

Immunity to *Bordetella pertussis*

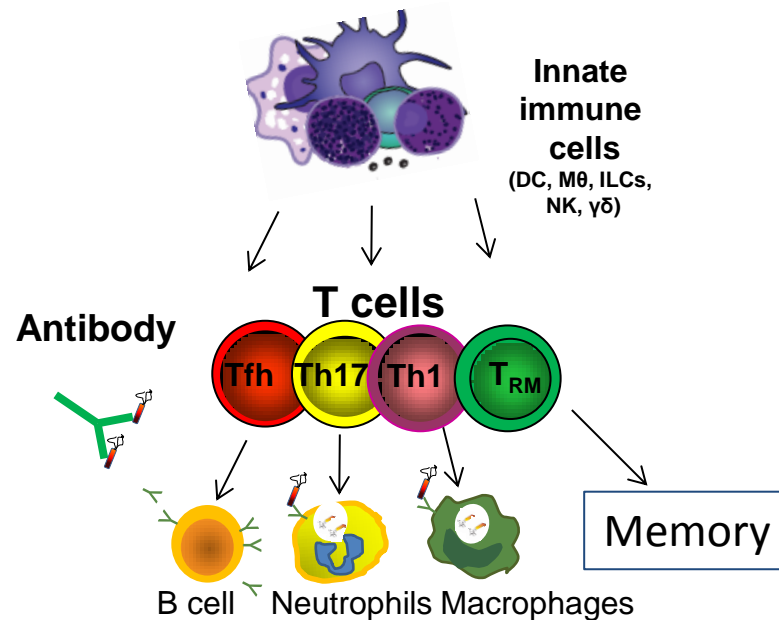
Kingston Mills

*Trinity Biomedical Sciences Institute
Trinity College Dublin, Ireland*



Correlates / mechanisms of immunity

Vaccine/ Infection	Efficacy in Children	Efficacy in mice	Protect Against	IgG (ELISA)	Th2 cells	Th17 cells	Th1 cells	Antibody Subclass
wP or Infection	90-95%	High	Disease, Infection & Transmission	++	-	++	++++	IgG2a/c (mouse) Opsonizing
aP	70-85% (40% 5yrs)	Medium	Disease	++++	++++	+	-	IgG1 (mouse) Toxin neutralizing

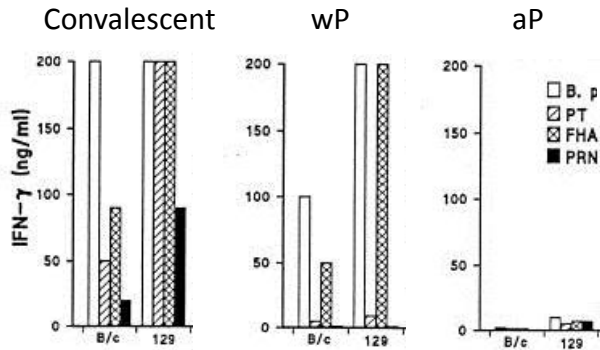


T cell responses

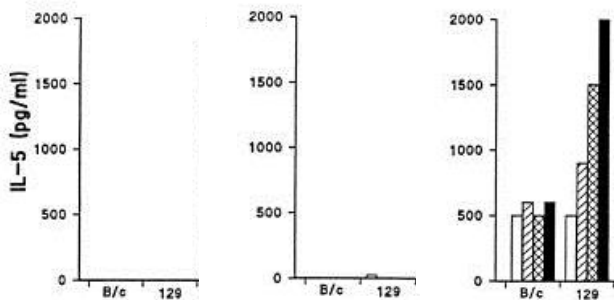
Consistency across species

Mouse

Th1



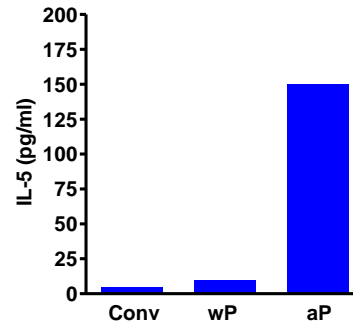
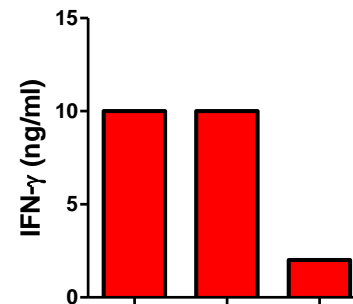
Th2



