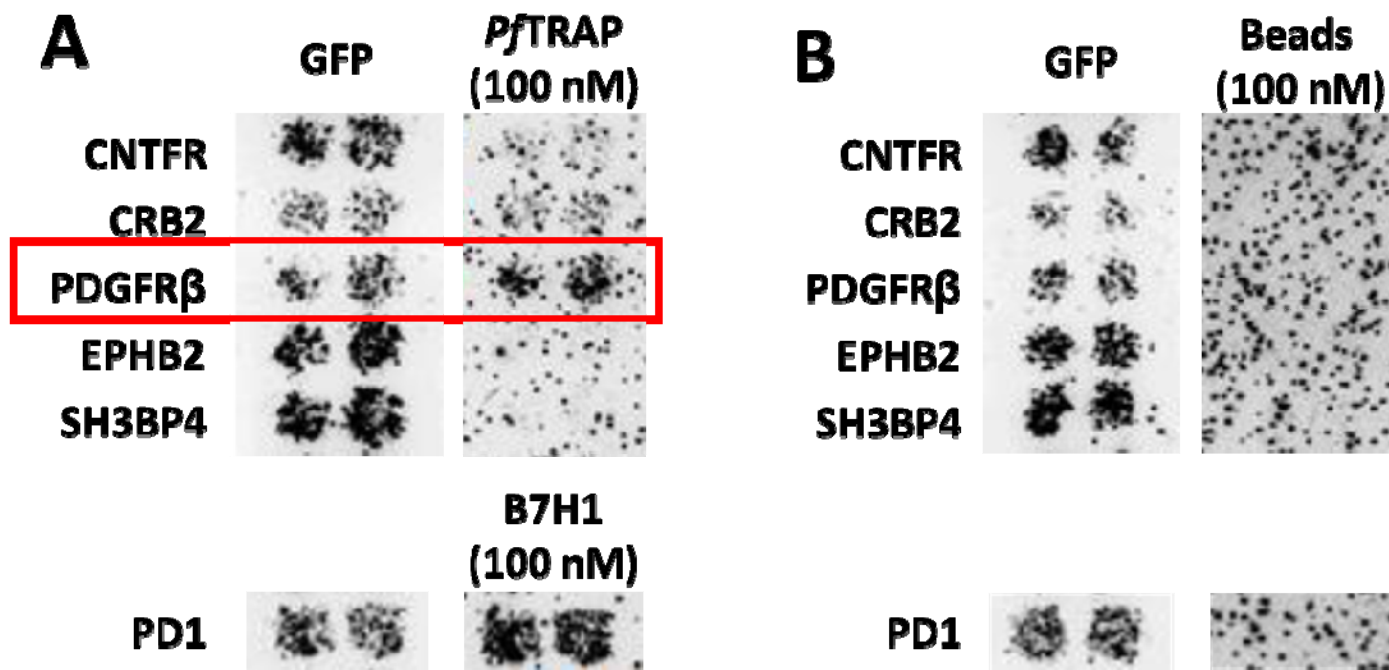
Challenge with labeled ligand



Assess bound ligand

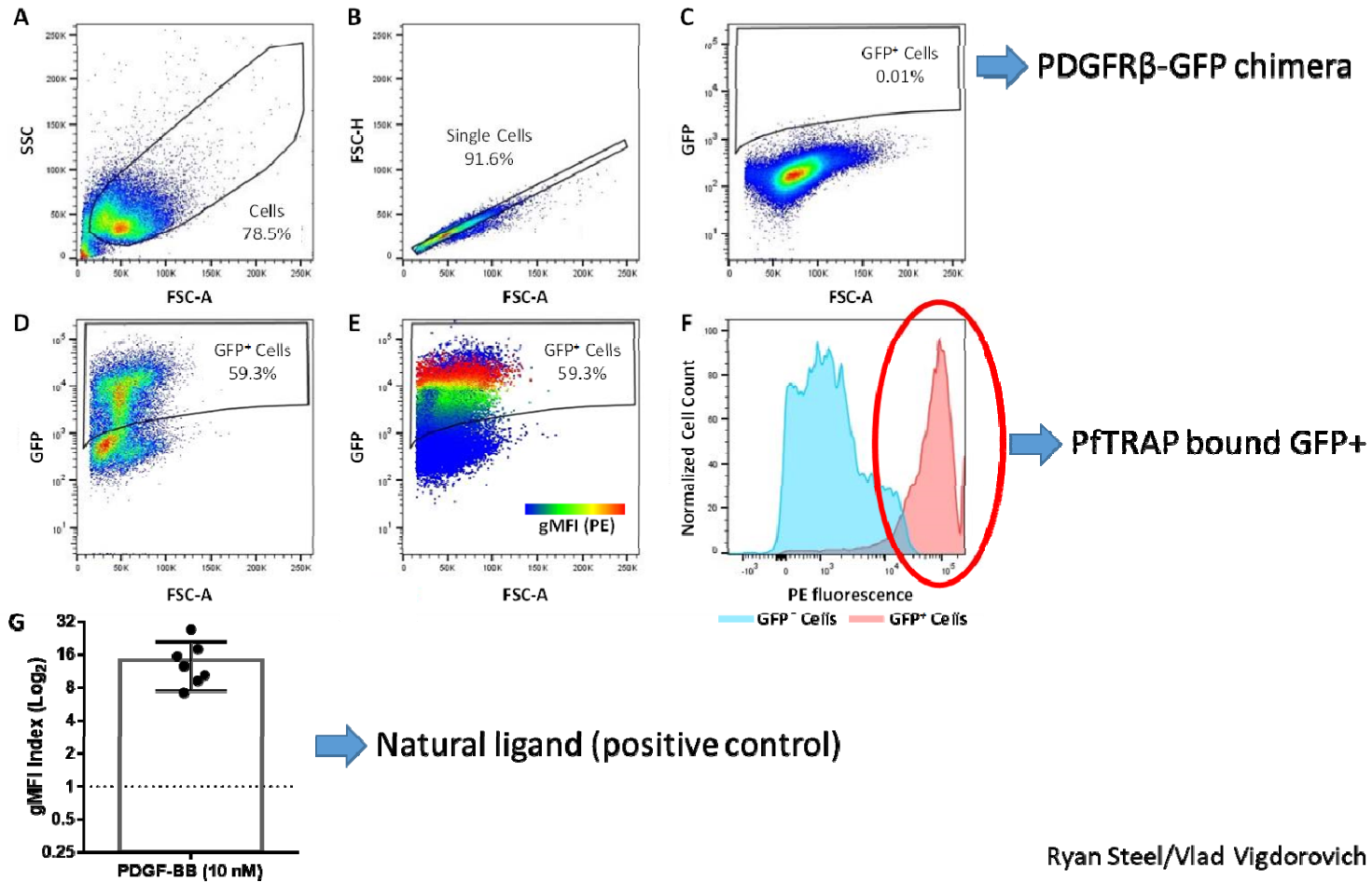


