Developing a MAPS vaccine against *Salmonella* Typhi and Paratyphi

Ying-Jie Lu, PhD
Rick Malley, MD
Boston Children's Hospital
Harvard Medical School

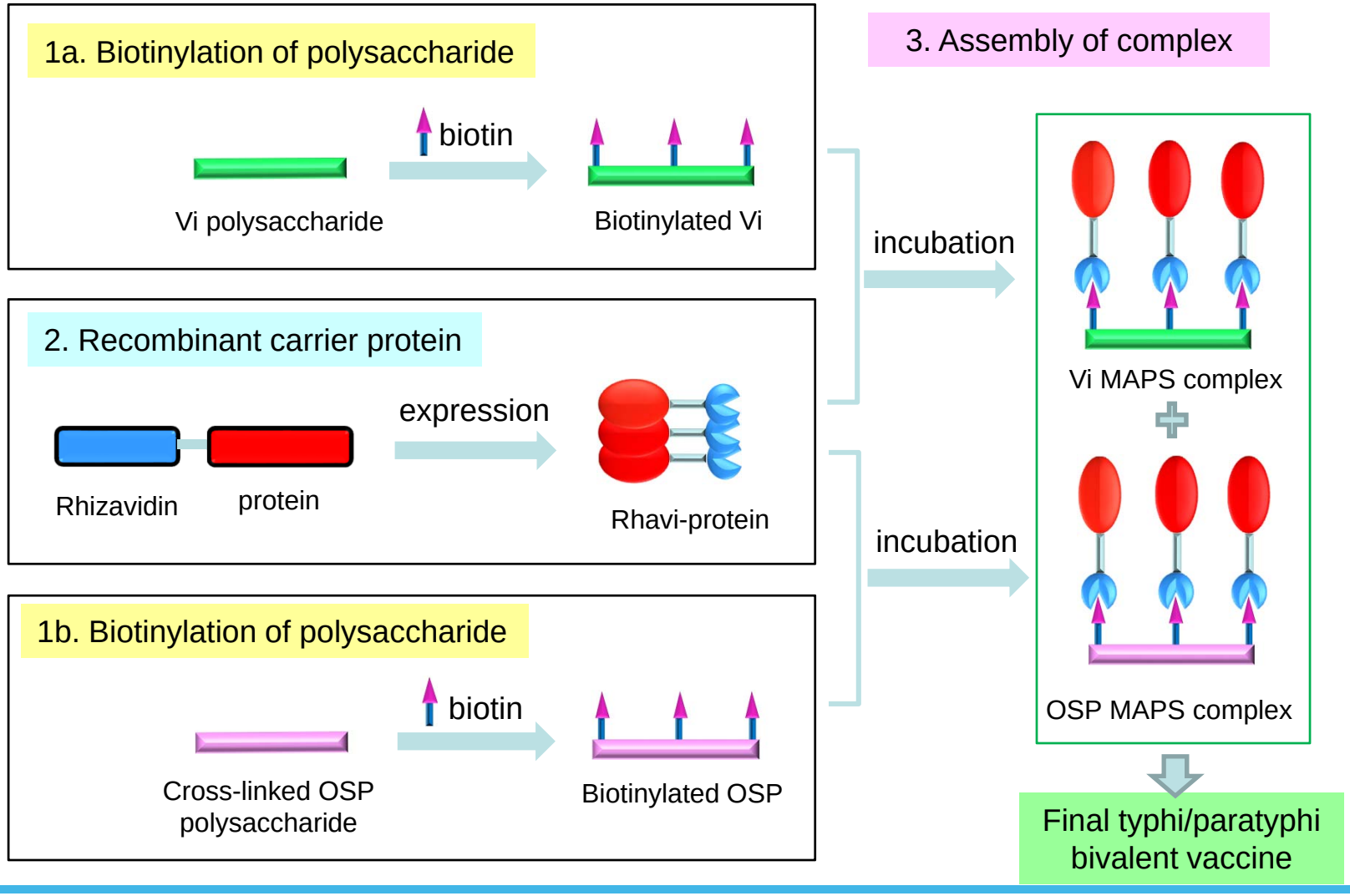
Boston Children's Hospital
Until every child is well™