Mouse strain

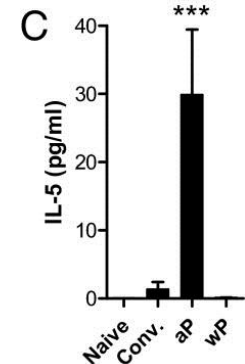
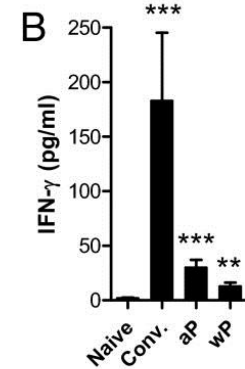
Redhead and Mills, I&I 1993

Human



Mills et al
Buisman et al
Mascart et al
Mertosola et al
Ausiellio et al
De Magistis, Pizza and Rappuoli

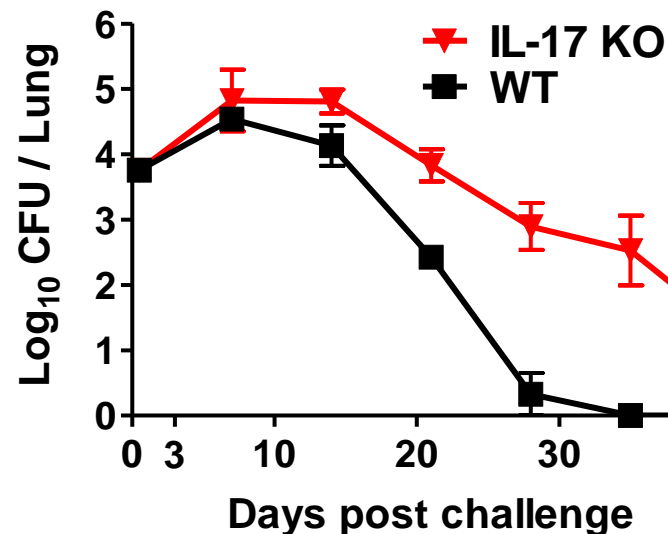
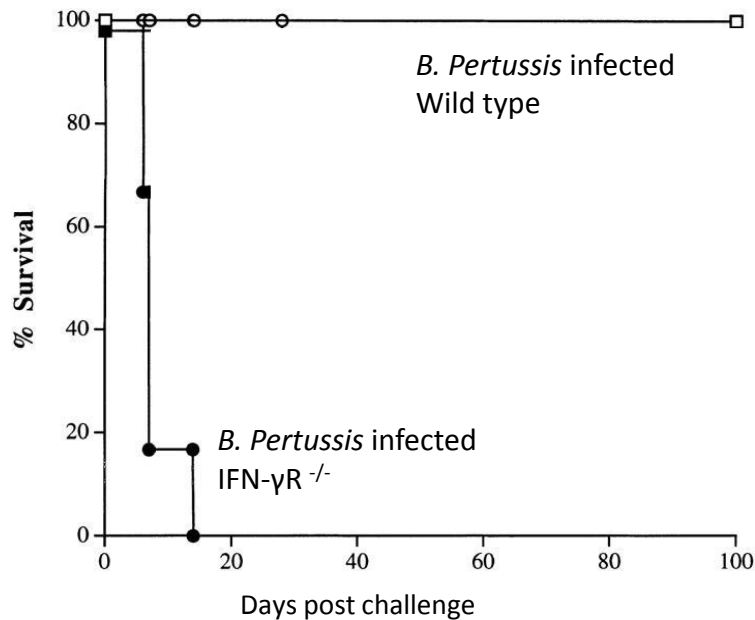
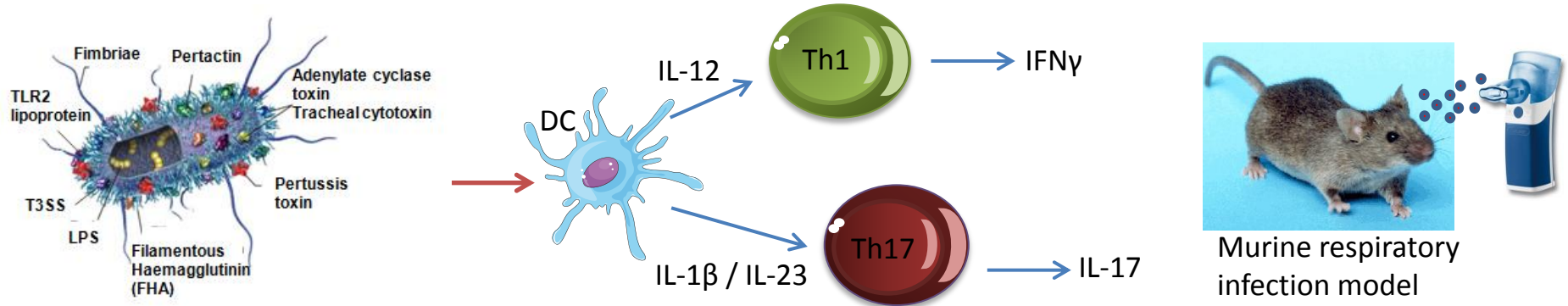
Baboon