Screening the human surface proteome



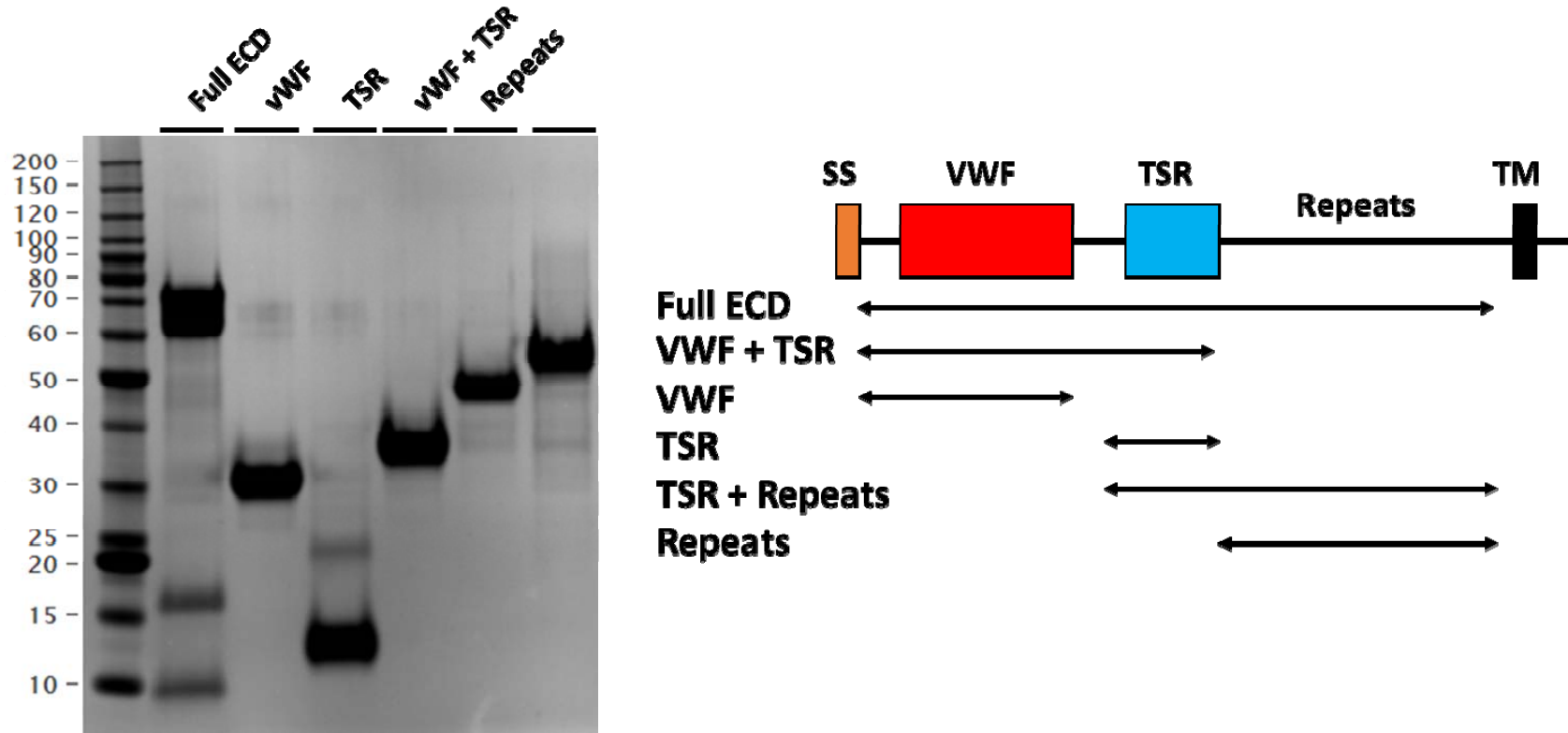
***Platelet Derived Growth Factor Receptor β**