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

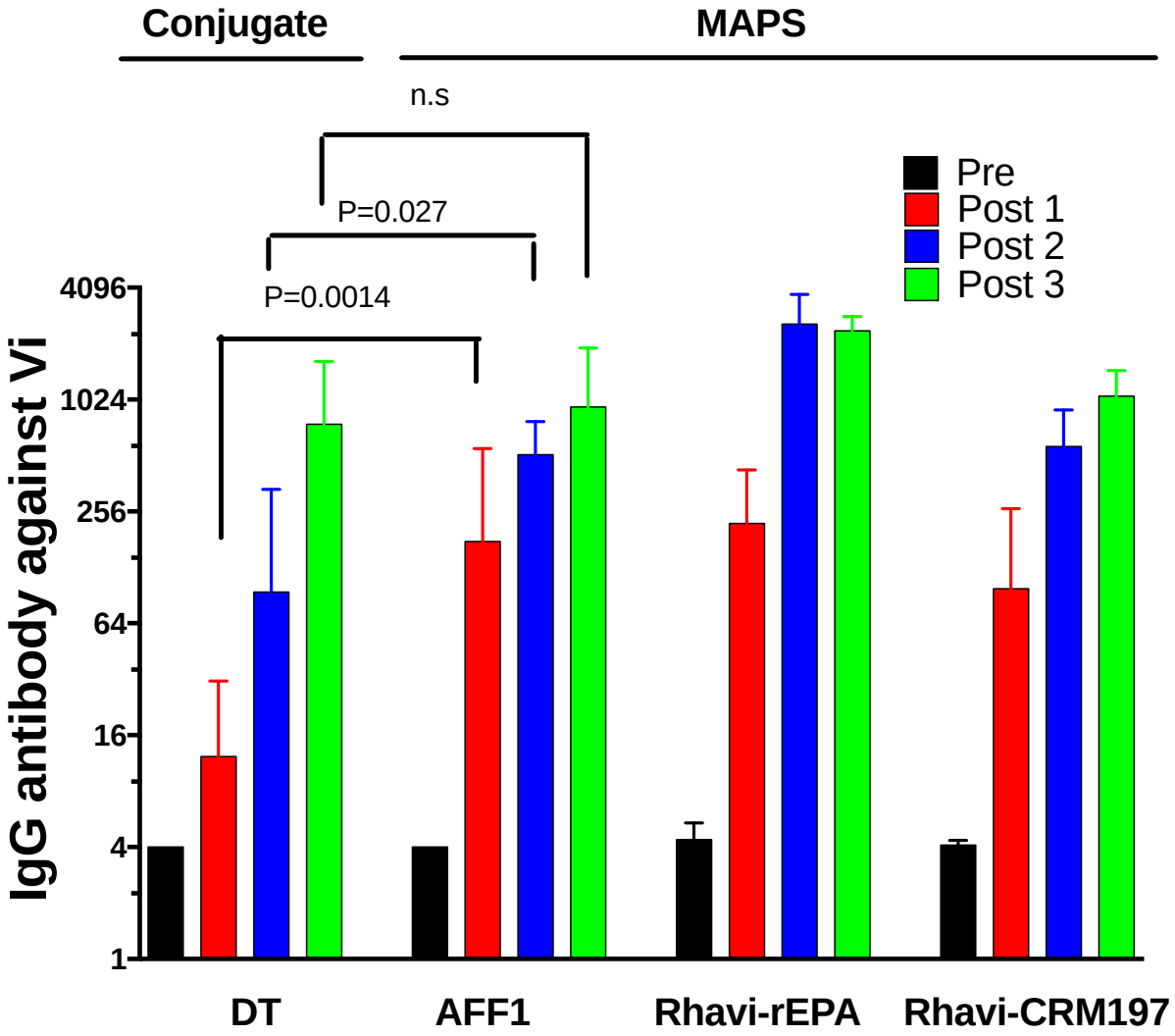
Outline of presentation

1. Overview of MAPS technology
2. Choice of carrier protein
3. Immunogenicity testing of combination vaccine in rabbit model
4. Function analysis of antibodies

