Mapping vaccines for the developing world: A tale of affinities

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Potential Conflict of Interest Disclosure

I disclose the following financial relationships with commercial entities that produce health care-related products or services relevant to the content I am planning, developing, or presenting:

Company	Relationship	Content Area
GSK	Consultant	Vaccines
Merck	Consultant	Vaccines

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Member, Board of Directors, Corner Therapeutics
Member, Scientific Advisory Board, Amplitude Therapeutics and Limmatech

Outline

1. General (primarily pneumococcal) vaccine concepts
2. Development of a platform and examples of applications
3. Development of a biotechnology company
4. Epilogue

Background

- Born in NYC
- Moved to France age 4
- Journalist father expelled from France in 1980, returned 1981
- College in US 1982, "temporary"
- Med school Tufts 1986-90
- Internship, residency, fellowship in ID and ER and stayed at BCH ever since
- Primary focus on early vaccine development, with emphasis on vaccines for LMICs

M&M analogy

Pneumococcus Bacterium

Protein Core

- Virulence factors
- Polysaccharide surface protects protein core from host's defenses

Sugar Coating

- Polysaccharide outer surface critical in distinguishing various strains of bacterium
- 100+ different serotypes of pneumococcus
- Diverse sugar surfaces require multiple valencies in a vaccine to combat bacterium

Pure polysaccharides are immunologically boring

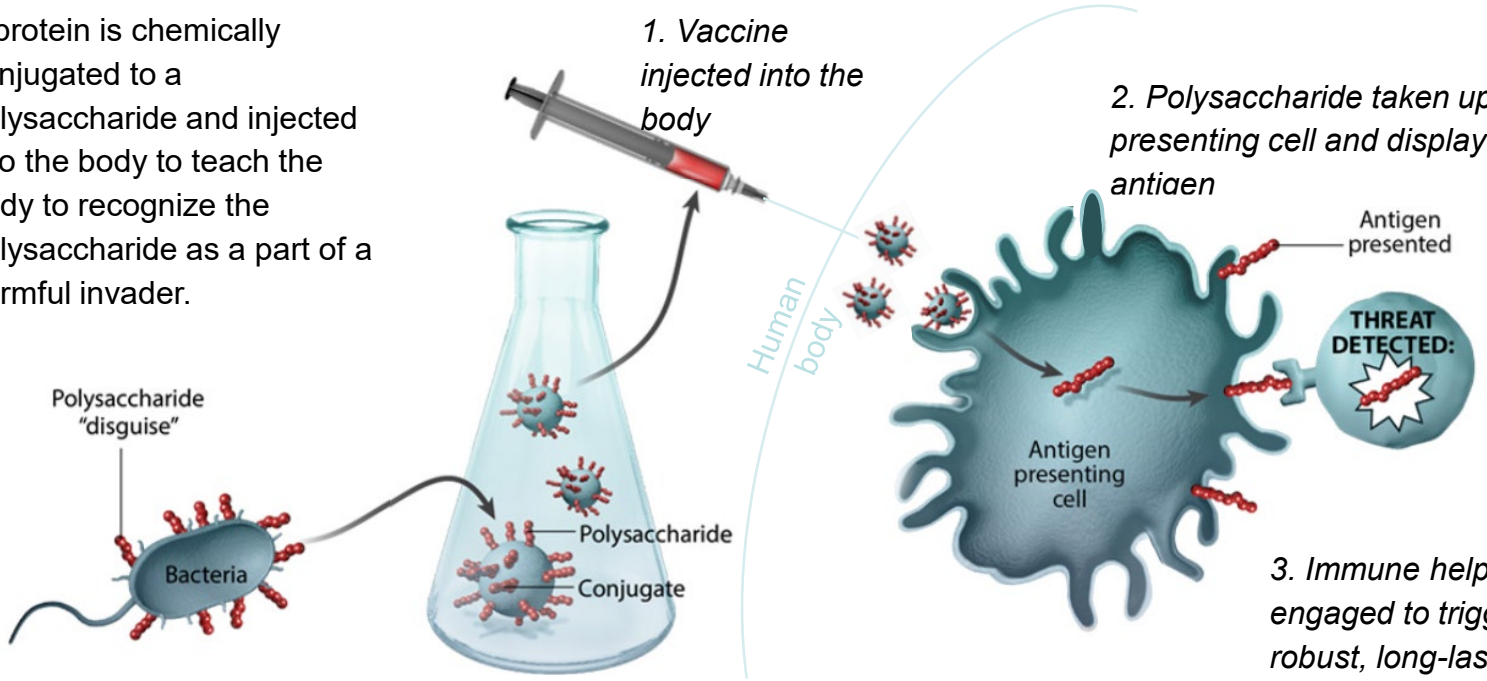
Pure polysaccharide

T-cell independent (humoral)

IgM, IgG short-lived
Ineffective in children

Protein-Polysaccharide Conjugate Vaccines

A protein is chemically conjugated to a polysaccharide and injected into the body to teach the body to recognize the polysaccharide as a part of a harmful invader.



1. Vaccine injected into the body

2. Polysaccharide taken up by antigen presenting cell and displayed on surface as antigen

3. Immune helper cells are engaged to trigger a more robust, long-lasting immune response

**Images courtesy of the CDC website*

Conjugate vaccines are much more immunologically exciting

Pure polysaccharide	Pure polysaccharide + Conjugated carrier protein
	
T-cell independent (humoral)	T-cell dependent (humoral and cell-mediated)
IgM, IgG short-lived Ineffective in children	Robust IgG with memory Highly effective in children First one: Hib conjugate (Anderson and Smith, originally from BCH)

February 17th, 2000: US FDA approves the licensure of a seven-valent pneumococcal vaccine (PCV7, Wyeth/Pfizer)

Since then:

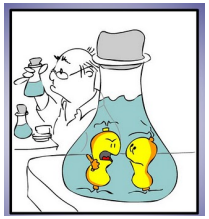
- PCV10 (GSK) in Europe in 2009
- PCV13 (Pfizer) in US in 2010
- PCV13 (Walvax) in China in 2019
- PCV10 (SII) in India in 2020

Recently licensed for adults, infants and children:

- Merck's PCV15
- Pfizer PCV20
- Merck PCV21 (adult only)
- Other vaccines in development

Some issues with pneumococcal vaccine conjugates (PCV)

1. Serotype replacement



I'm fed up with this guy – let's become pathogenic

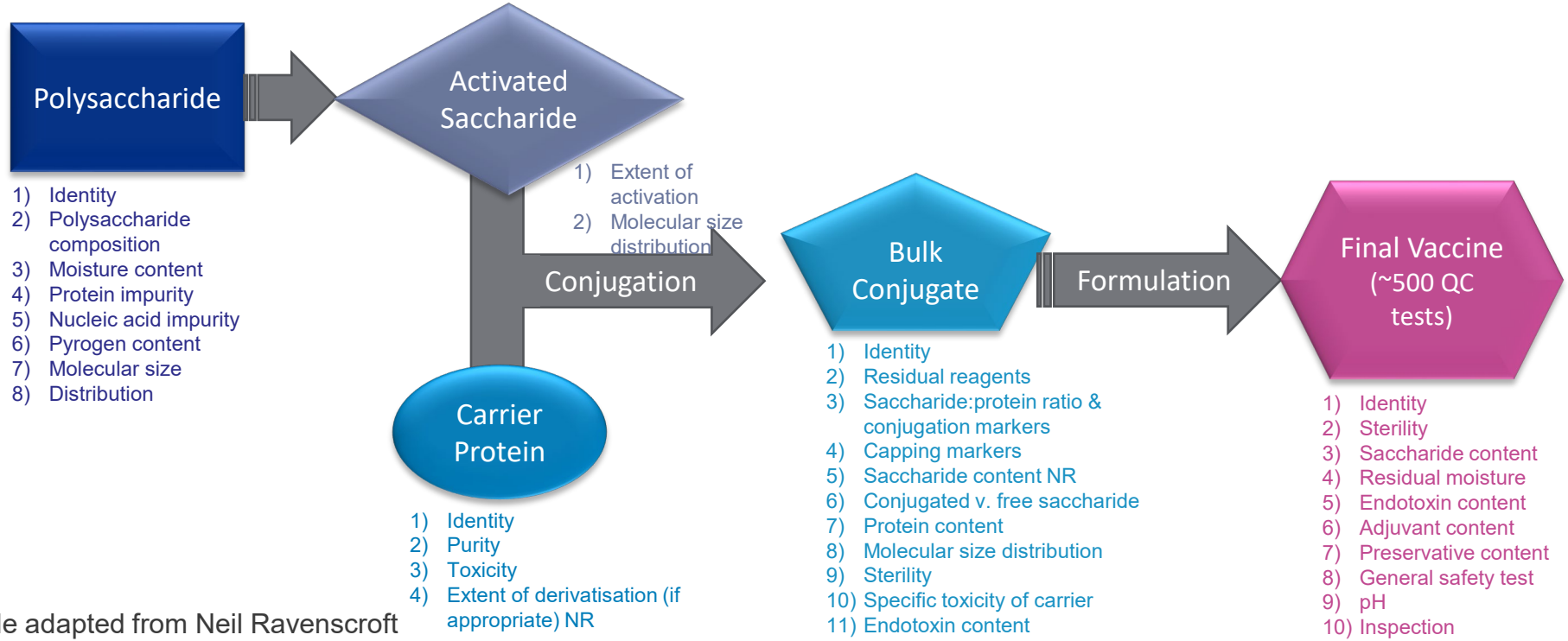
2. Cost

$180 per PCV13 dose (3-4 doses per child)