Verifying protein-protein interactions

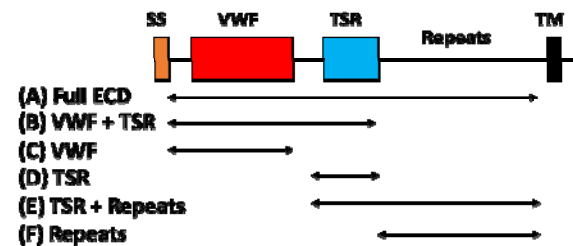
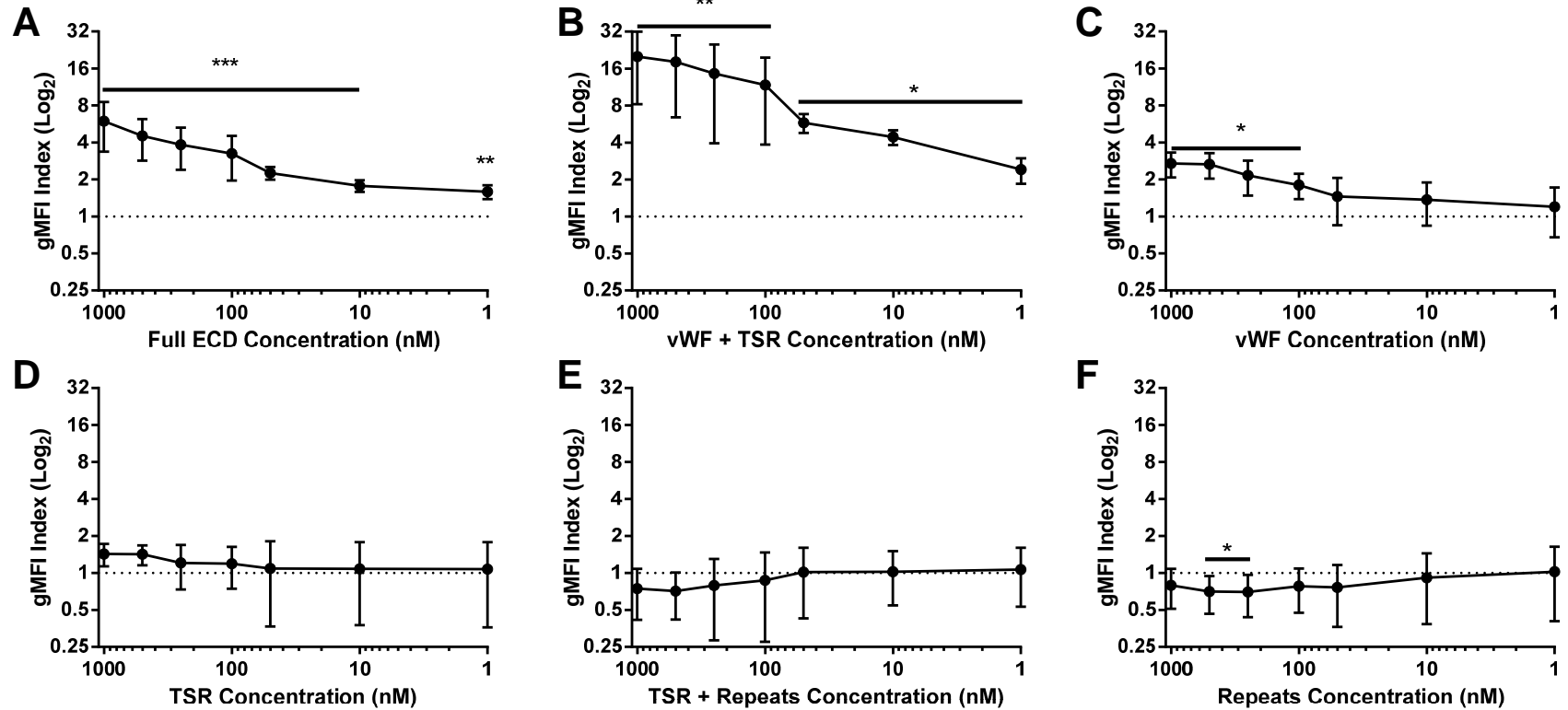