Multiple Antigen Presenting System (MAPS) for Vi and paratyphi OSP



Vi antibody titers in Guinea Pigs after immunizations with Vi MAPS

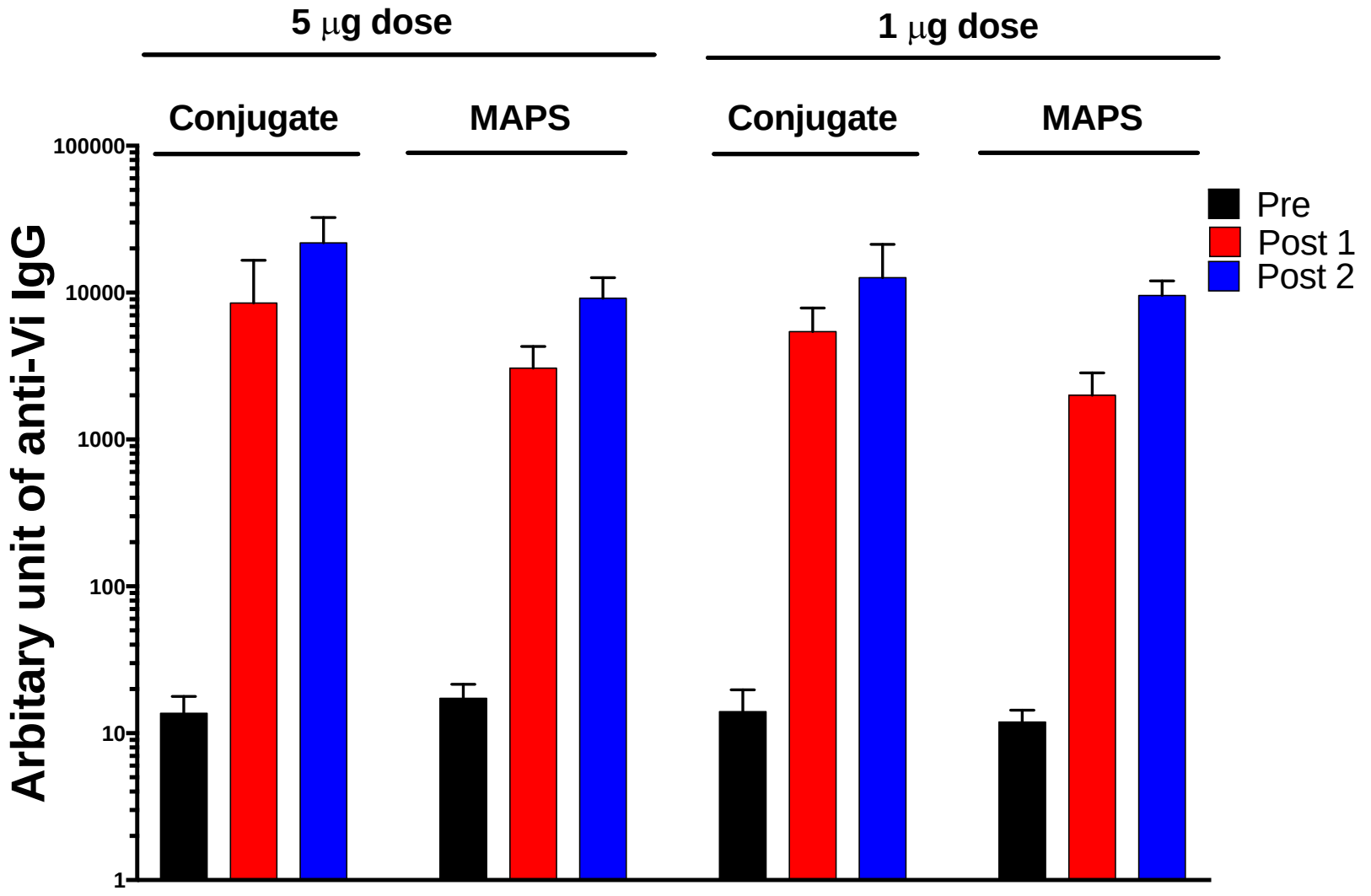


Vi-DT conjugate kindly provided by IVI

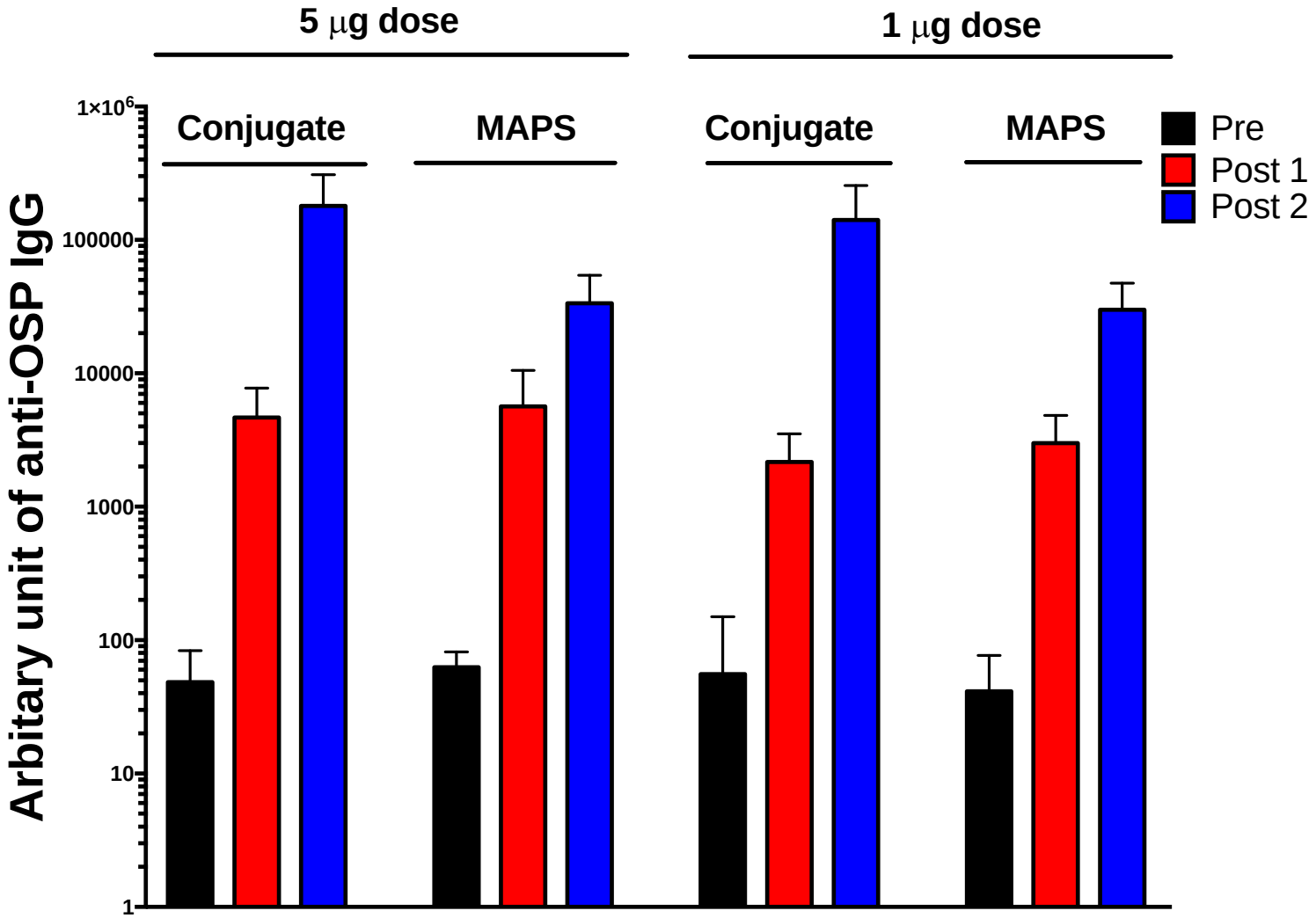
AFF1 chosen as our carrier

Carriers	Advantages	Potential issues	Carrier function
Rhavi-rEPA	Highly immunogenic; rEPA has been tested in multiple human clinical trials, good safety track record	Toxin mutant; not used in licensed vaccines; purification scheme needs to be established	Mice: +++ Guinea pigs: +++ Rabbit: ++
