

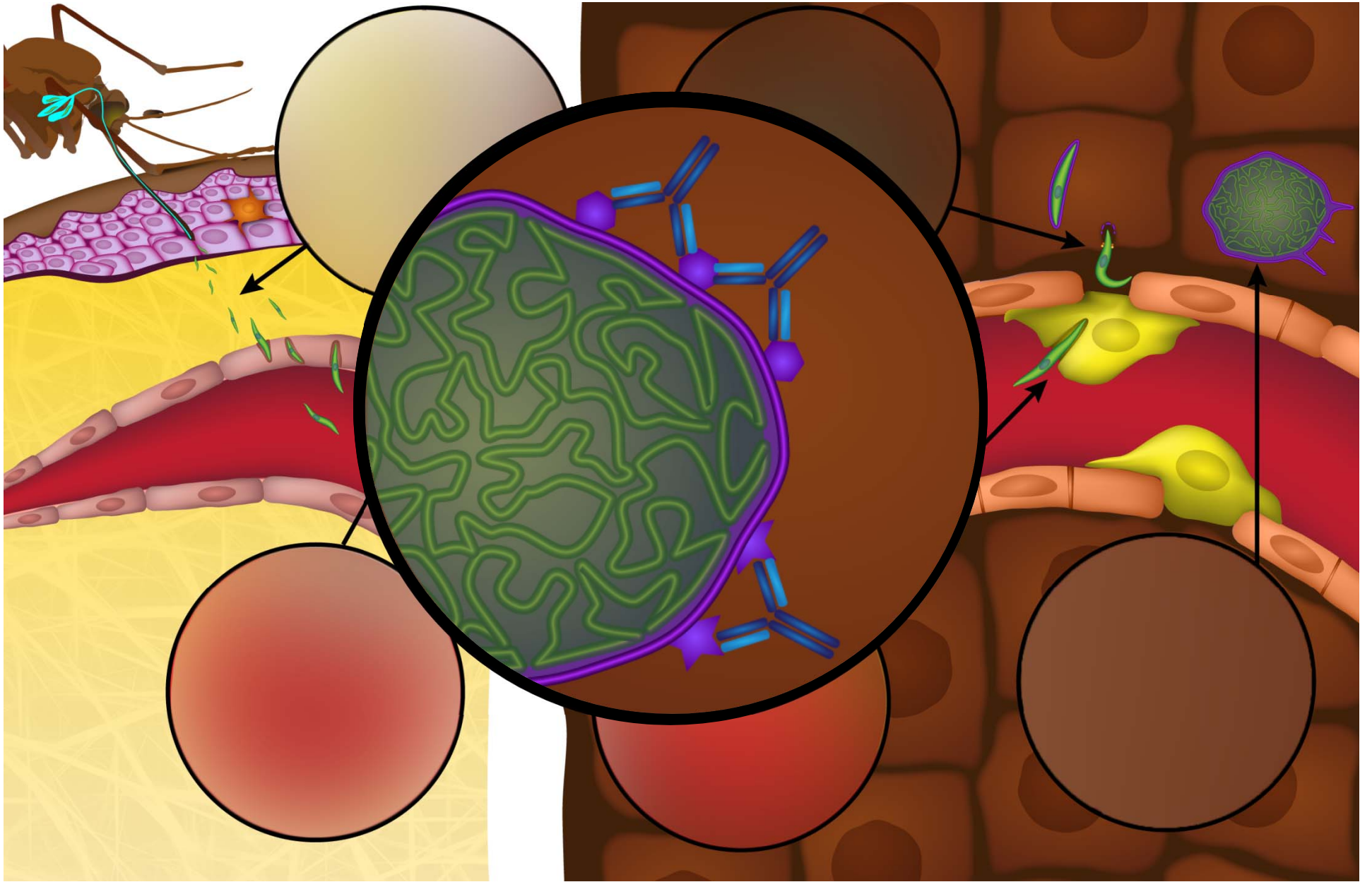
Toward rational vaccine design for pre-erythrocytic malaria vaccines

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Center for Infectious
Disease Research