Ryan Steel/Vlad Vigdorovich

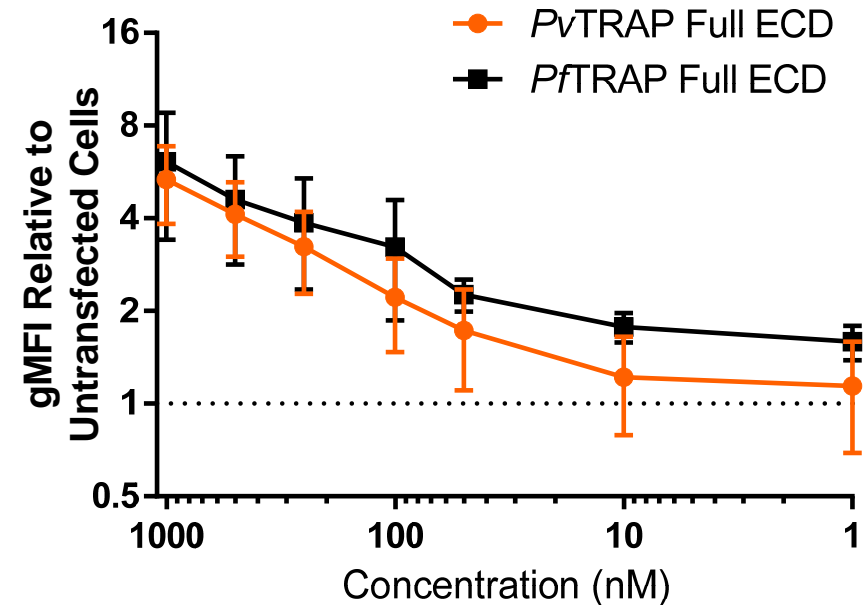
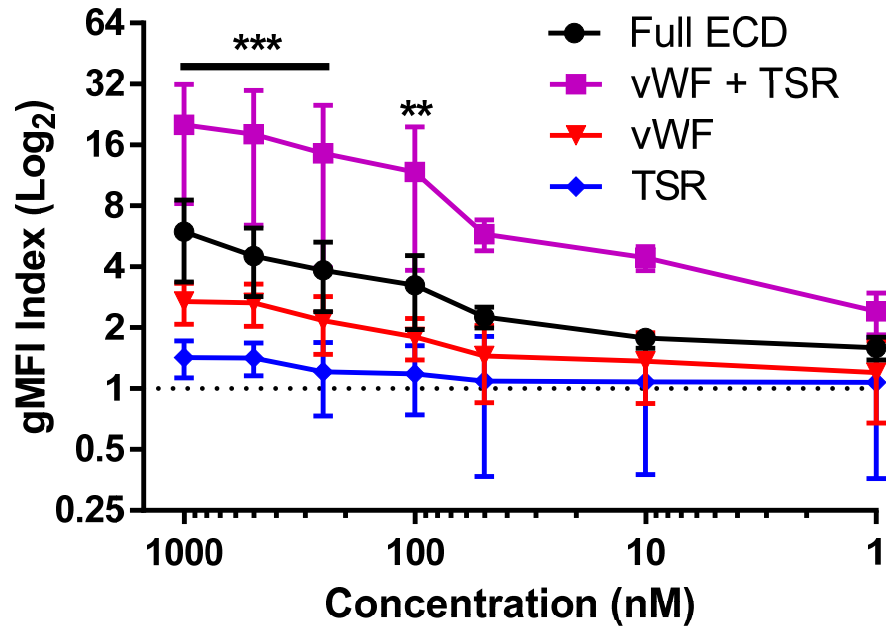
Dissecting PfTRAP interaction domains



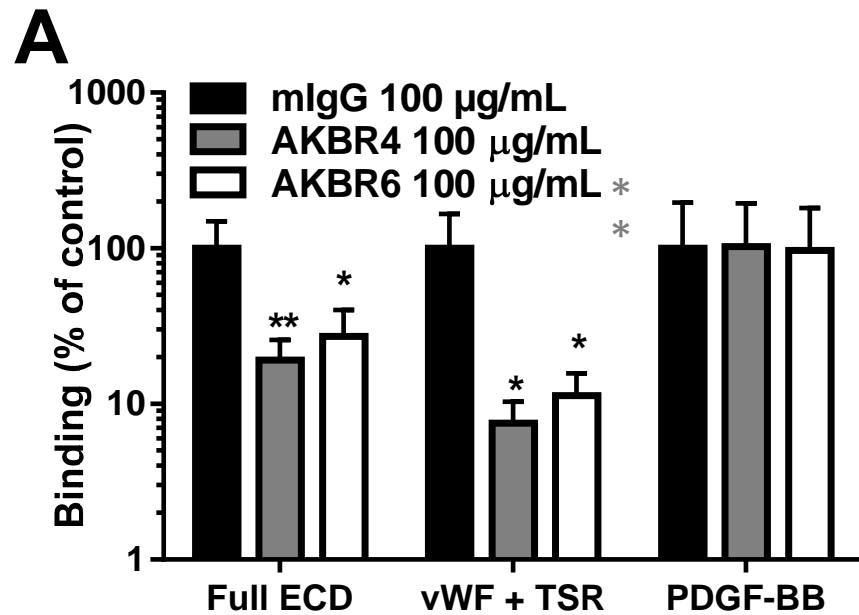
Binding to PDGFR- β is dependent on the vWA and TSR domains