3. Immunogenicity does not always imply clinical efficacy

Serotype 3 – no efficacy
Serotype 19A/F -- resurgence

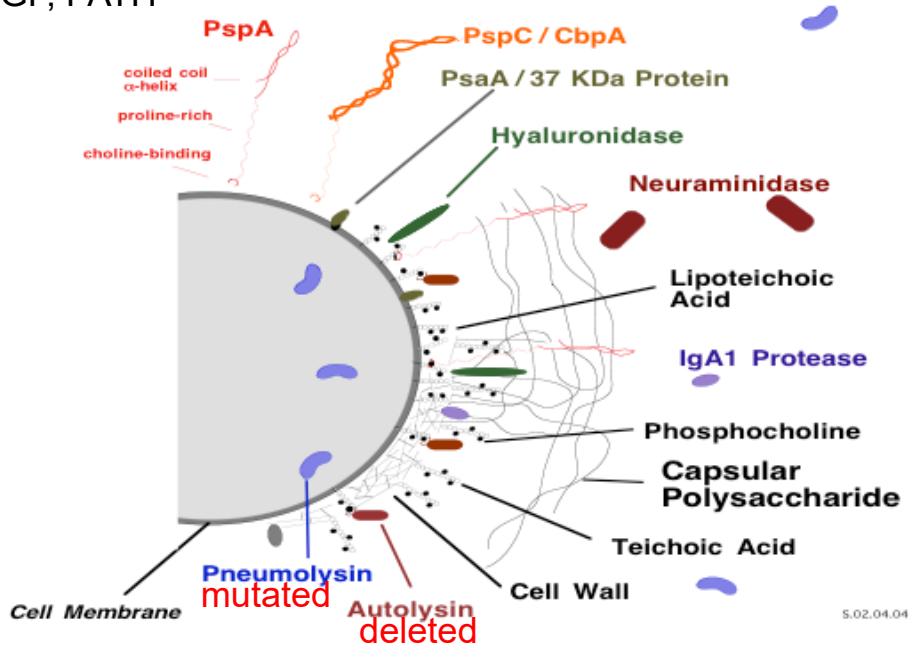
Hundreds of Quality Control Tests Required for Conjugate Vaccine

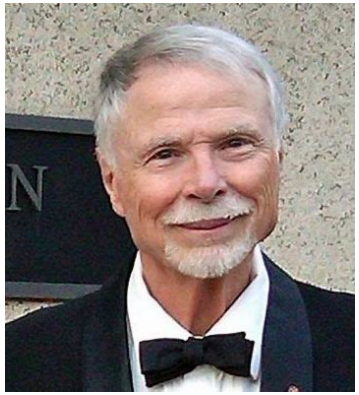


Slide adapted from Neil Ravenscroft

A potential alternative: Killed whole cell pneumococcal vaccine (WCV)

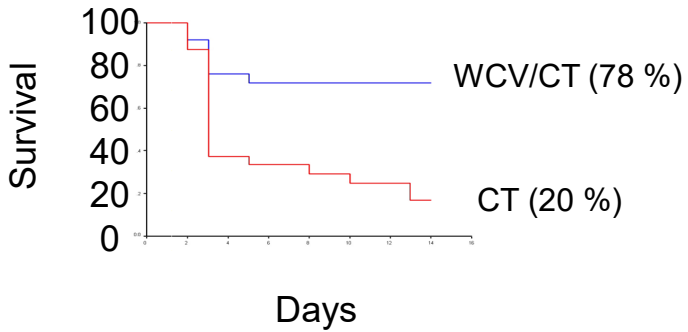
First pneumococcal vaccine: Killed whole cells (ca. 1911)
Revisited in 1996 by Porter Anderson (+ student)
Support from MRF, NIH, BMGF, PATH





First observations (ca. 2000)

Protection by unencapsulated antigen against pneumonia/sepsis with encapsulated type 3 SP (intrathoracic injection)



Antibody-mediated (noncapsular)
Identified several antigens that mediate protection against sepsis

Malley, Lipsitch, Anderson, 2001

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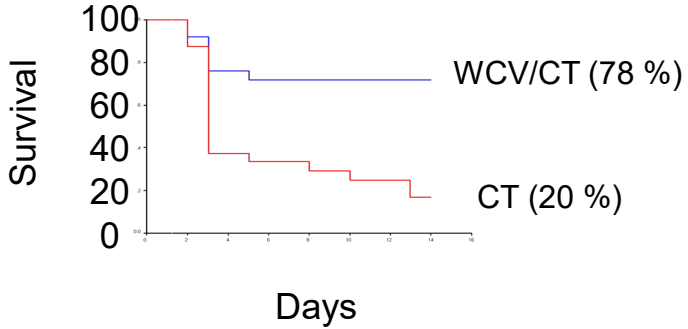
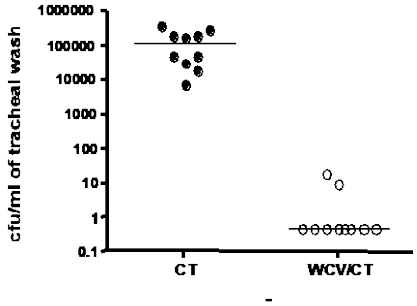


Antibody-mediated (noncapsular)
Identified several antigens that mediate protection against sepsis

Protection against encapsulated type 6B pneumococcal nasopharyngeal carriage



Antibody-mediated (noncapsular)?

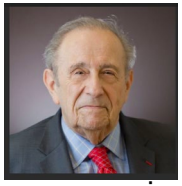
Malley, Lipsitch, Anderson, 2001

Carriage and transmission are all that matter

index carrier

Slides borrowed, with some minor modifications, from Marc Lipsitch

Carriage and transmission are all that matter



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Carriage and transmission are all that matter


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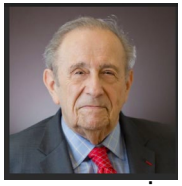
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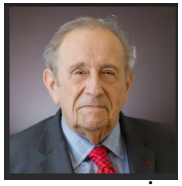
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Carrier, circa 1982

Carriage and transmission are all that matter


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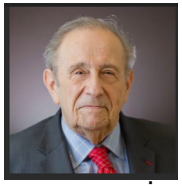
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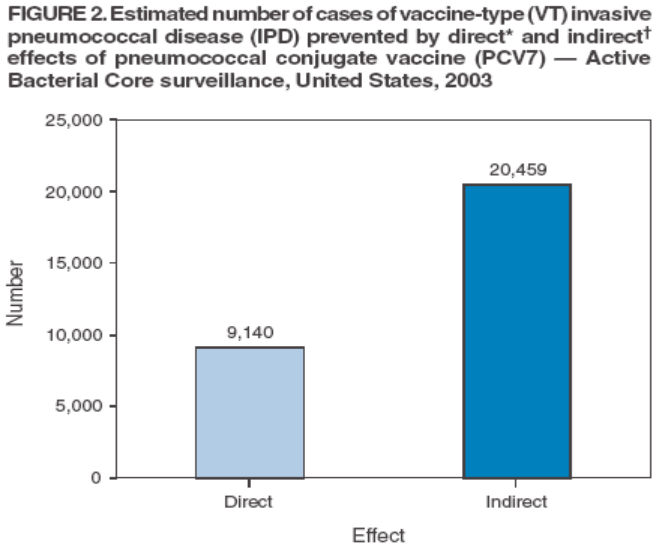
Carrier, circa 1982


Invasive Disease patient (now)

Herd Immunity: 2/3 of the invasive disease reduction in US following introduction of PCV



Reingold et al. *MMWR* 2005

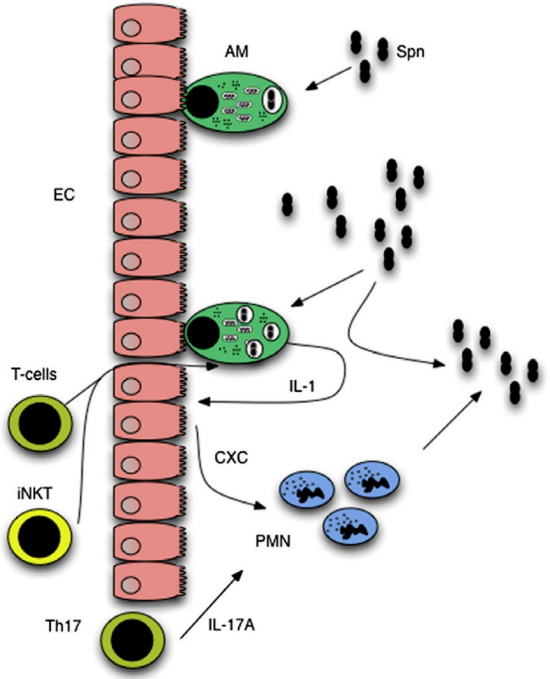
With capsular-based vaccines, reduction in colonization in infants and toddlers, and thus transmission to the elderly, is via serotype-specific antibodies (i.e., capsule-type dependent).

There is no capsule (no polysaccharide) in the WCV. So, what is the mechanism of protection?

What is the mechanism of protection against mouse nasopharyngeal pneumococcal carriage?

We were frustrated early on by our inability to identify antibodies derived from animals immunized with the WCV that could protect against carriage. This led us to question whether antibodies played any role in protection.