Warfel & Merkl PNAS 2014

Infection and wP, and more variably aP, also induce Th17 cells

Natural immunity induced by infection with *B. pertussis* is mediated by Th1 and Th17 cells



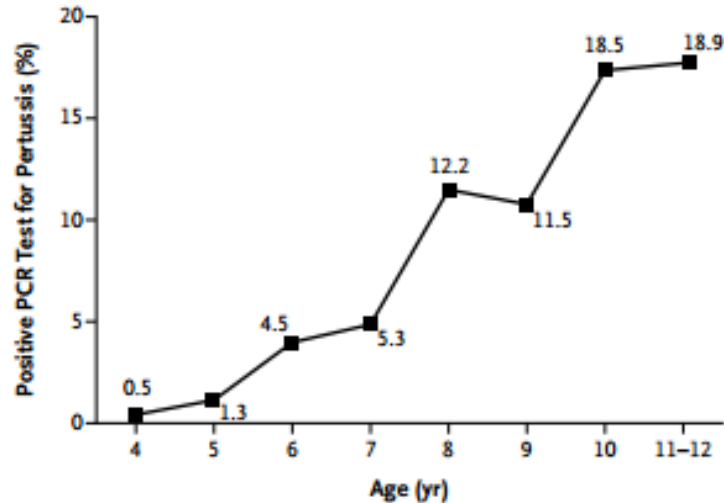


ORIGINAL ARTICLE

Waning Protection after Fifth Dose of Acellular Pertussis Vaccine in Children

Nicola P. Klein, M.D., Ph.D., Joan Bartlett, M.P.H., M.P.P., Ali Rowhani-Rahbar, M.D., M.P.H., Ph.D., Bruce Fireman, M.A., and Roger Baxter, M.D.

N Engl J Med 2012; 367:1012-1019 | September 13, 2012 | DOI: 10.1056/NEJMoa1200850

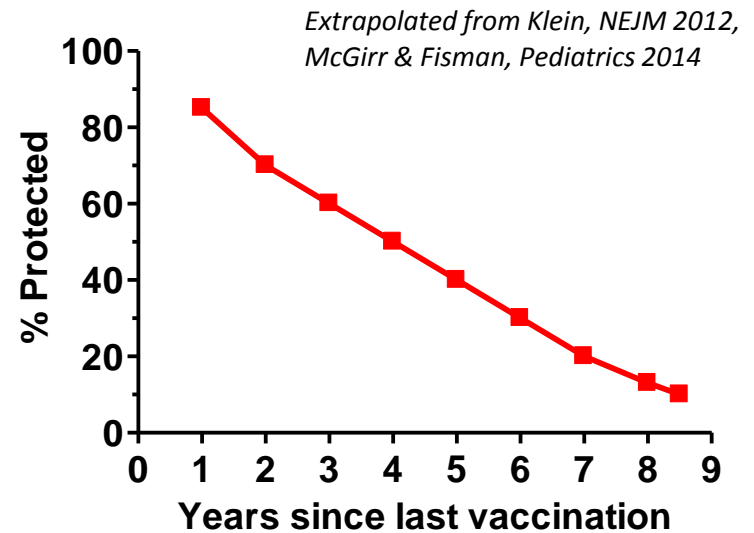


No. of PCR Tests for Pertussis

Positive	2	9	25	25	47	49	77	43
Total	405	700	560	472	386	427	417	228

‘after the fifth dose of DTaP, the odds of acquiring pertussis increased by an average of 42% per year’