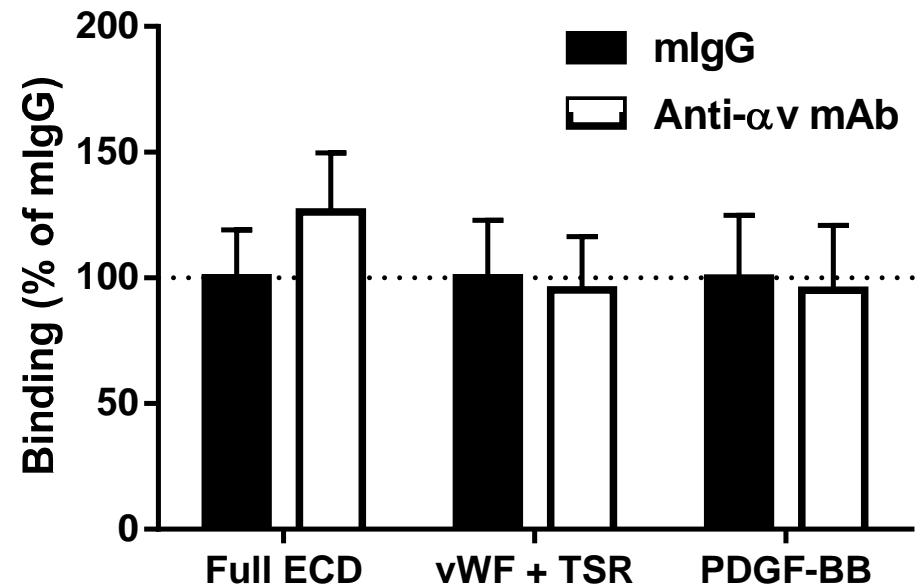
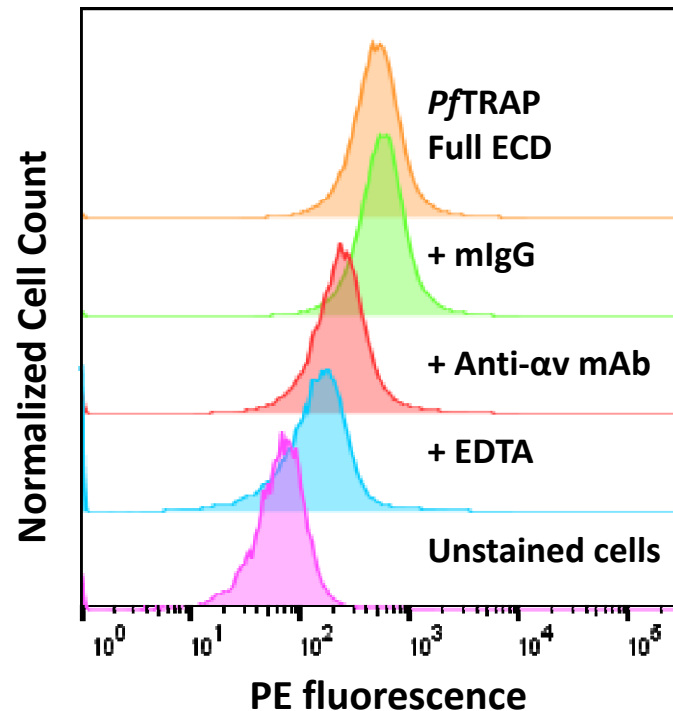
PfTRAP interaction is mediated by vWA/TSR domains and is conserved



Interaction is blocked by mAbs to PfTRAP or PDGFR- β



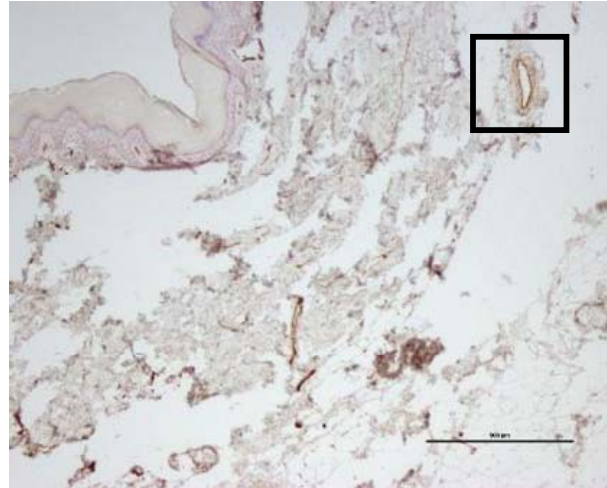
PDGFR- β binding is independent of $\alpha V\beta 3$



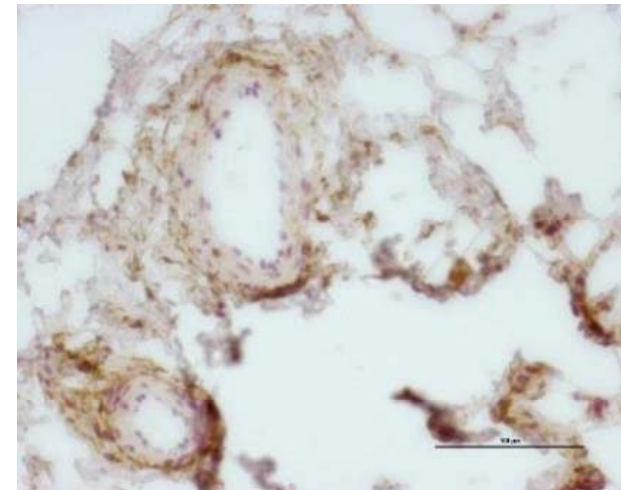
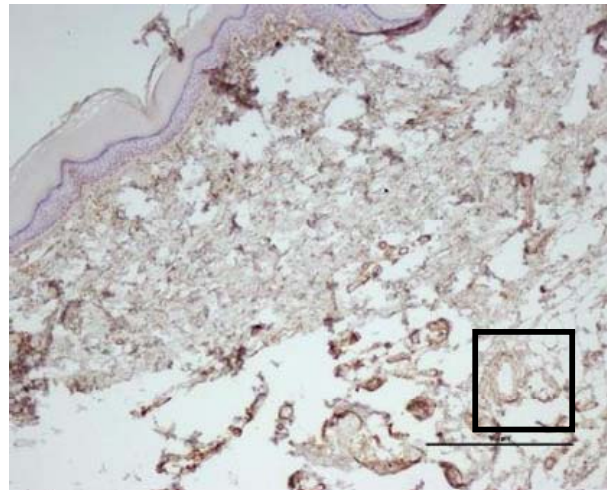
- Binding is not metal dependent
- Binding is independent of integrin $\alpha V\beta 3$
- We confirmed interaction of *Pf*TRAP and $\alpha V\beta 3$