AFF1	Excellent carrier; purification established and yield is high (>1g/L); no toxin concern	Currently being tested in humans as part of pneumococcal MAPS	Mice: ++ Guinea pigs: ++ Rabbit: +++
Rhavi-CRM_{197}	CRM_{197} Used in licensed conjugate vaccines, fewer safety concerns	Yield at lab scale is low. May increase COG	Mice: +++ Guinea pigs: ++ Rabbit: Not tested

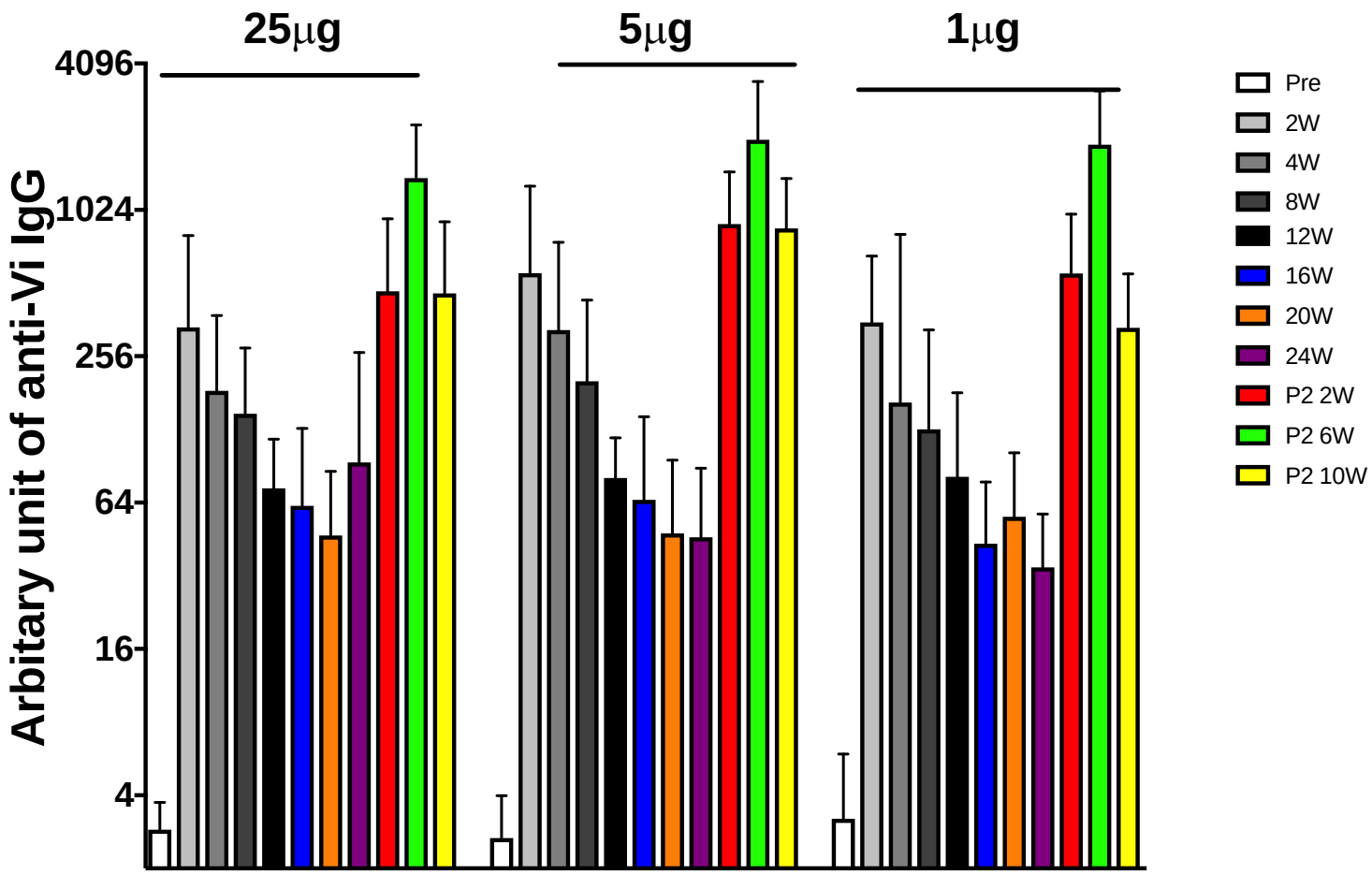
Immunogenicity of Vi as part of combination typhoid/paratyphi MAPS vaccine