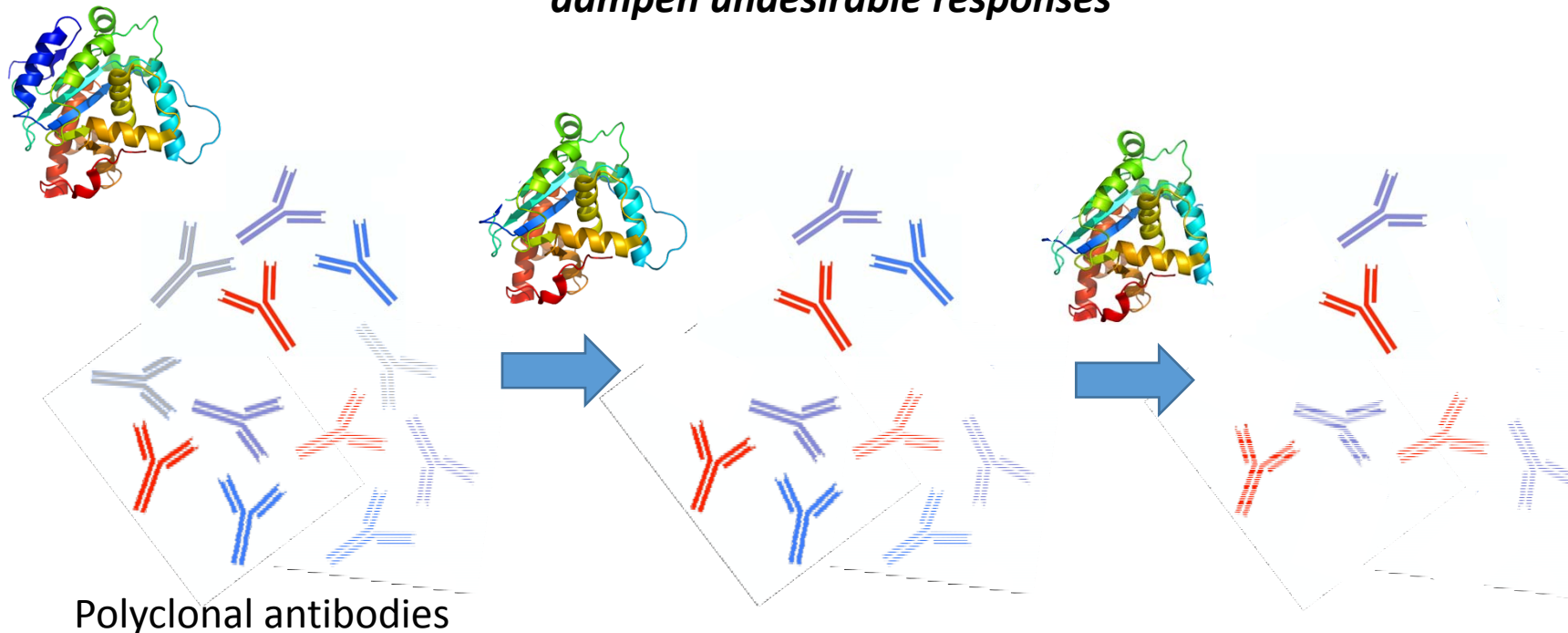
PEOPLE. SCIENCE. HOPE.



What is rational vaccine design?



Iterative refinement of vaccine antigen to enhance desirable responses and dampen undesirable responses