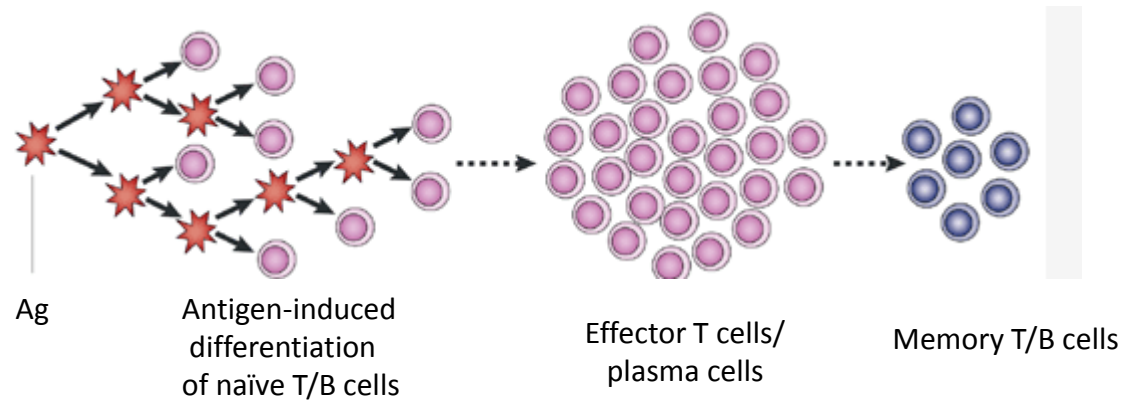
‘Our findings highlight the need to develop new pertussis-containing vaccines that will provide long-lasting immunity.’



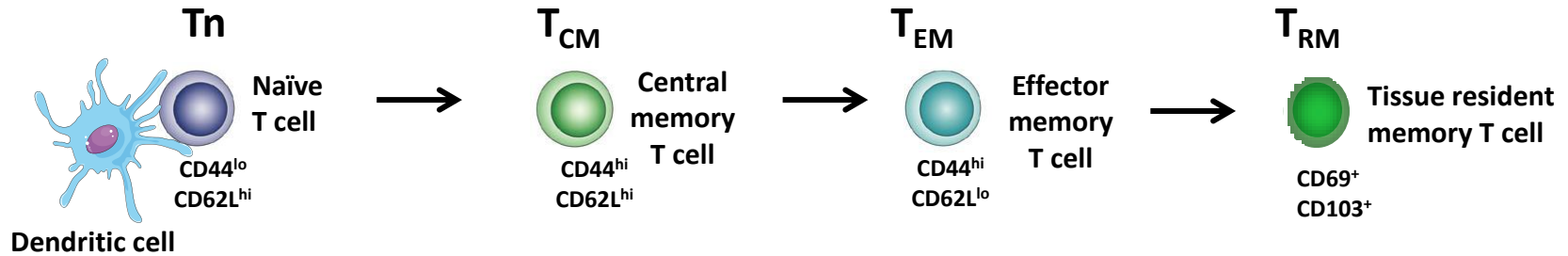
Suggests aP are poor at inducing Immunological memory

Figure 2. Percentage of PCR Tests That Were Positive for Pertussis from January 2006 through June 2011, According to Age and Time since Vaccination.