CD4+ Th17 responses help control mucosal colonization by encapsulated organisms



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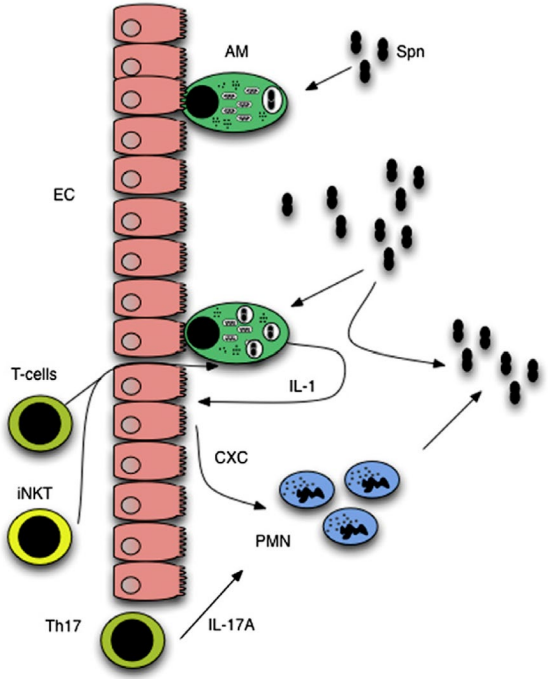
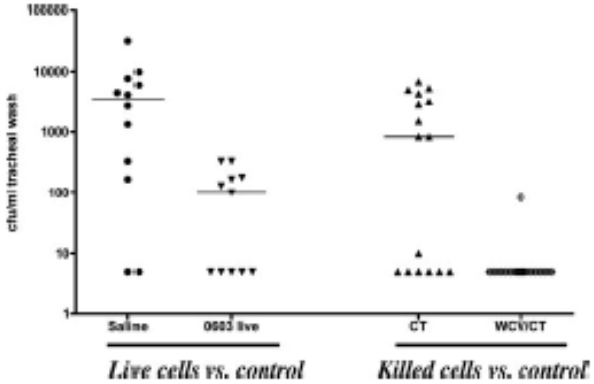


Impaired T_H17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome

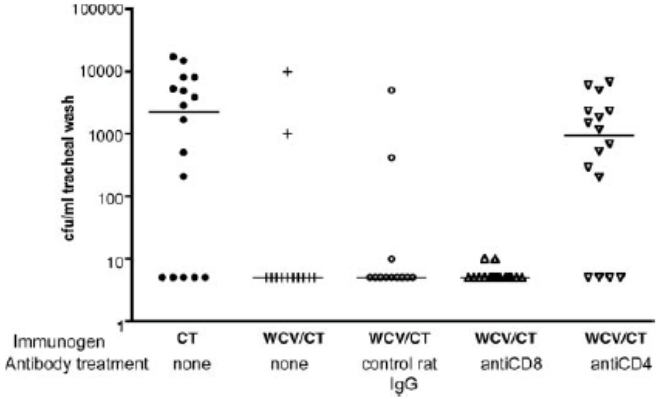
Joshua D. Milner[1]*, Jason M. Brenchley[2]*†, Arian Laurence[3], Alexandra F. Freeman[4], Brenna J. Hill[2], Kevin M. Elias[3,5], Yuka Kanno[3], Christine Spalding[4], Houda Z. Elloumi[4], Michelle L. Paulson[4], Joie Davis[4], Amy Hsu[4], Ava I. Asher[2], John O'Shea[3], Steven M. Holland[4], William E. Paul[1] & Daniel C. Douek[2]

ID phenotype includes recurrent sino-pulmonary infections with *S. pneumoniae* and *Staphylococcus aureus*, recurrent *S. aureus* boils and candidal skin infections

Protection against carriage: CD4+ T cells are required at time of challenge



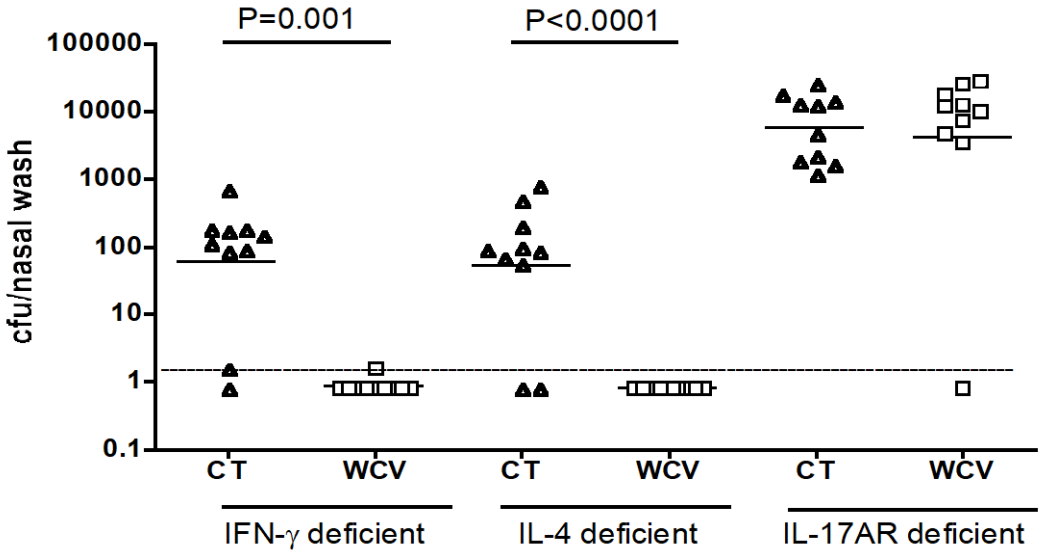
μMT mice, no antibody



T-cell depletion in WCV-immunized mice

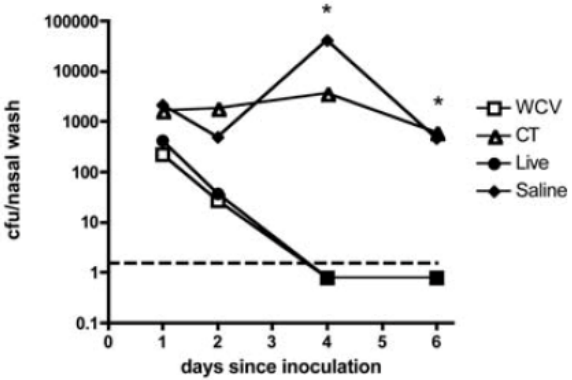
Malley, Anderson, Lipsitch, PNAS 2005

Protection against carriage: Critical role of IL-17A



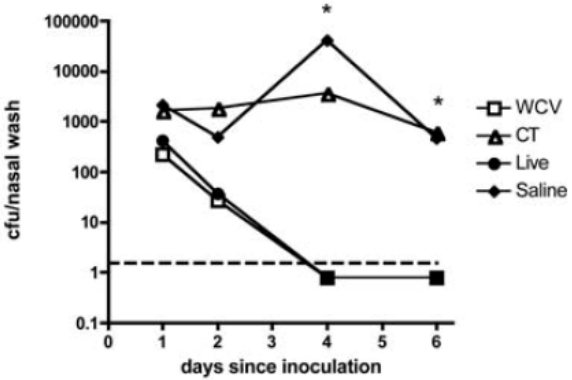
Lu et al., PLoS Path, 2008

WCV-induced protection against carriage represents reduction in duration of carriage



Lu et al, PLoS Path, 2008

WCV-induced protection against carriage represents reduction in duration of carriage, as seen in children



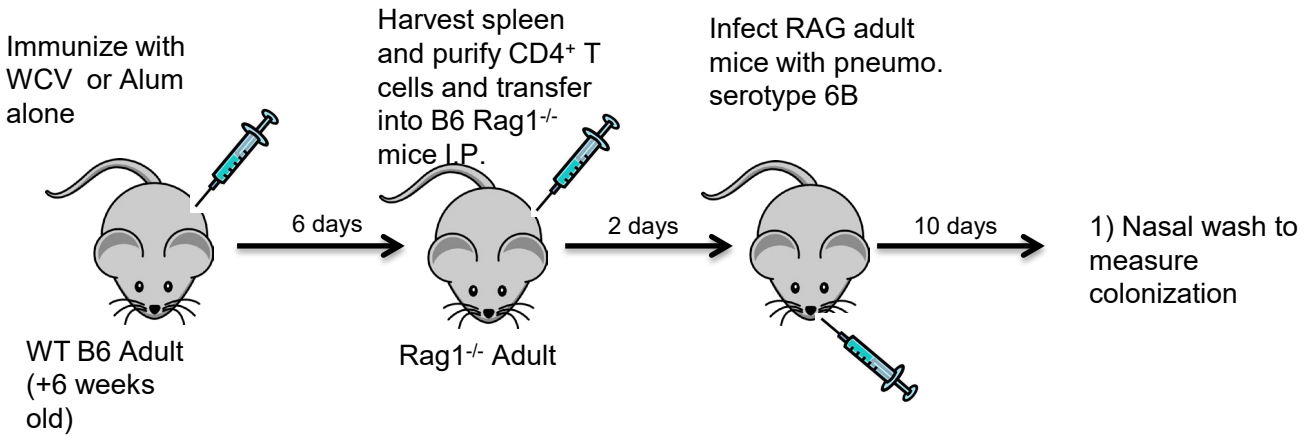
Lu et al, PLoS Path, 2008

TABLE 2. Observed duration of nasopharyngeal carriage of PNSP for all cases

Serogroup	Mean duration (days) (95% CI)						
	<1 yr (n = 79)	1–2 yr (n = 715)	3–4 yr (n = 632)	5–6 yr (n = 339)	7–18 yr (n = 153)	>18 yr (n = 256)	All cases (n = 2,174)
All (n = 2,174)	74 (61–93)	47 (44–51)	34 (31–37)	26 (23–28)	26 (22–30)	25 (22–28)	37 (35–38)
6 (n = 192)	143 (80–298)	62 (51–77)	55 (43–73)	19 (12–35)	28 (17–52)	27 (17–47)	56 (49–65)
9 (n = 1125)	51 (35–80)	37 (33–41)	31 (28–34)	26 (23–30)	20 (17–25)	23 (20–27)	30 (28–32)
14 (n = 147)	49 (28–102)	41 (31–54)	30 (23–40)	23 (14–42)	43 (23–93)	24 (16–38)	34 (29–40)
15 (n = 156)	82 (44–180)	49 (37–67)	35 (27–47)	24 (18–34)	42 (23–94)	35 (21–65)	39 (34–46)
19 (n = 265)	96 (57–184)	54 (45–65)	34 (27–42)	23 (16–32)	36 (20–74)	31 (21–48)	43 (39–49)
23 (n = 183)	74 (45–133)	67 (54–84)	35 (27–47)	30 (20–47)	27 (14–61)	25 (15–44)	50 (43–58)