Not necessarily talking about structure guided design

Testing Malaria antibody targets

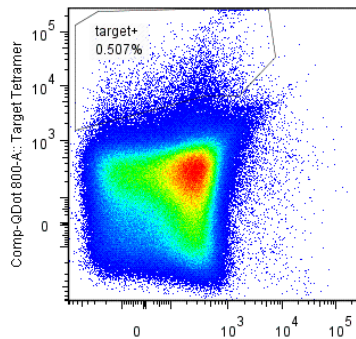


Adjuvax

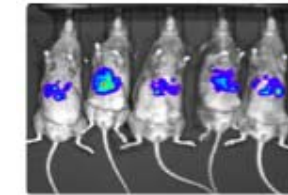


BALB/cJ

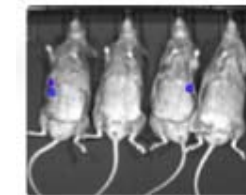
MAB



Mosquito challenge



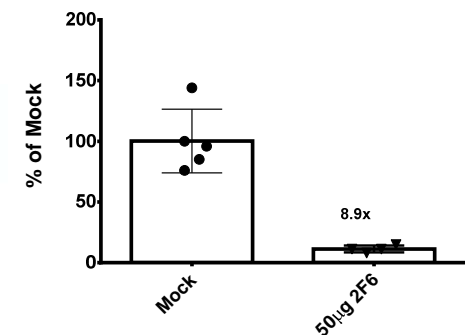
Control



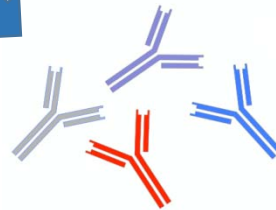
Antibody

liver burden by IVIS

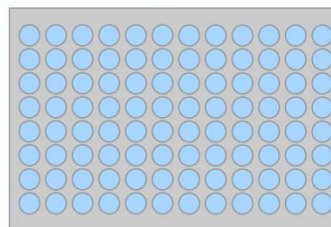
44h post 20 MosBite



Polyclonal Ab



In vitro assays

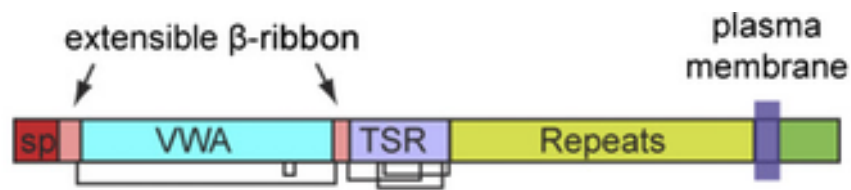


Invasion

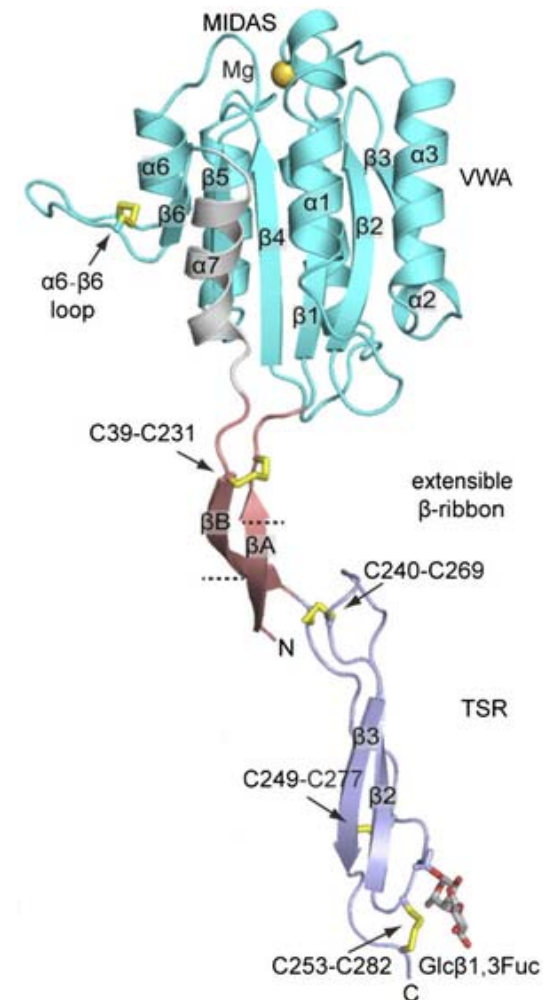
Example: PfTRAP (Thrombospondin Related Anonymous Protein)



- Critical gene in the PE stages
- Role in parasite motility and invasion
- Multiple domains
- Partial structure is known
- Clinical trials with rec PfTRAP have failed



All of the makings are there for a great vaccine...so why hasn't it worked?