PDGFR- β is expressed near vasculature

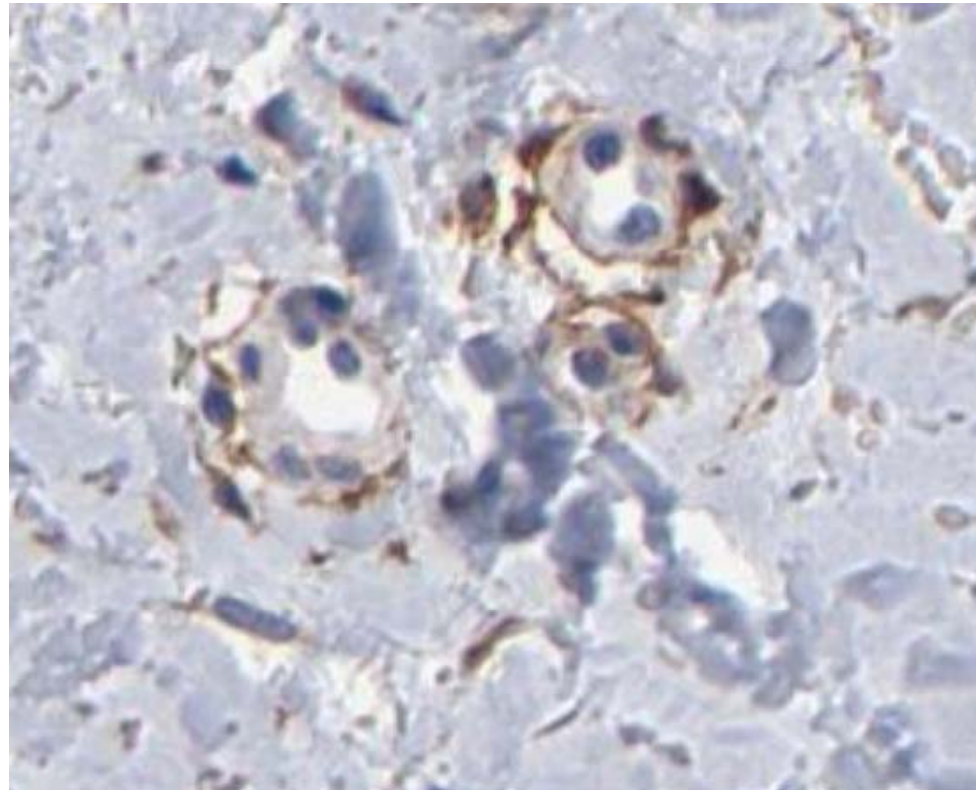
α -CD31



α -PDGFR β

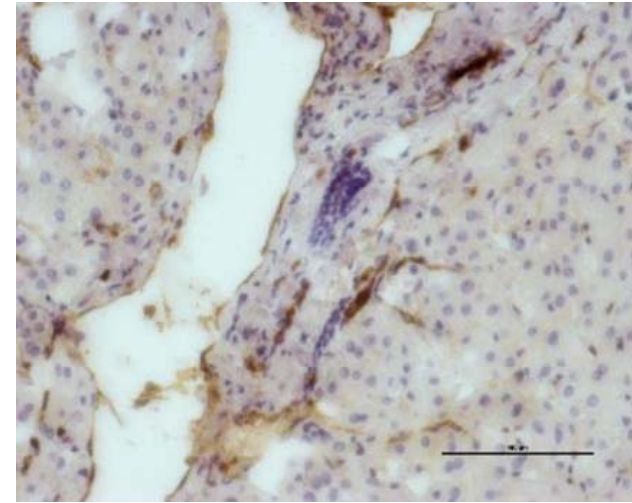
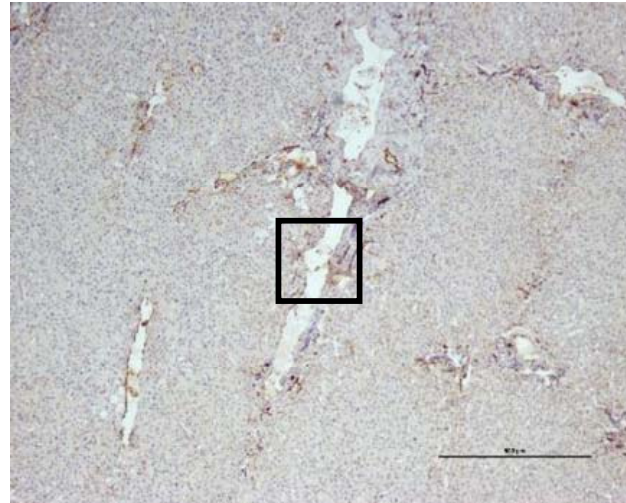