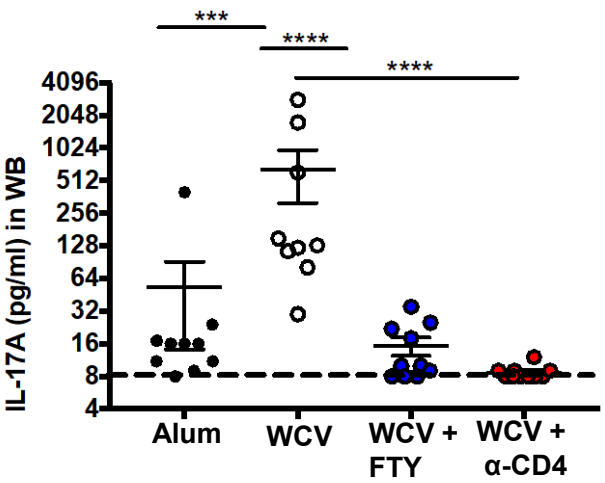
Hogberg L, JCM, 2007

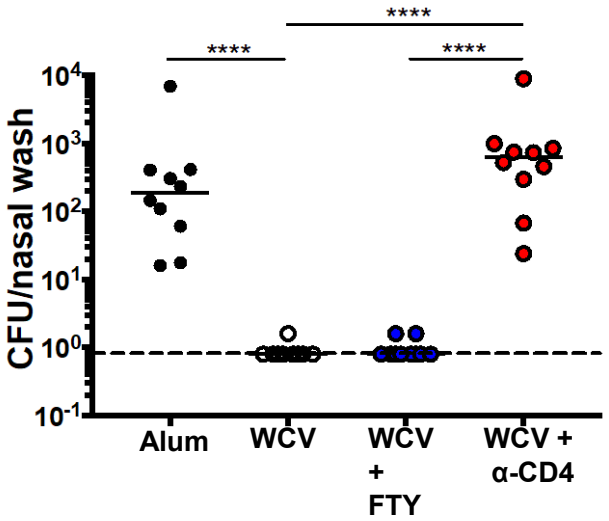
Where are these T cells?
Multiple adoptive transfer experiments: failed



one of many...

Tissue residency: Protection against colonization is abrogated by CD4 depletion but unaffected by FTY720 treatment





O'Hara et al., Mucosal Immunology,. Jan 2020

20 years of work summarized in one slide

- Rationale for WCV very strong, supported by BMGF, PATH, MRF, NIH, even FDA
- Very strong preclinical evidence in support
- Simplicity of manufacture, stability of product > years, very low cost of goods
- Phase 1 trial in adults in US very encouraging
- Phase II trials (2) in Kenya:
  - A bit of a mess
  - Inconclusive
- Most recently, program resurrected in collaboration with Michael Pichichero (Rochester) and Serum Institute of India, funding from NIAID

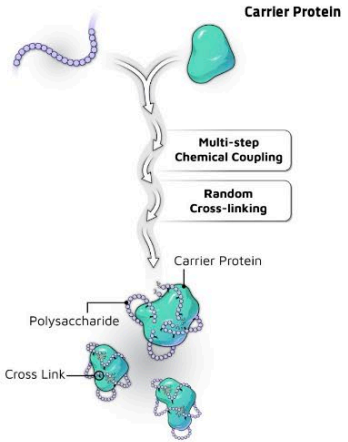
Part 3: Development of novel vaccine platform: MAPS

- We and others observed that the WCV was significantly more immunogenic that soluble proteins, potentially due to its particulate nature

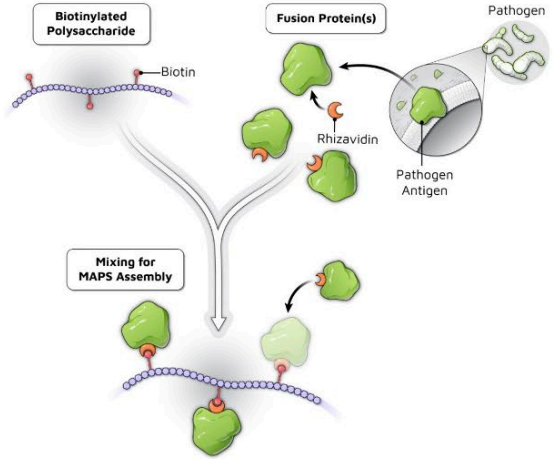
- We reasoned that the use of larger complexes may mimic the increased immunogenicity of the WCV, including both B- and T-cell responses, without the complexity of a whole cell antigen

The Multiple Antigen Presenting System (MAPS)

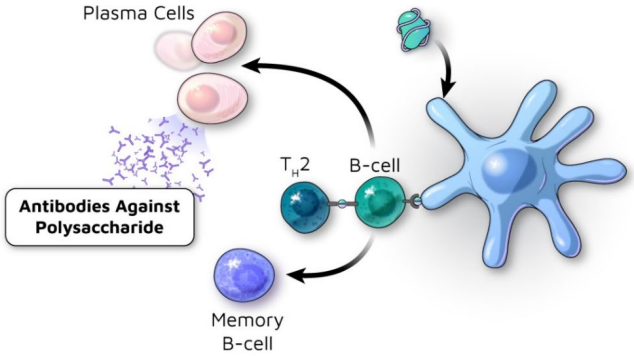
Conventional Conjugate Vaccine
"Spaghetti and Meatballs"



MAPS™ Vaccine
"Beads on a String"

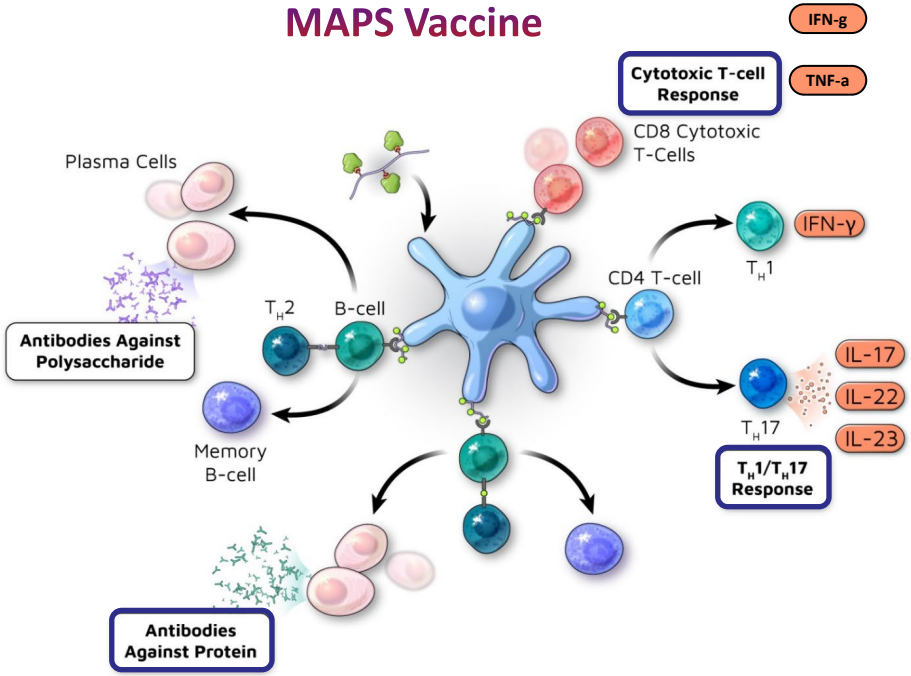


Conjugate Vaccine



Conjugate vaccine provides only antibody-mediated immunity

MAPS Vaccine



MAPS vaccine candidates are designed to provide both antibody- and cell-mediated immunity