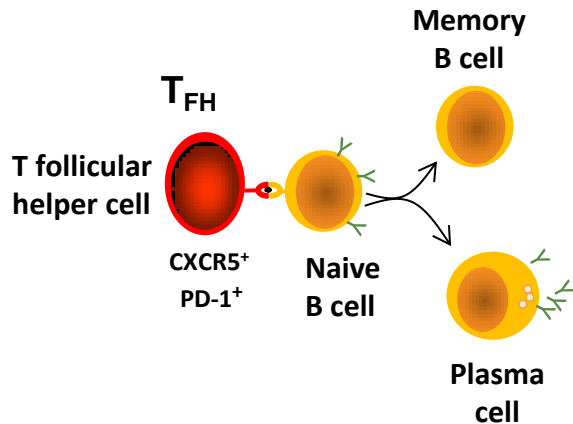
Mechanisms of Immunological memory



T cells

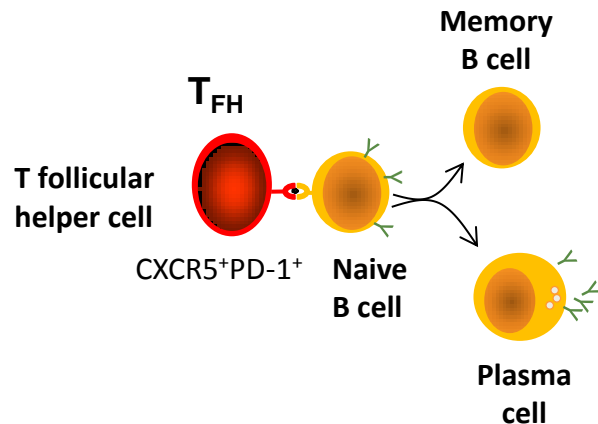


B cells

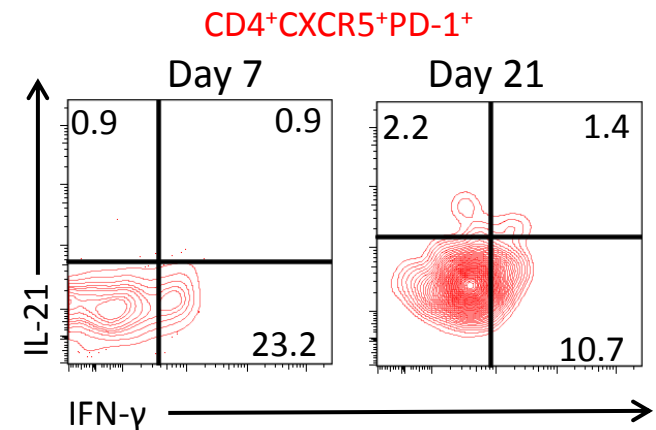
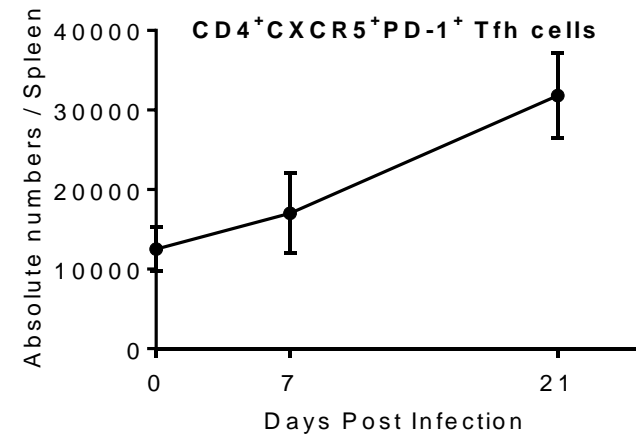


T follicular helper (Tfh) cells

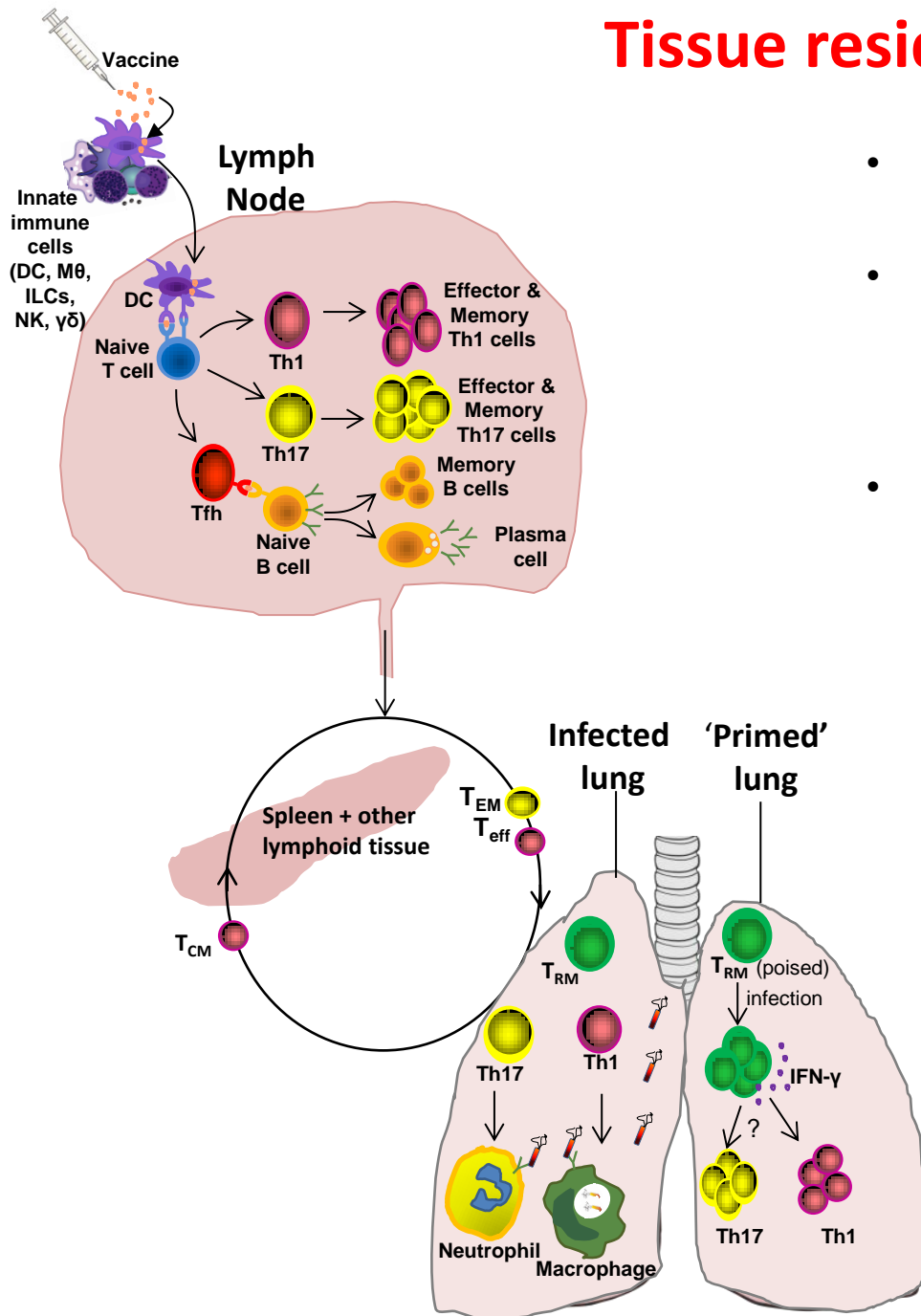
- Facilitate germinal center formation, B cell activation, antibody production & generation of long-term **memory B cell** responses.
- Secrete IL-21 and IL-4/IFN γ
- Induced during infection
- Induction influenced by adjuvants