Human protein ATLAS- expression in fibroblasts around vascular tissue

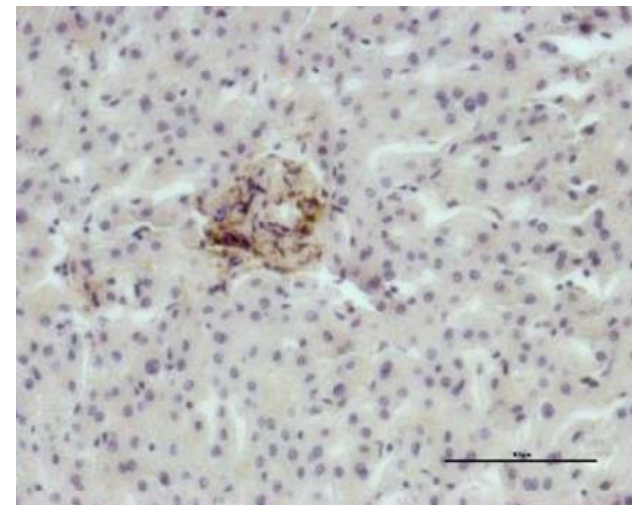
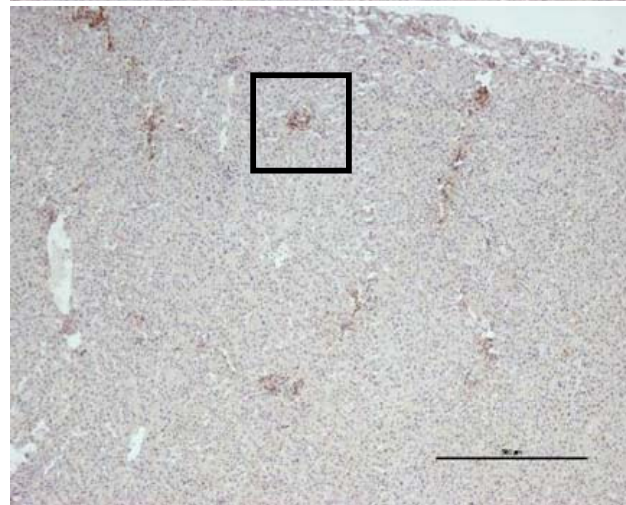


PDGFR- β is expressed near thin wall vessels in liver, but not in sinusoids or hepatocytes