Applications of MAPS investigated to date

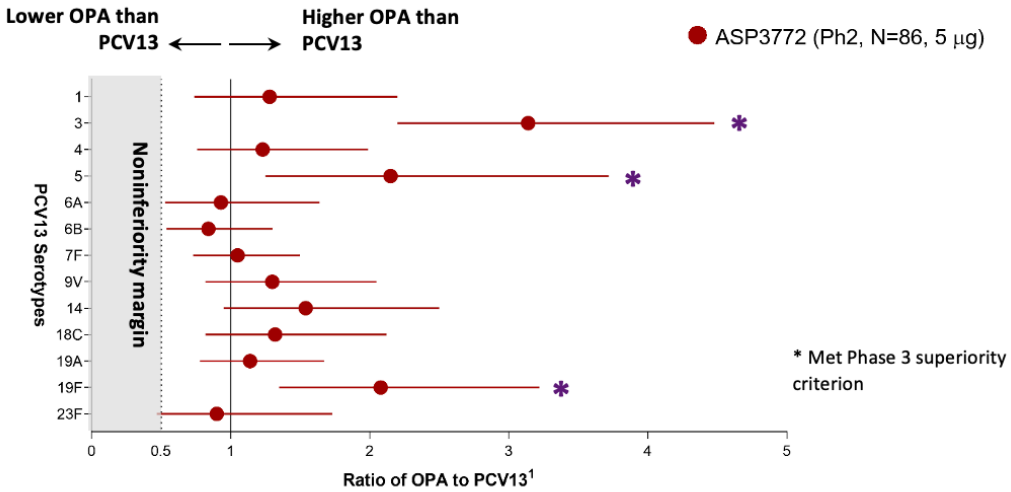
1. *S. pneumoniae* (Phase 2 clinical trial completed in older adults, pending in infants)
2. *Mycobacterium tuberculosis*
3. Salmonella typhi and paratyphi
4. Shigella (4)

} 8 valent

5. *Staphylococcus aureus*
6. Group A Streptococcus
7. Group B Streptococcus (7-valent)
8. Nosocomial GNR (PSA (8), Klebsiella (4) – 8 valent)

24-valent Pneumococcal MAPS: Phase 2 older adult trial

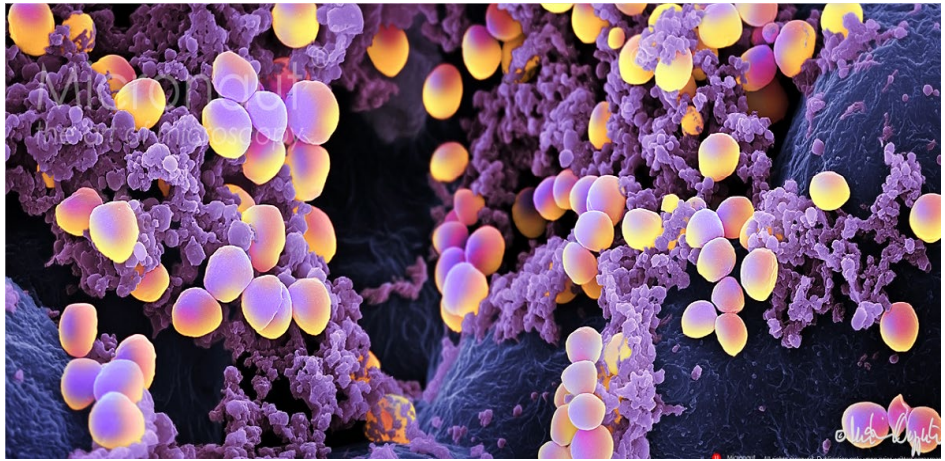
ASP3772 OPA Ratio to Prevnar 13 (PCV13) in Older Adults (aged 65 – 85)



Phase 2 infants in process
Phase 3 older adults in planning

MAPS30+ under development

What about *S. aureus?*



Staphylococcus aureus is an important human pathogen

- Colonizes 20-50% of the human population at any given time
- Causes a variety of diseases, including soft tissue infections, sepsis, pneumonia, endocarditis…
- Dramatic increase of cases caused by MRSA infection in the past decade (recent decline)

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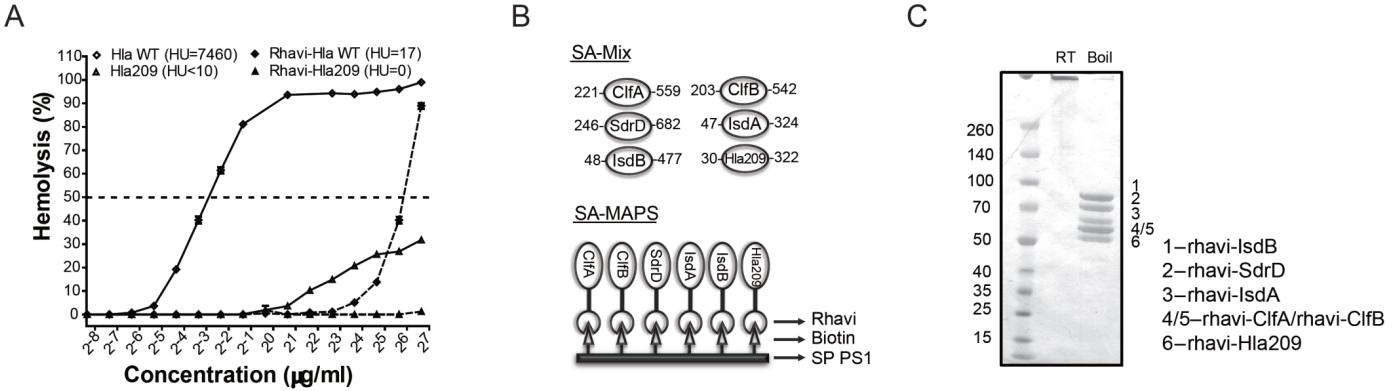
The development of vaccines against S. aureus has not been successful to date

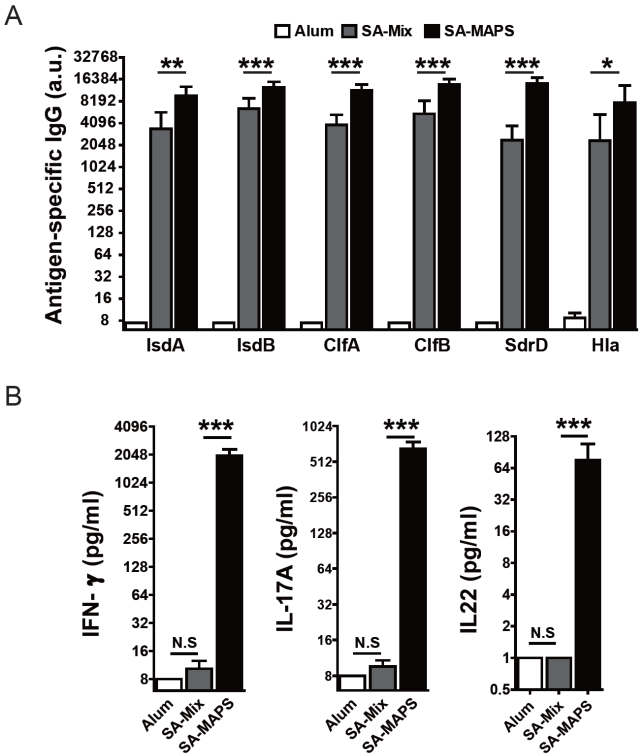
- Pathogenesis is not well understood
- Mechanism of protection is not well understood
- A vaccine trial (Merck) was associated with increased mortality in recipients
  - Association between mortality and low Th17 responses
- More recently, Pfizer's vaccine trial (2 PS, 2 proteins) and GSK trials (2 PS, 2 proteins) were discontinued due to futility

Preparation of vaccines



Zhang et al., mBio 2018

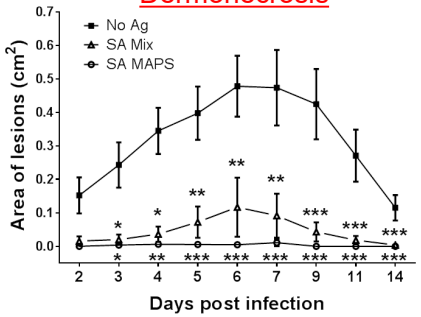
Immunization of mice with SA MAPS elicits both antigen-specific antibodies and T-cell responses

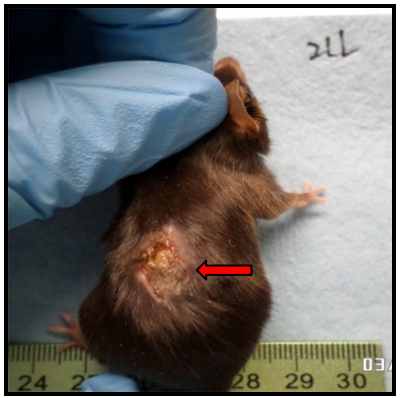


Zhang et al., mBio 2018

Staph MAPS: Protection in animal models

Dermonecrosis





Staph MAPS: Protection in animal models

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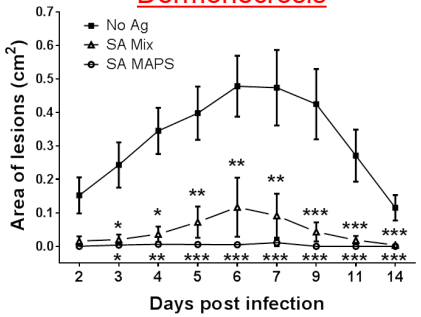
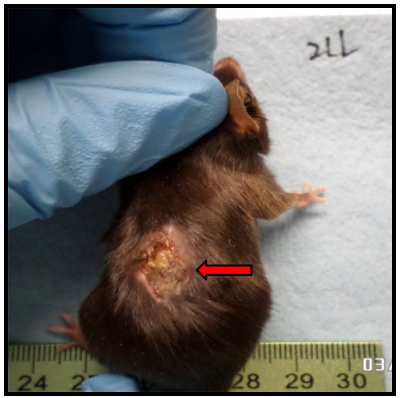
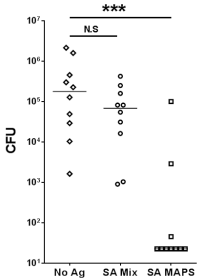