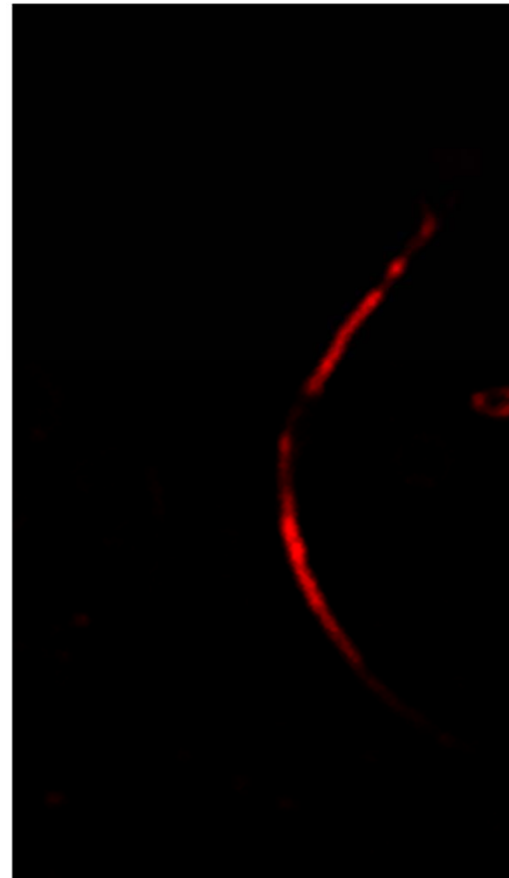
Do vaccine-elicited pAbs see the bug?



DAPI
(nuclear)



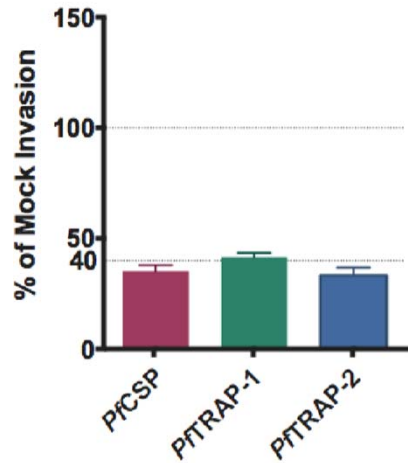
TRAP



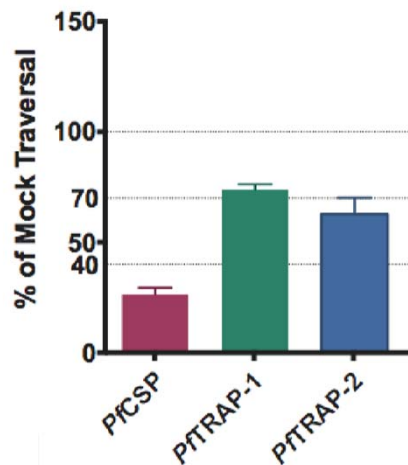
Partial protection after immunization with TRAP