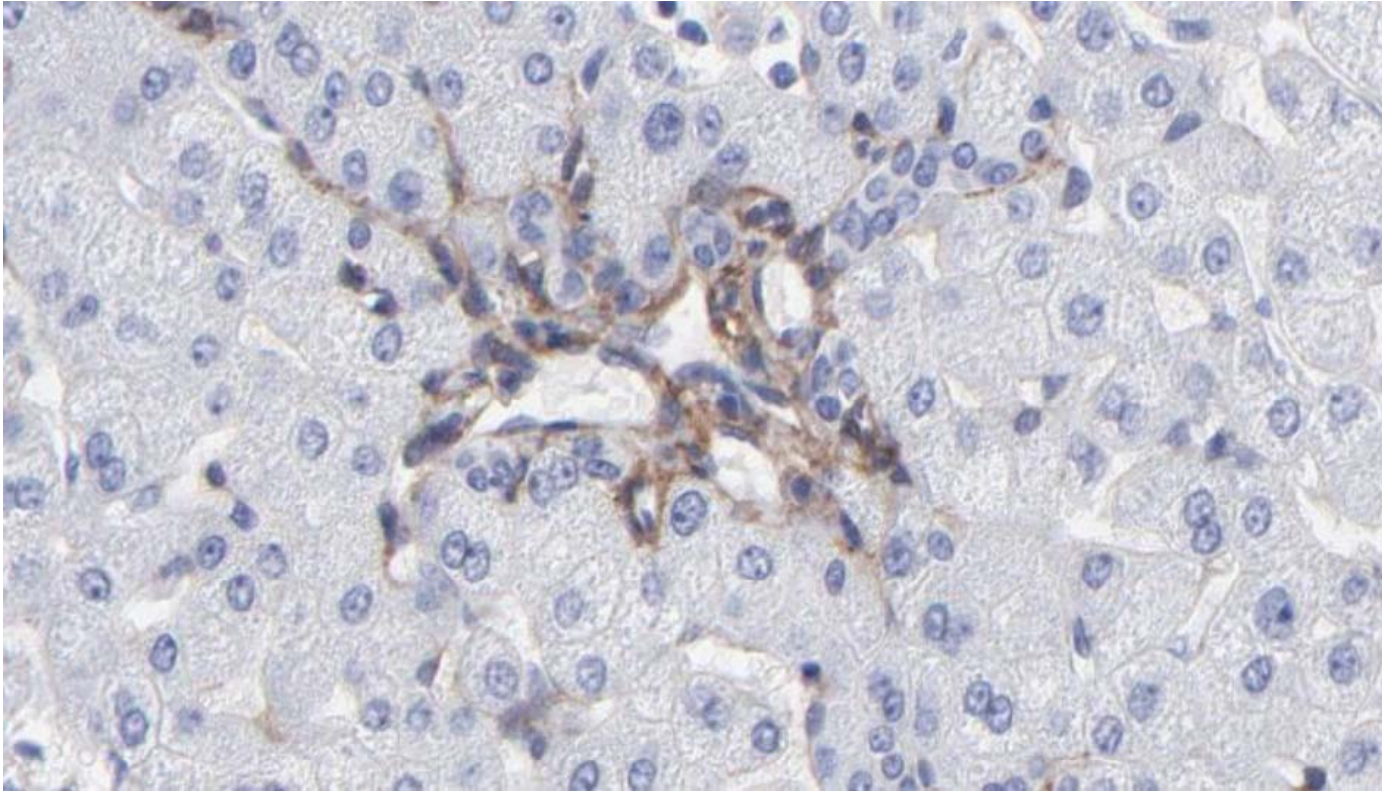
α -CD31



α -PDGFR β



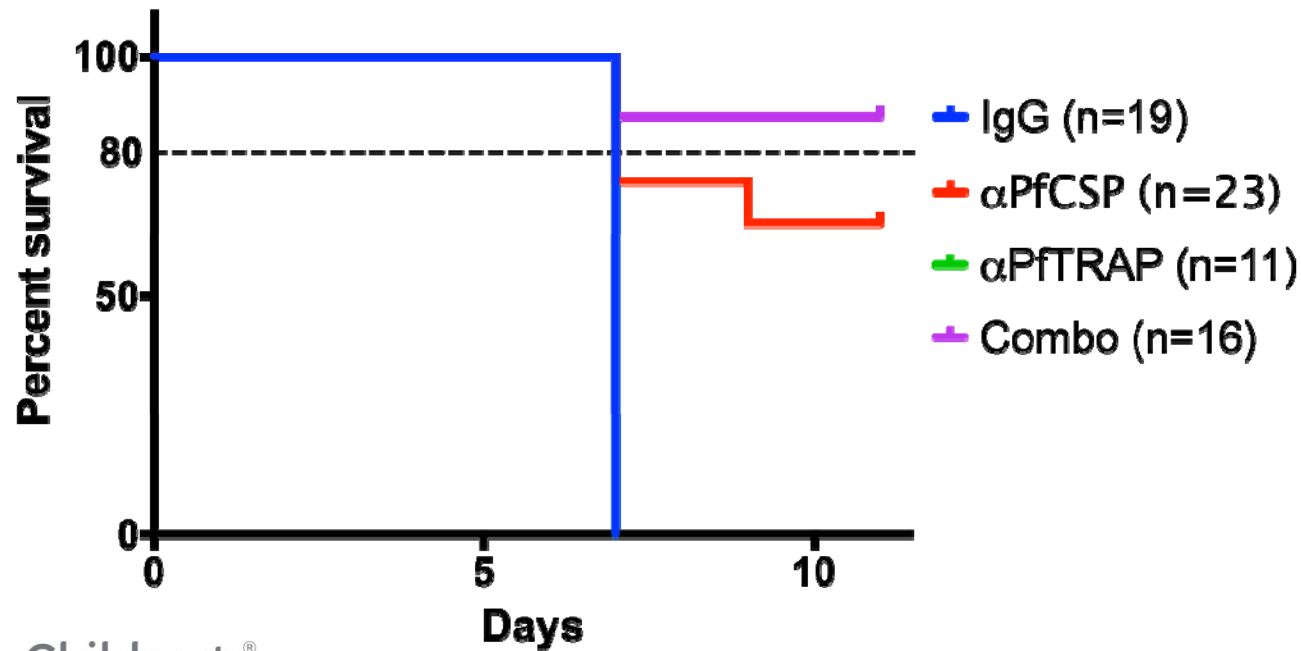
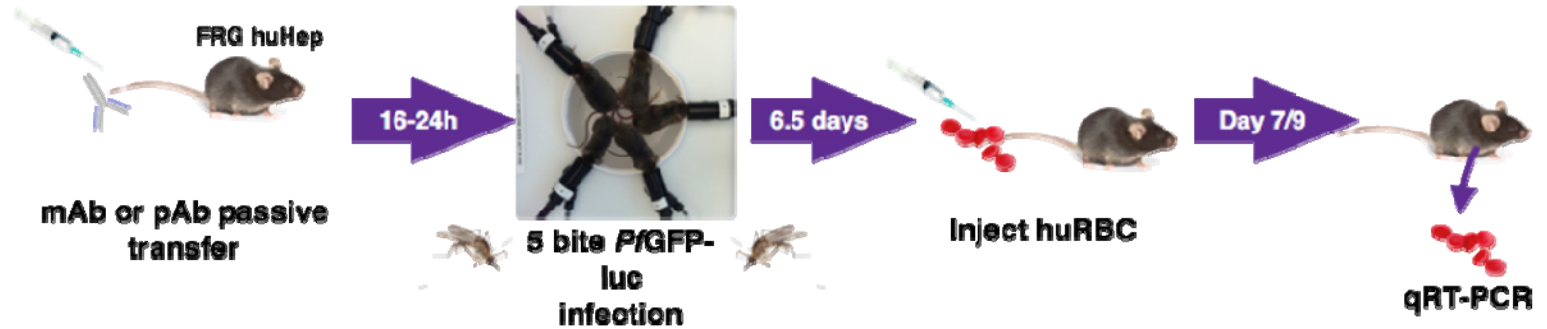
Human Protein ATLAS – human liver



Potential role for PfTRAP multi-modal binding

- Our results complement the recent studies on $\alpha V\beta 3$ interactions, which appear to be important for motility in the skin
- PDGFR β is not completely ubiquitous in skin or liver, but is concentrated around and in vasculature
- Could concentrations of PDGFR β around vessels be important for entry and/or exit into the circulatory system?
- Potential complementary model with $\alpha V\beta 3$ interaction for motility in the skin, and PDGFR β for entry and exit in the vasculature.

Can these studies inform vaccine design?



Acknowledgements

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