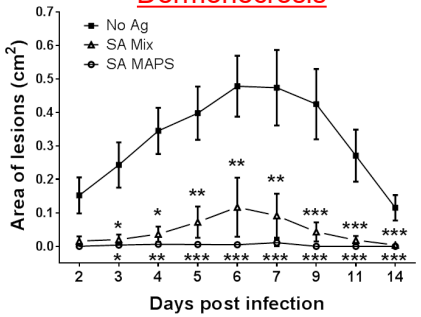


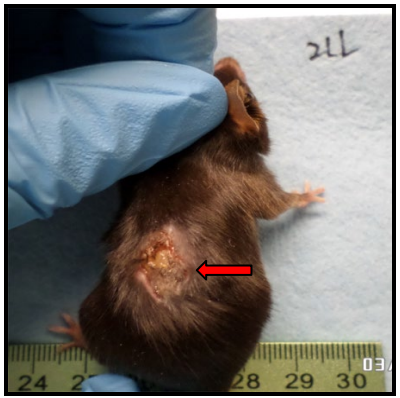
Skin abscess



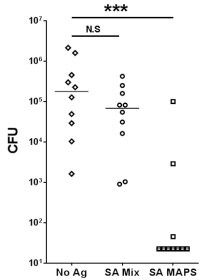
Staph MAPS: Protection in animal models

Dermonecrosis

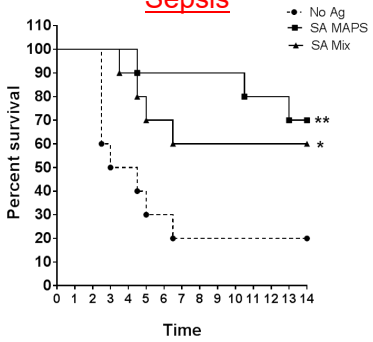




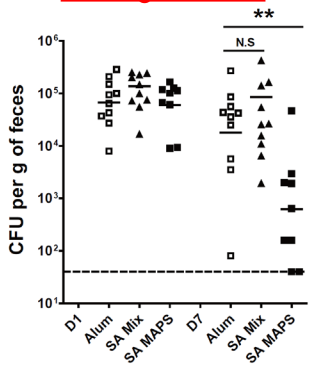
Skin abscess



Sepsis



Carriage in stool



Role of B- and T-cell immunity in protection?

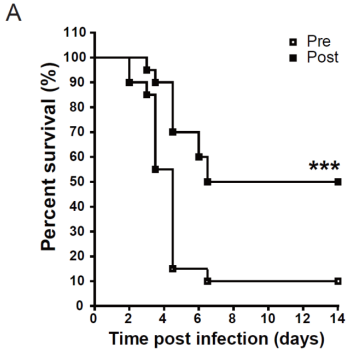
To understand which component of the acquired immune response was contributing to protection, two complementary strategies were used:

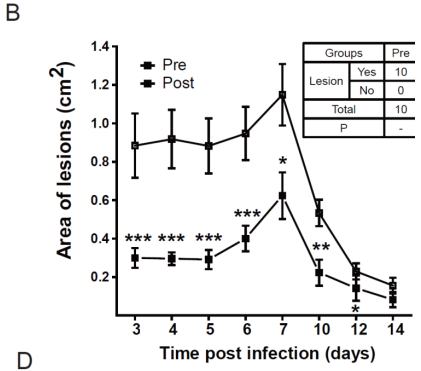
1. Passive transfer of rabbit-generated high-titered antibodies to mice

2. Immunization of $\mu MT^{-/-}$ (congenitally antibody-deficient) mice with MAPS followed by challenge

Protection by passive transfer of antibodies

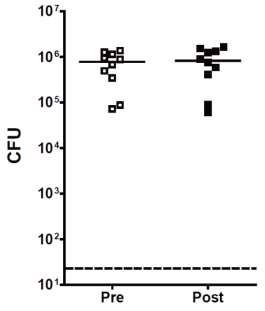
Sepsis

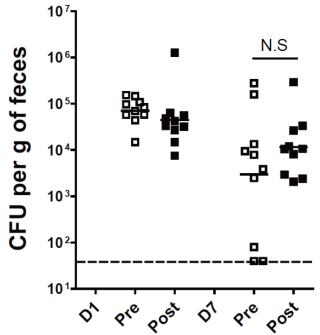




Dermonecrosis

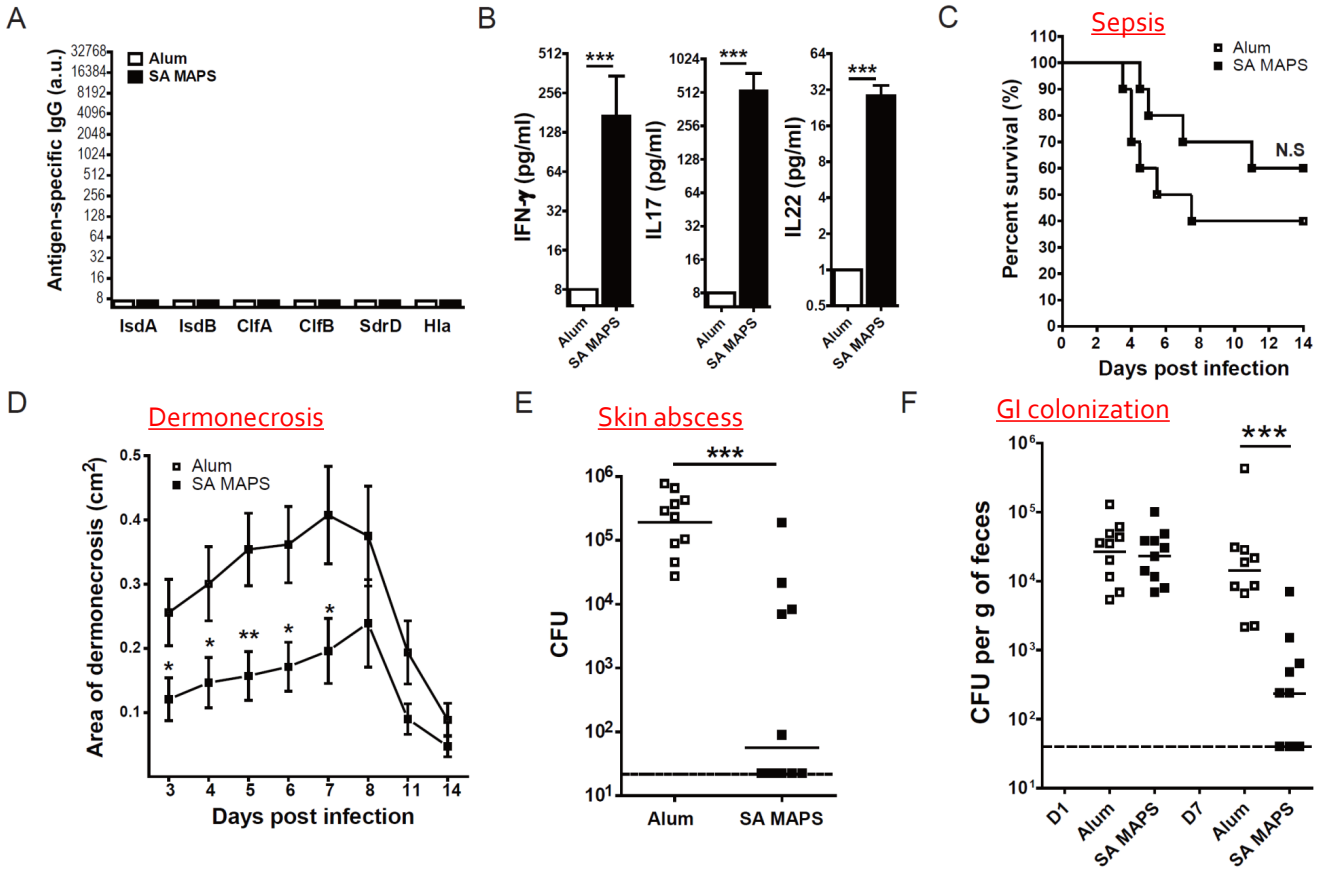
Abscess





GI colonization

Immunization of μMT$^{-/-}$ mice with SA MAPS and challenge in animal models



From Technology to Company

Article Published

TIDO/DOM Support

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Moved to Kendall Square lab

Clinical Trials
-Adult and Toddler Phase I & II Completed
-Infant Phase II Ongoing