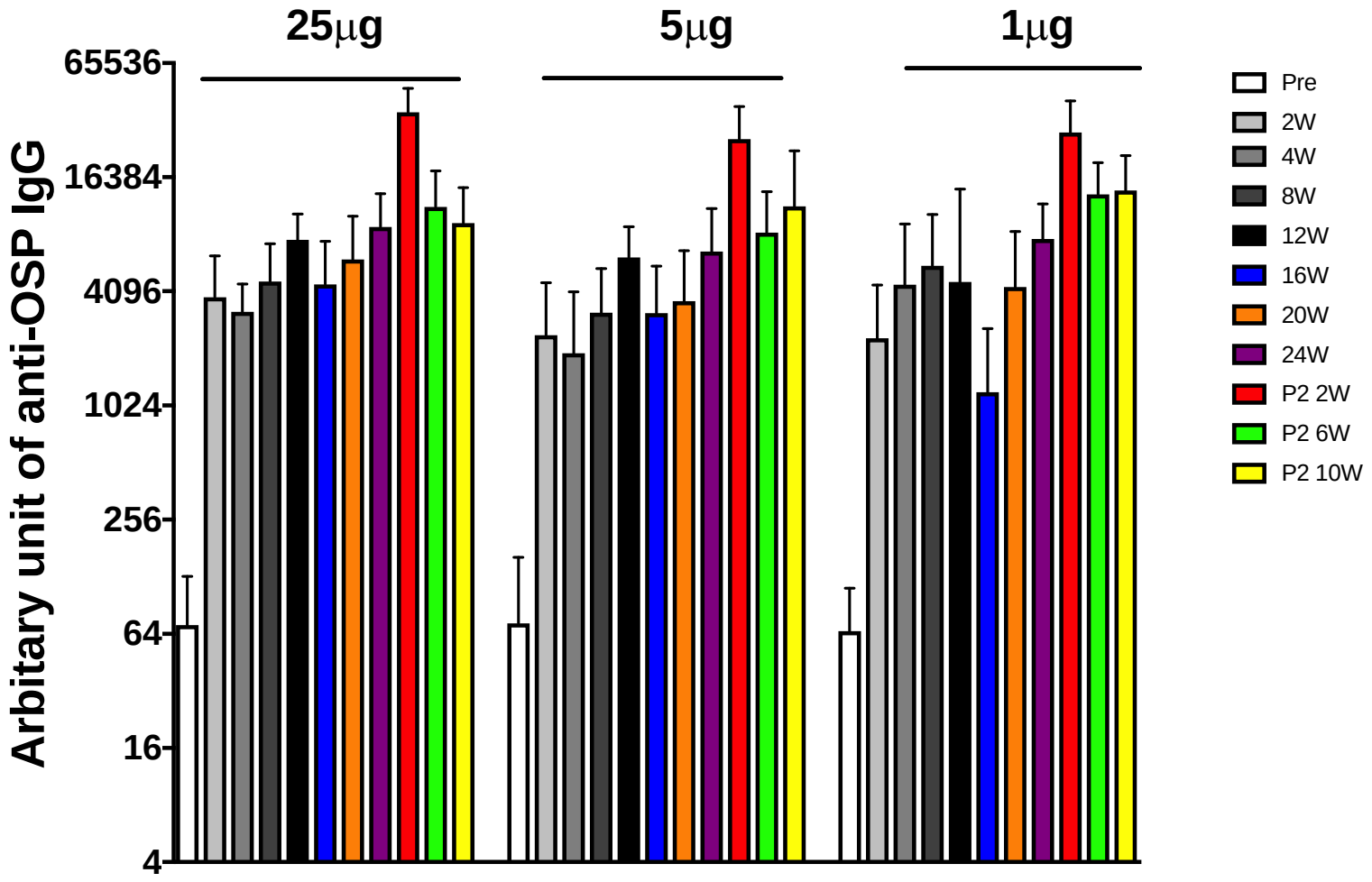
Immunogenicity of OSP as part of combination typhoid/paratyphi MAPS vaccine