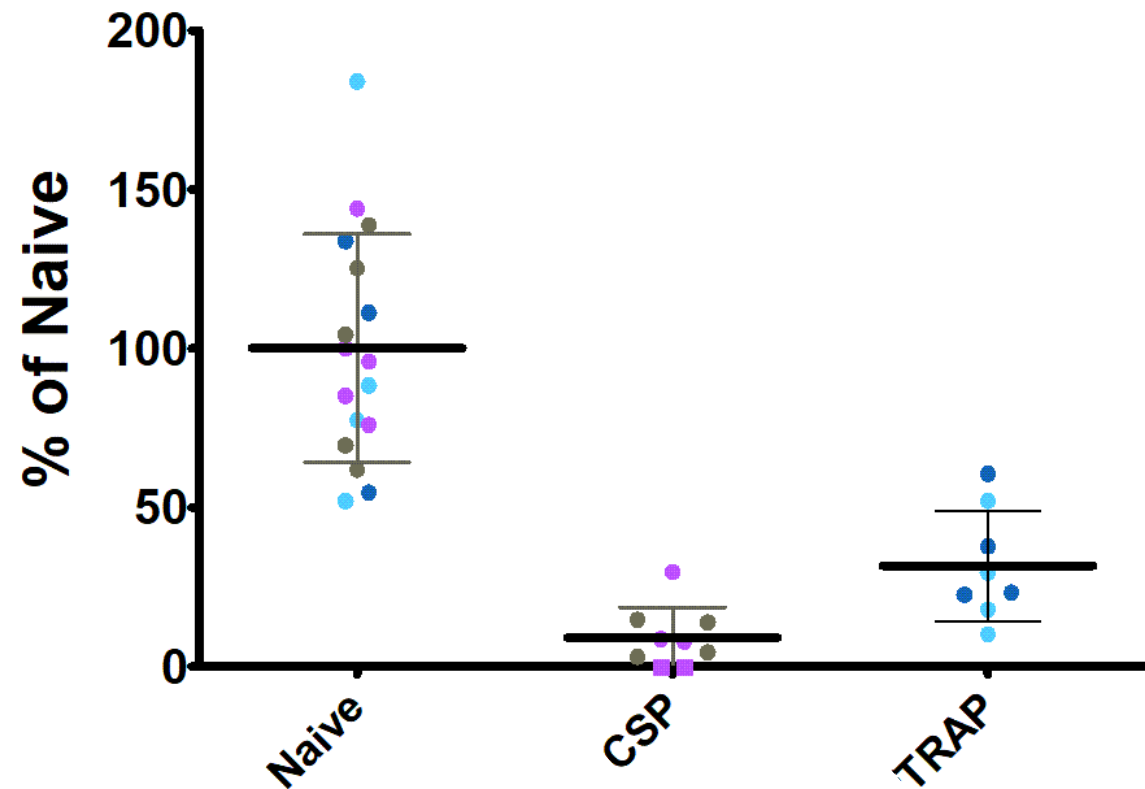
Serum ISTI Invasion



Serum ISTI Traversal



Infection Challenge

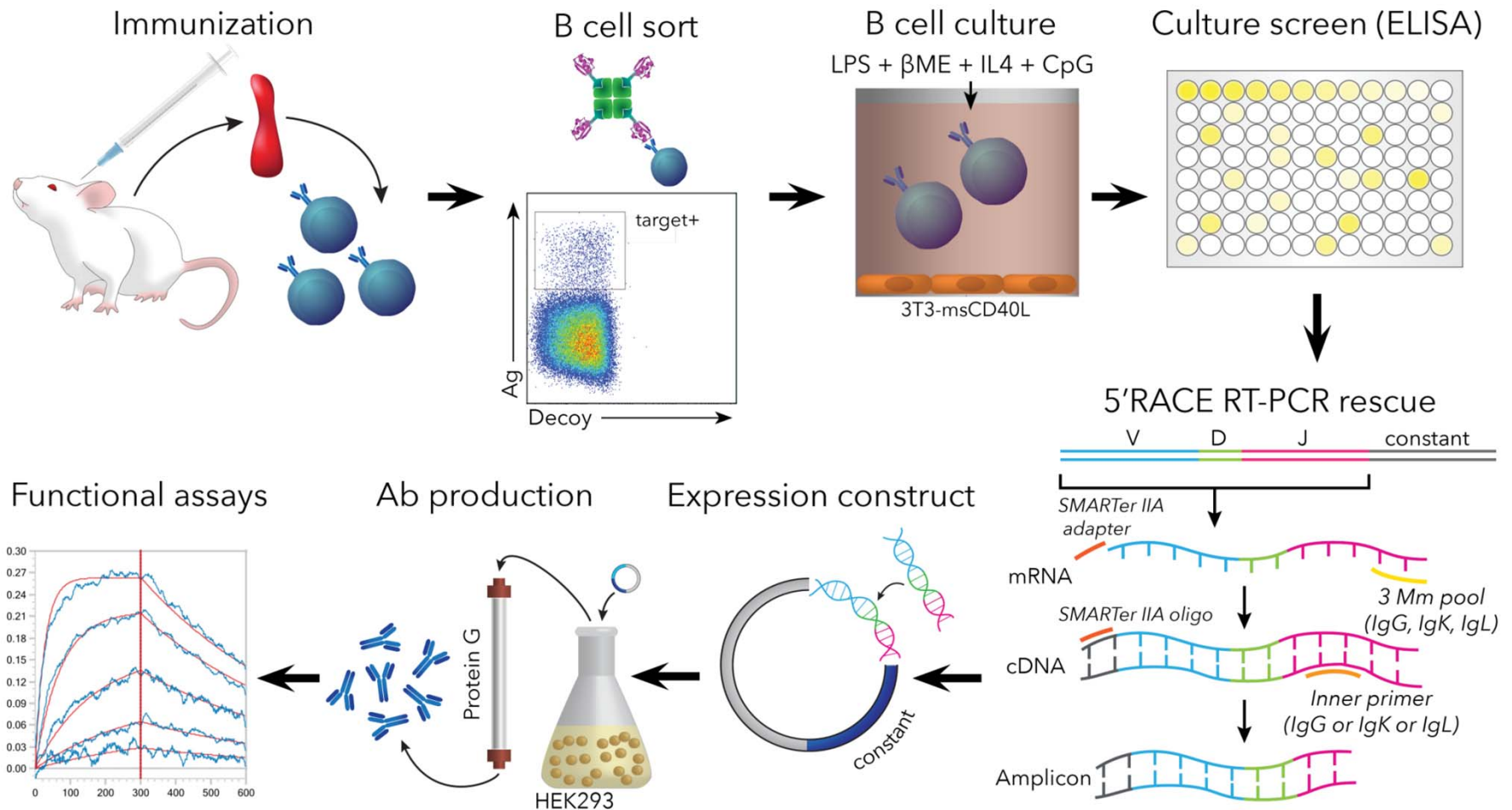


So, why doesn't PfTRAP give sterilizing protection?

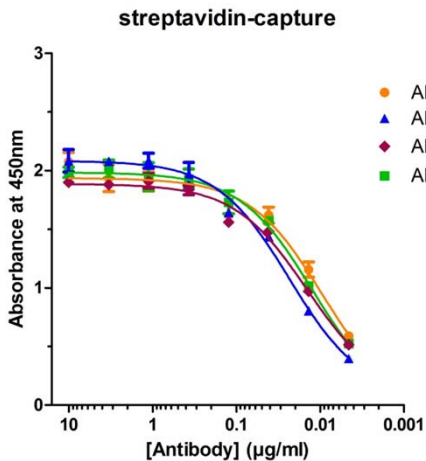
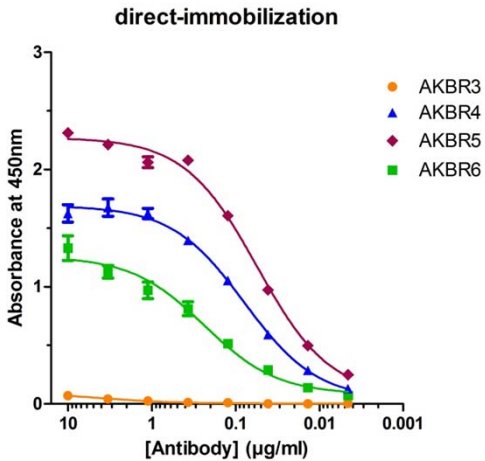