T_{FH} cells in spleen
of *B. pertussis* infected mice



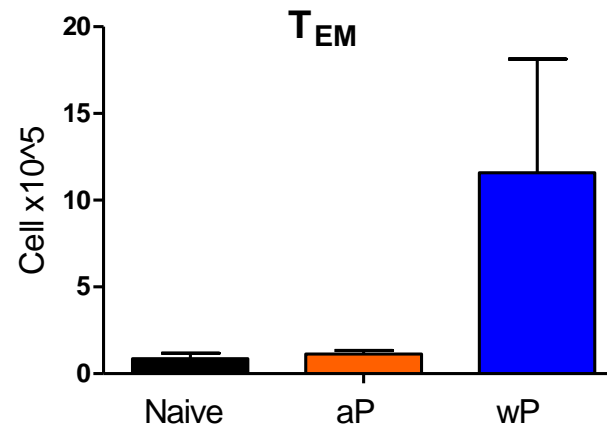
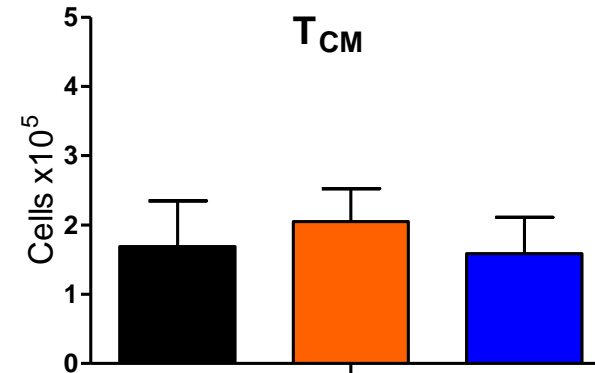
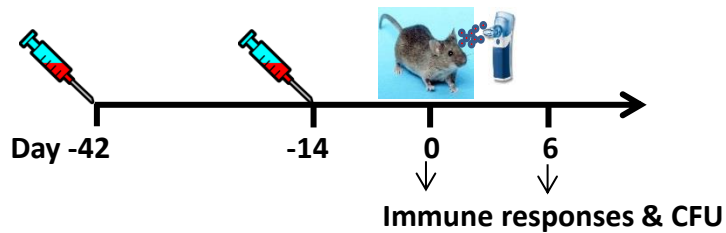
Tissue resident memory (T_{RM}) cells