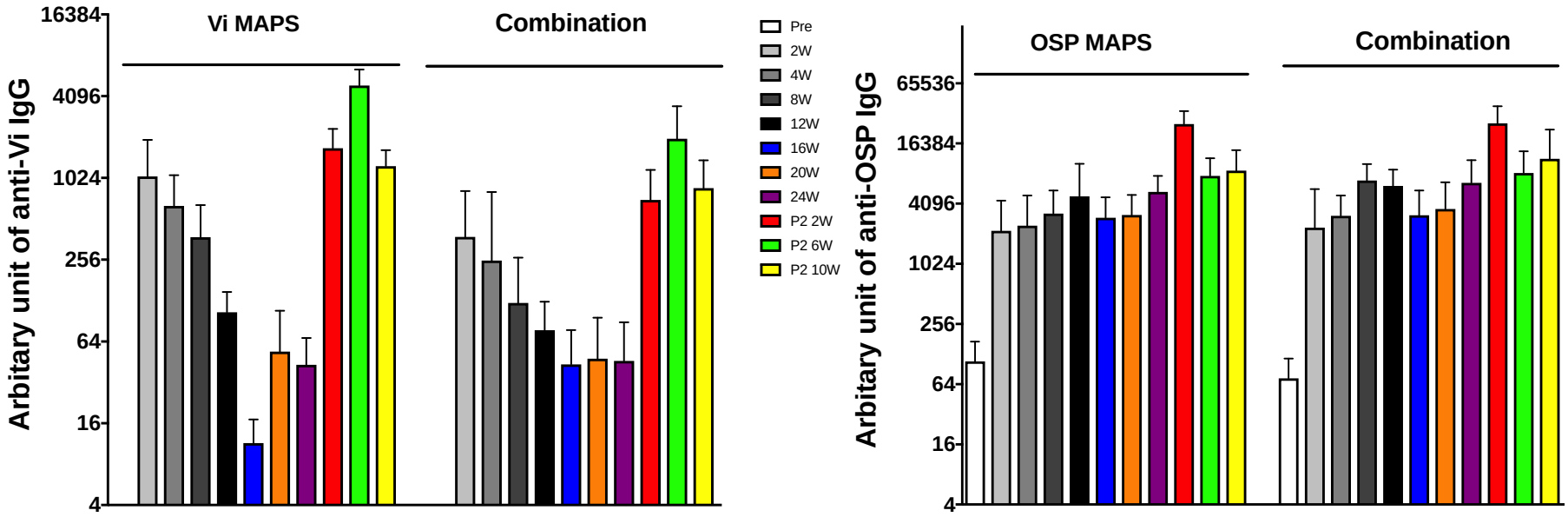
Vi: Antibody duration and boosting



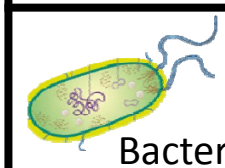
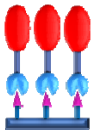
OSP: Antibody duration and boosting



Evaluation of possible interference in combination vaccine



Immune response to PS antigens

Antigen	Antibody response	Source of help	Ig	Affinity maturation	Memory response
 Free PS	TI	BCR cross-linking	IgM/ IgG	-	-
 Bacteria	Non-classic TD (CD1d)	T cells	IgG	-	+/-
 Indirect conjugate	Non-classic TD (CD1d)	T cells	IgG	-	+/-
 Conjugate	Classic TD (MHCII)	Th2 cells	IgG	+	+
 MAPS	?	?	?	?	?

Testing for immunological memory: Adoptive transfer experiments

Concept: Infuse B cells from immunized wild type mice into $RAG^{-/-}$ (immunodeficient) mice and evaluate whether boosting can be demonstrated