- Not the right vaccine antigen?
- Not the right vaccine adjuvant?
- Not the right vaccine formulation?
- Not the right vaccine modality?
- Not the right antibodies??

Monoclonal antibodies

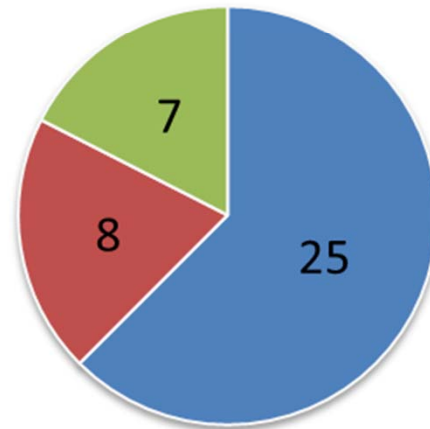
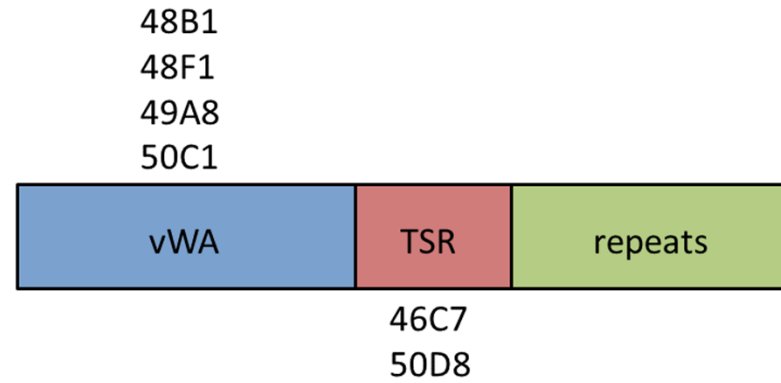