CARB-X

CEPI

GSK Affinivax
Official Merger

2013 2014 2015 2017 2019 2020 2021 2022

Epilogue

GSK agreement finalized August 2022

GSK-Affinivax created

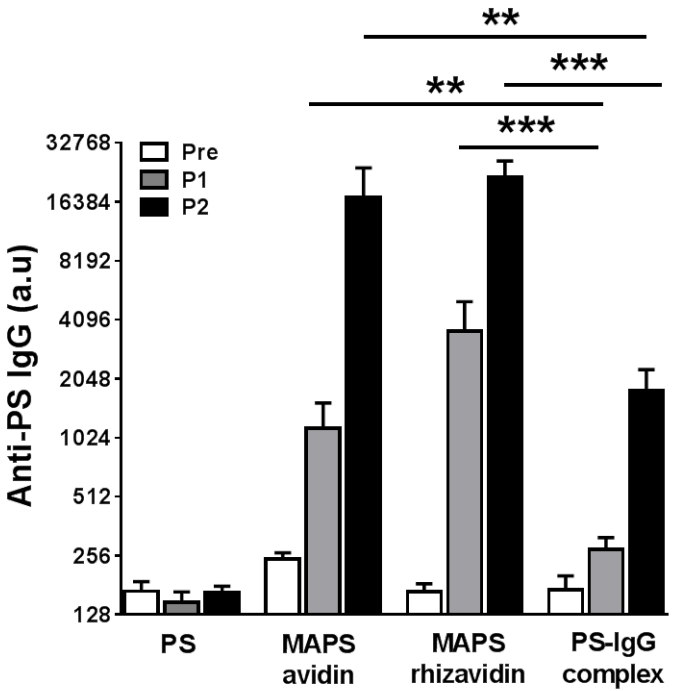
GSK Binney Street

April 1, 2023…

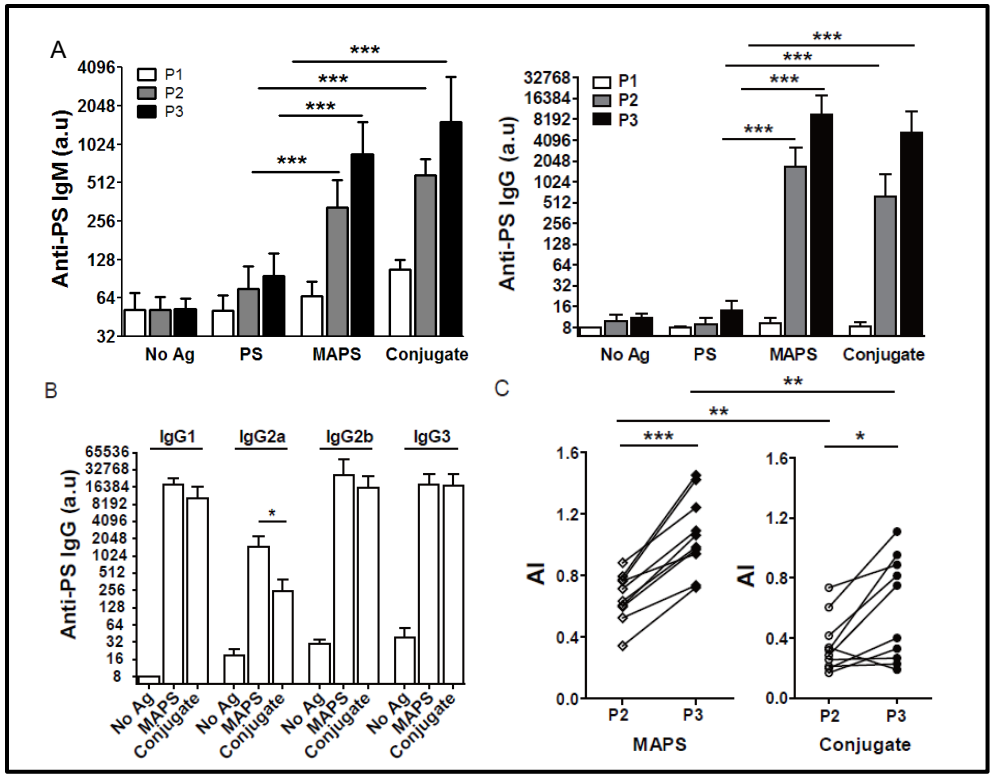
Questions/Comments?

Questions/Comments?

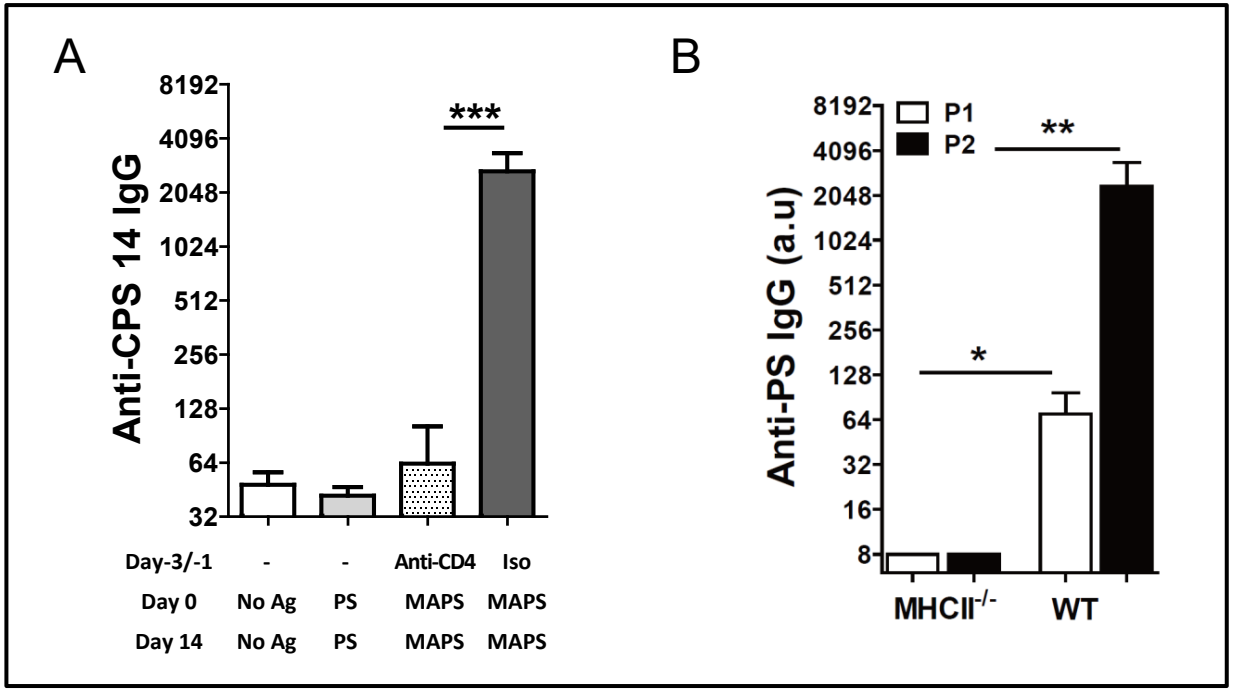
Strength of binding between PS and protein impacts the magnitude of MAPS-induced anti-PS responses



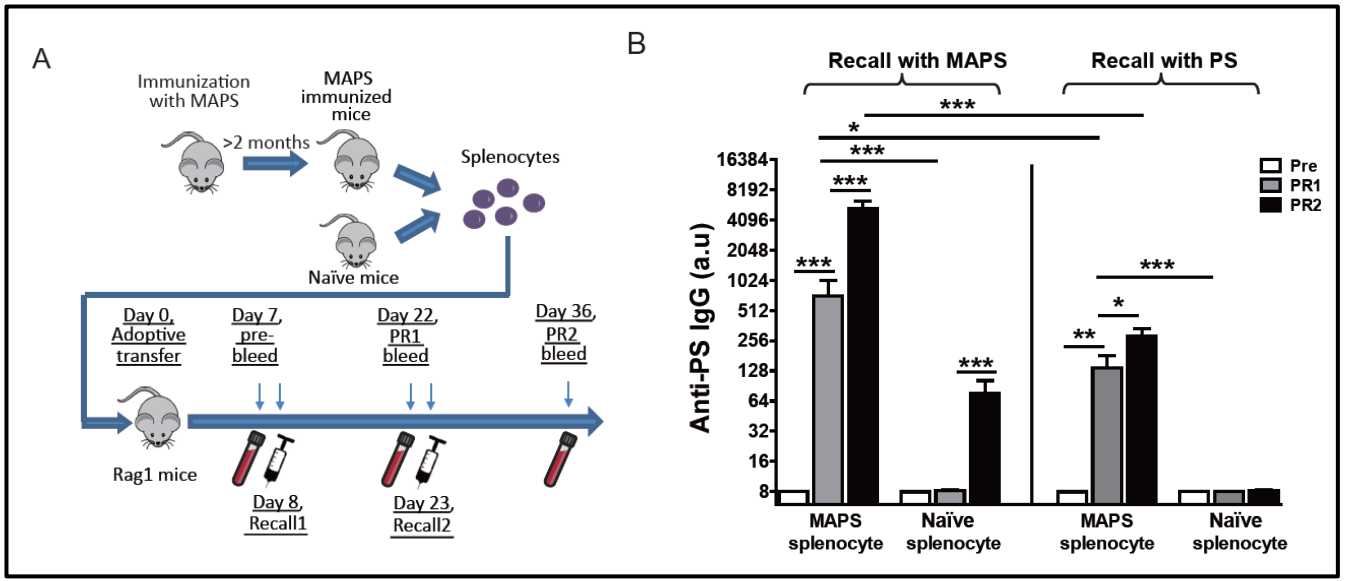
MAPS elicits robust anti-PS IgG Ab with affinity maturation



MAPS-induced PS-specific responses are CD4+ T-cell- and MHCII-dependent



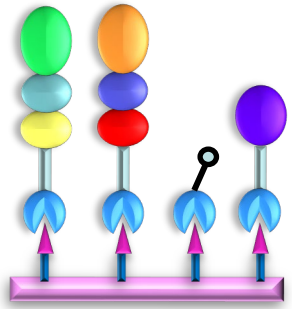
MAPS-induced PS-specific immune memory can be adoptively transferred