WT C57

Immunization with
Vi-DT or
rEPA-Vi MAPS
Wait > 4 weeks

Adoptive transfer

$RAG^{-/-}$

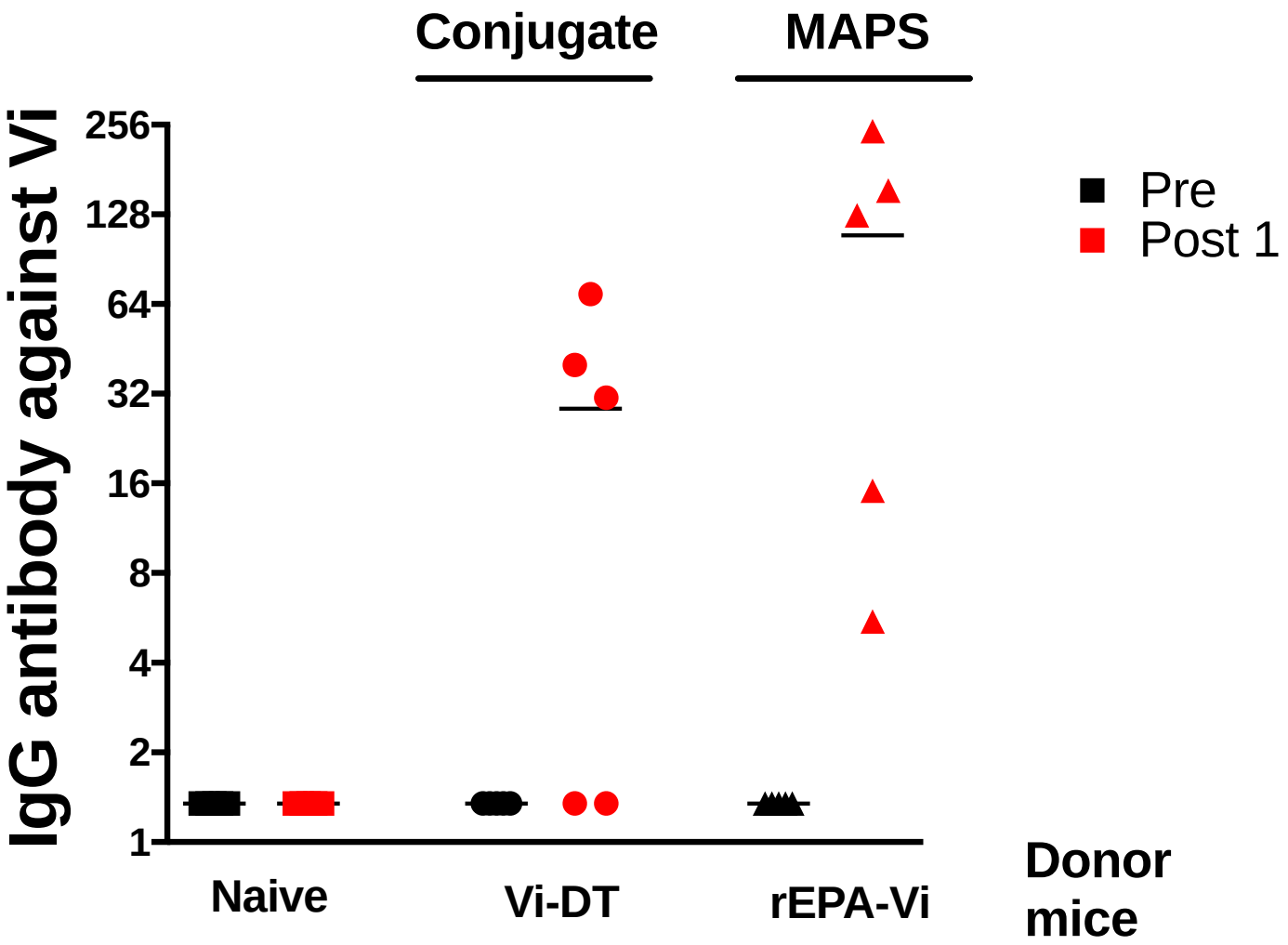
7 days

Bleed
Immunize with
a mixture of Vi,
DT and rEPA

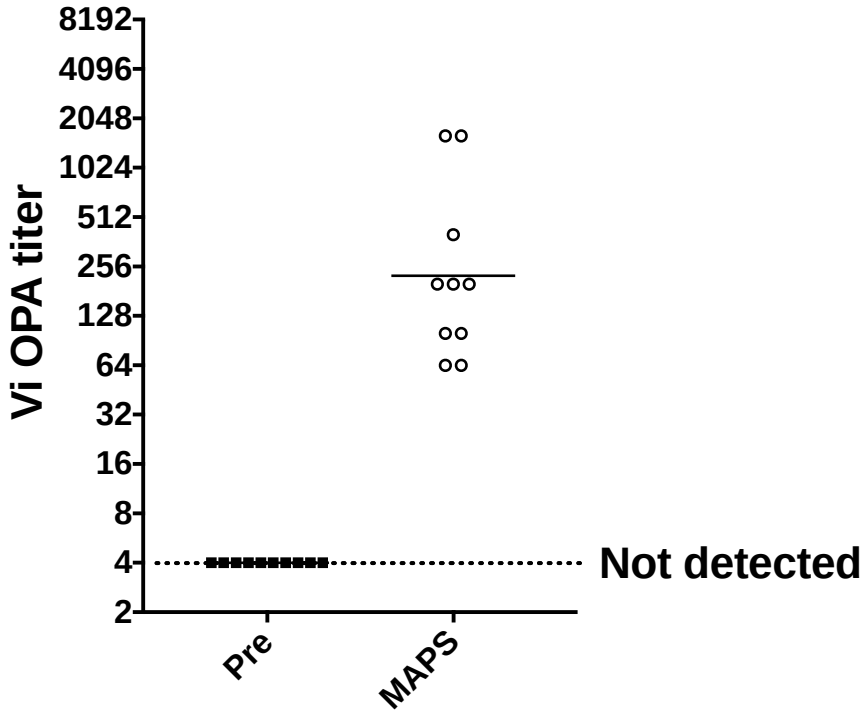
14 days

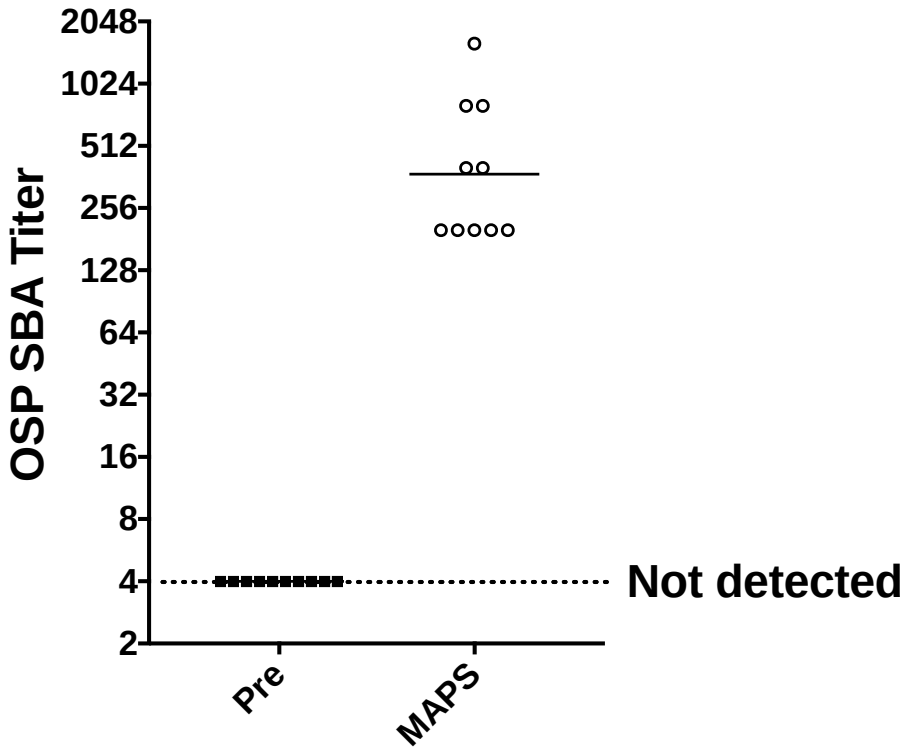
Bleed

Boosting

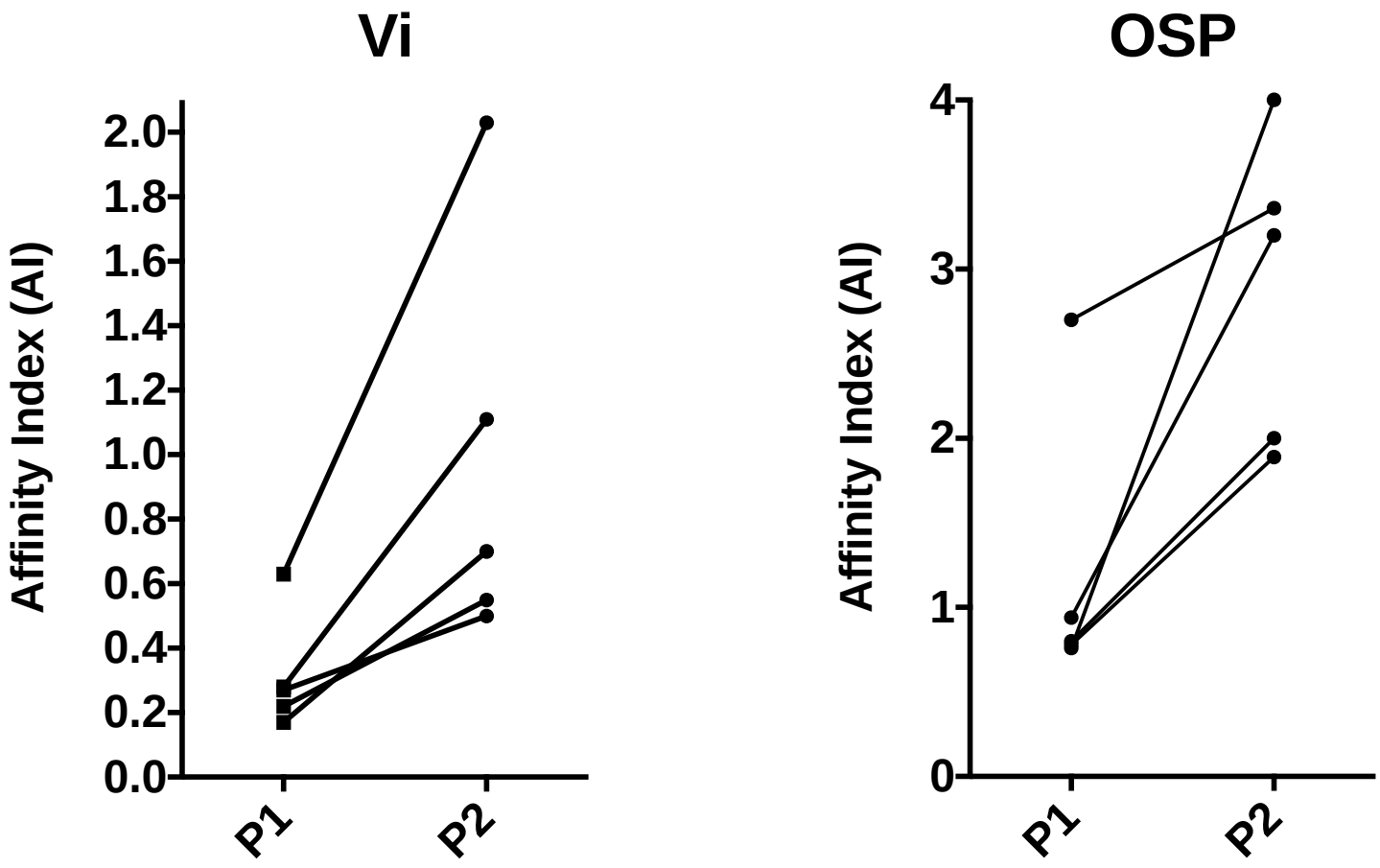

Conjugate
MAPS
IgG antibody against Vi
256
128
64
32
16
8
4
2
1
Pre
Post 1
Naive
Vi-DT
rEPA-Vi
Donor mice

Bactericidal activity in MAPS-immune sera

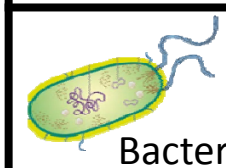
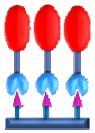




Affinity maturation



Summary

Antigen	Antibody response	Source of help	Ig	Affinity maturation	Memory response
 Free PS	TI	BCR cross-linking	IgM/ IgG	-	-
 Bacteria	Non-classic TD (CD1d)	T cells	IgG	-	+/-
 Indirect conjugate	Non-classic TD (CD1d)	T cells	IgG	-	+/-
 Conjugate	Classic TD (MHCII)	Th2 cells	IgG	+	+
 MAPS	Classic TD (MHCII)	Th2 cells	IgG	+	+

Summary

- Vi-MAPS generated Vi-specific memory response
- Both Vi and OSP MAPS are highly immunogenic in animal models.
- Functional antibody generated (correlates with titer) and shows affinity maturation
- GLP production in preparation for GLP toxicology studies is currently ongoing

Acknowledgments

BCH Lab

Yingjie Lu
Fan Zhang
Mark Reglinski
Olivia Ledue
Nicole Ma
Katherine Lucas

BCH TIDO

Abbie Meyer
Irene Abrams

Others…

Velupillai ("Puvy")
Puvanesarajah
Bob Corder
Shite Sebastian
Sharon Tennant

BMGF

Anastazia Older Aguilar
Lyou-Fu Ma