Mapping mAb responses to functional domains



	full-length	vWA	vWA + TSR	TSR	TSR + repeats	repeats
79A4	++	++	++	--	--	--
79F5	++	+++	++	--	--	--
80A8	+++	++	++	--	--	--
80C6	+++	++	++	--	--	--
80E3	+++	+++	+++	--	--	--
80E9	++	++	++	--	--	--
80F1	+++	+++	+++	--	--	--
80F4	+	+	+	--	--	--
80F9	++	++	++	--	--	--
82A2	+++	--	+++	+++	+++	--
82A3	++	++	++	--	--	--
82A9	++	+++	+++	--	--	--
82B1	+++	+++	+++	--	--	--
82B5	++	+	++	+	--	--
82B9	+++	--	++	+	++	--
82C3	+++	--	+++	++	+++	--
82C5	++	++	++	--	--	--
82C7	+++	--	--	--	++	++
82C9	+++	+++	++	--	--	--
82D1	++	+++	+++	--	--	--
82D2	++	--	+++	++	+++	--
82D4	++	+	++	--	--	--
82D5	+++	+++	+++	--	--	--
82D6	+++	+++	+++	--	--	--
82D8	+	+	++	--	--	--
82E1	+	--	--	--	+++	+++
82E5	+++	--	--	--	+++	+++
82E6	+	--	--	--	+++	++
82F6	++	+	+	--	+	+
82F8	+++	--	--	--	++	++
83A6	+++	++	+++	--	--	--
83B6	++	+	++	--	--	--
83E7	+++	+	+++	+++	+++	--
84A2	+++	--	--	--	+++	+++
84B7	++	++	++	--	--	--
84C2	++	++	++	--	--	--
84C4	+++	+++	+++	--	--	--
84C5	+	--	--	--	+++	+++
84C7	++	--	++	++	++	--
84E3	+	--	++	+	+	--
	full-length	vWA	vWA + TSR	TSR	TSR + repeats	repeats