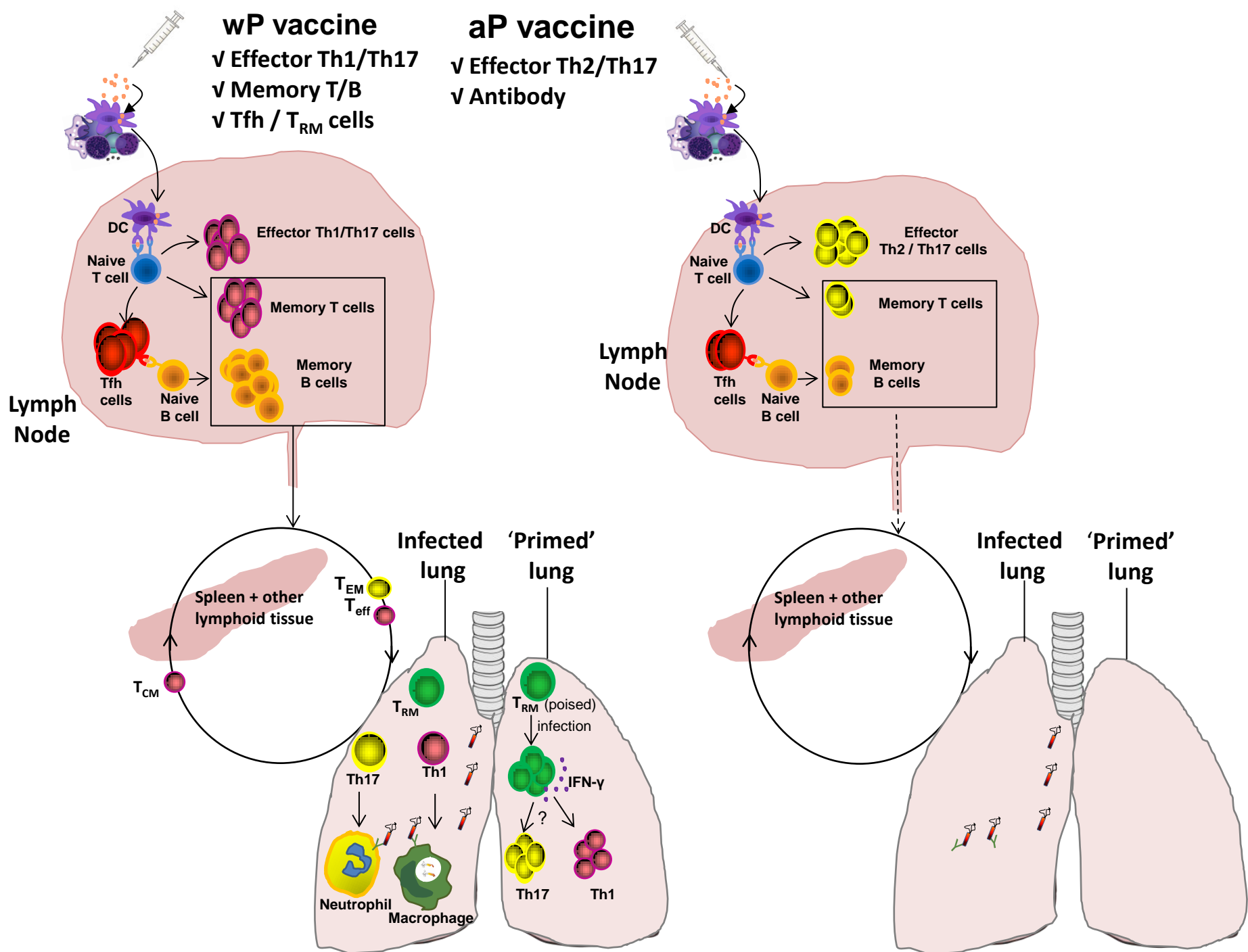


- Reside locally in **mucosal tissues** to provide the front line of defense against pathogens
- Derived from precursors that entered tissues during the effector phase of immune responses & remained poised within this compartment (i.e. **maintain memory**)
- A potential role in vaccine-induced immunity against microbes that infect mucosal tissues