TB MAPS

- Generate a multicomponent TB MAPS vaccine that induces multipronged antigen-specific humoral and cellular responses

- Biotinylated pneumococcal type1 CPS
- Rhavi-ESAT6-CFP10-MPT64
- Rhavi-TB9.8-TB10.4-MPT83
- Lipo-rhavi (a TLR2 agonist)
- Rhavi-MPT51

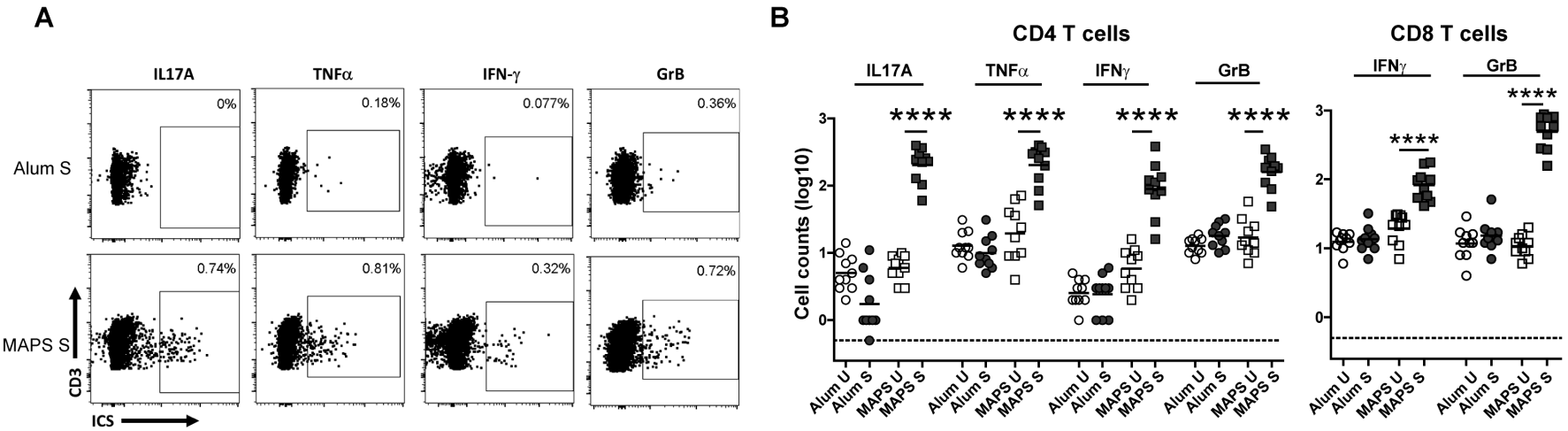


TB MAPS complex

- Antibodies
- Systemic cellular responses
  - Th1, Th17, CTL (CD4 and CD8)
- Tissue resident cellular responses (lungs and nasal tissues)
  - Th1, Th17, CTL (CD4 and CD8)
  - γδT cells and NKT cells

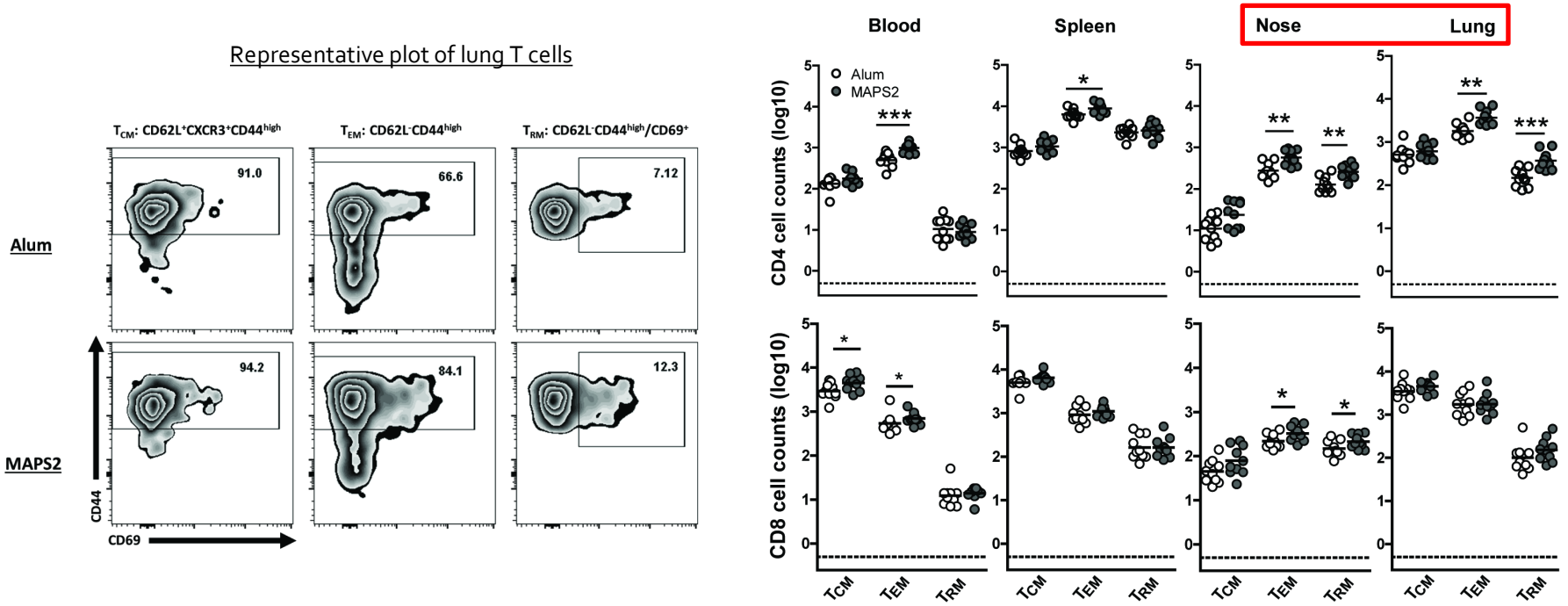
O'Hara...Thompson, Lu, Rubin, Malley, Zhang et. al., mBio 2023

TB MAPS induces systemic Th1, Th17, and cytotoxic CD4 and CD8 memory T cells in mice



- Isolated cells were incubated without (un) or with (S) a mixture of recombinant Mtb protein antigens overnight at 37 C
- Panel A: representative plots of cytokine-producing splenic CD4 T cells after stimulation with Mtb protein antigens
- Panel B: absolute counts of cytokine-producing CD4 or CD8 T-cells in 1/80 of total isolated splenocytes

TB MAPS induces tissue-resident $CD4^+$ and $CD8^+$ T cells in lung and nasal tissues of mice

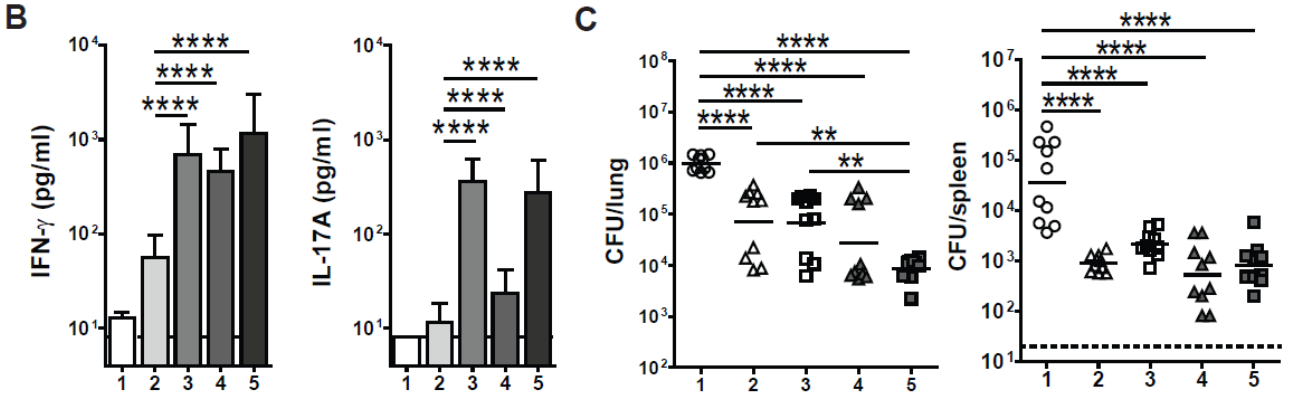


- C57Bl6 mice received three subcutaneous immunization with a TB MAPS vaccine.
- Flow cytometry analysis was done 6 months after the third immunization.

Combined use of TB MAPS and BCG provides significantly enhanced protection in mice compared to either vaccine used alone

A

Immunizations	Group 1	Group 2	Group 3	Group 4	Group 5
1st	Saline	BCG	MAPS2	BCG	BCG+MAPS2
2nd	Alum	Alum	MAPS2	MAPS2	MAPS2
3rd	Alum	Alum	MAPS2	MAPS2	MAPS2



Note: BCG+MAPS= concurrent immunization at different sites

- Panel B: whole blood samples were stimulated with Mtb lysates.

Nonhuman primate study

Groups

Groups	Treatment	Animal #	PET/CT(Total)
G1	None	n=7	6
G2	BCG	n=7	6
G3	BCG +TB MAPS (once) followed by 2 TB MAPS	n=8	6

Schedule

- NHP immunized every 4 weeks as needed
- 4 weeks after last immunization, challenged with 10-100 Mtb (Erdman) via bronchoscope
- Blood, BAL obtained at several timepoints during infection, for assays including T cell studies

Results of NHP study