The immunogenic landscape of PfTRAP

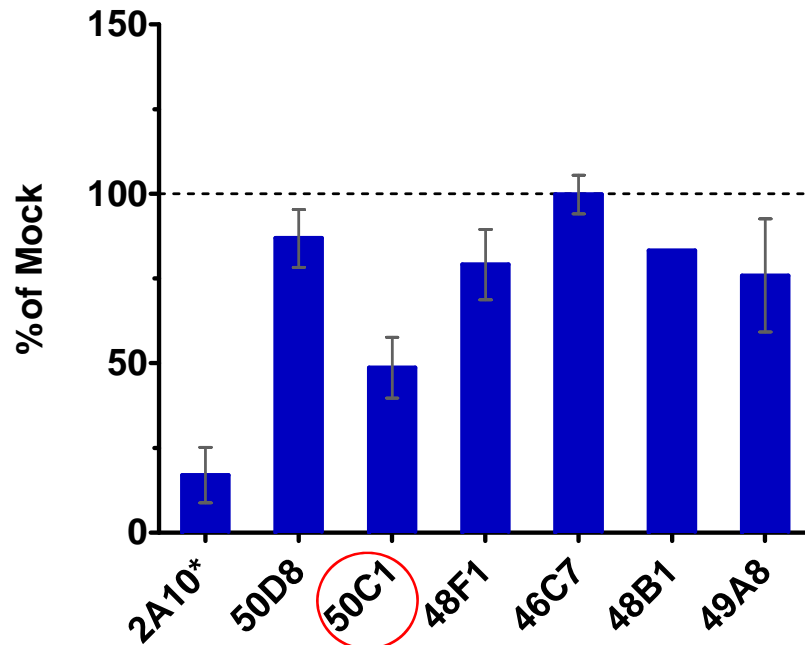


■ vWA ■ TSR ■ repeats

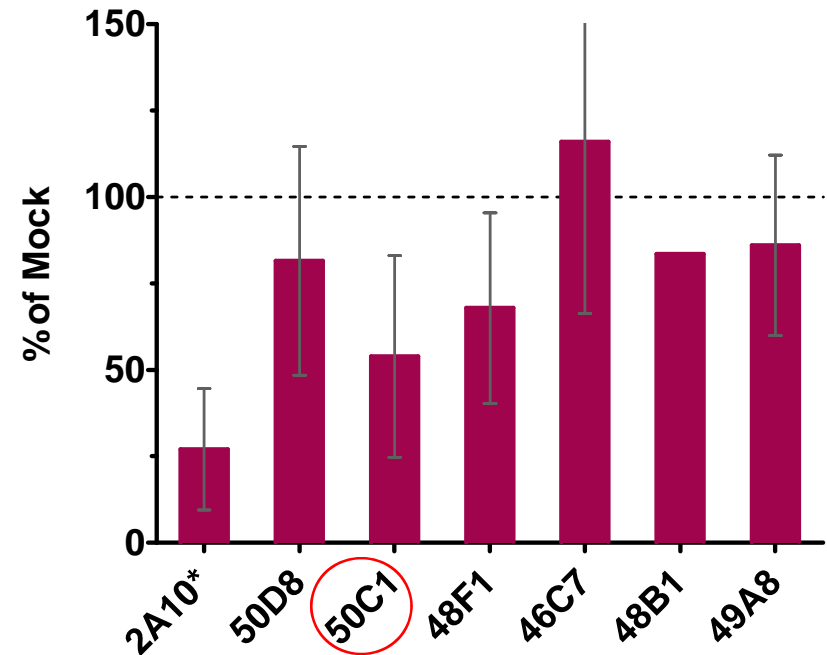
vWA domain may be a target for rational vax



mAb ISTI: Invasion



mAb ISTI: Traversal

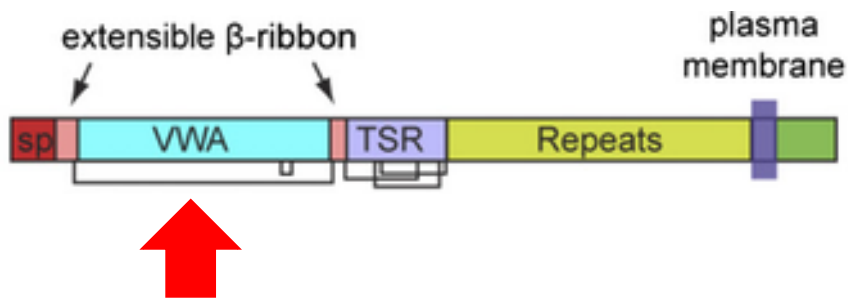


48B1
48F1
49A8
50C1

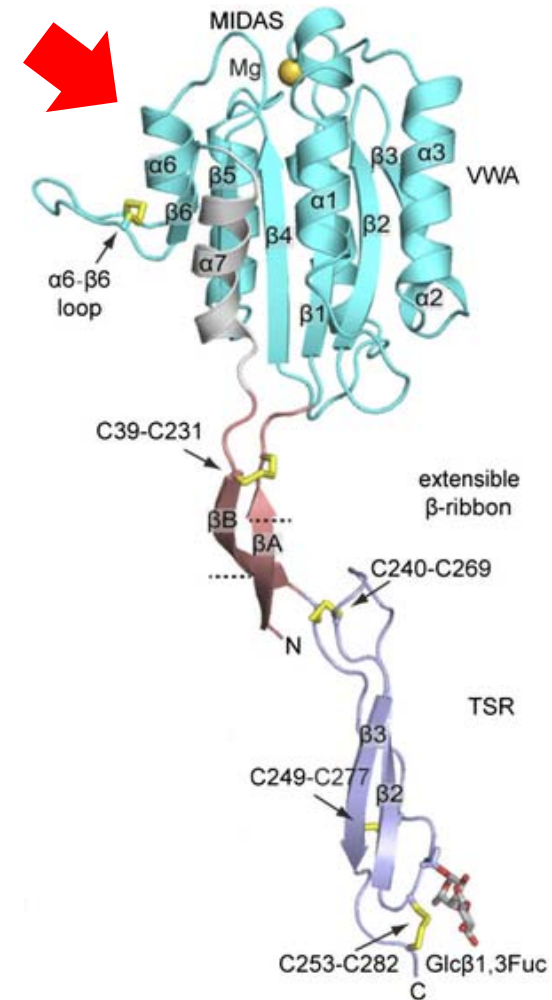


46C7
50D8

Example: PfTRAP (Thrombospondin Related Anonymous Protein)



vWA domain may be a rational vaccine target...



Conclusions



- Picking apart antibody responses using mAbs allows the fine dissection of anti-parasitic activity
- Allows for the identification of protein domains that can mediate protective immunity
- Identified vWA domain as a potential rational vaccine target
- Current studies aimed at co-crystallization, HDX epitope determination
- Identification of protective epitopes is the principle step toward rational vaccine design

Acknowledgements



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