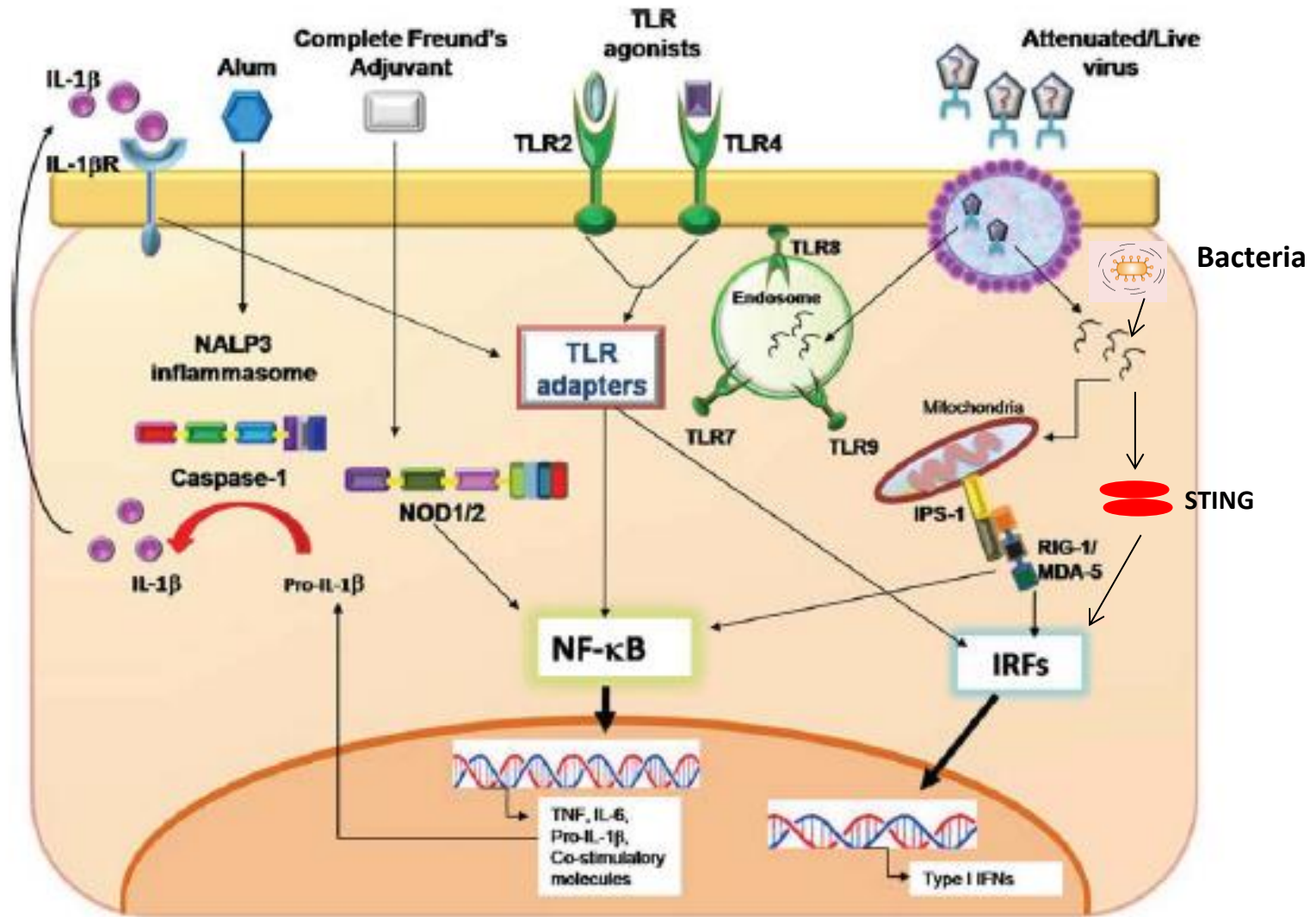
Immunization with wP induces superior effector memory T (T_{EM}) cells than an aP vaccine

Spleen day of challenge



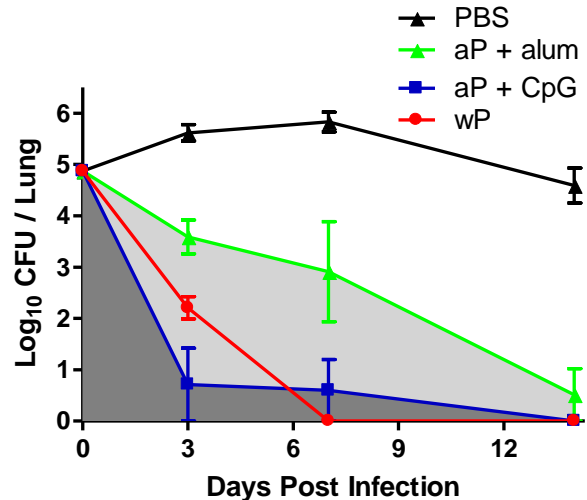
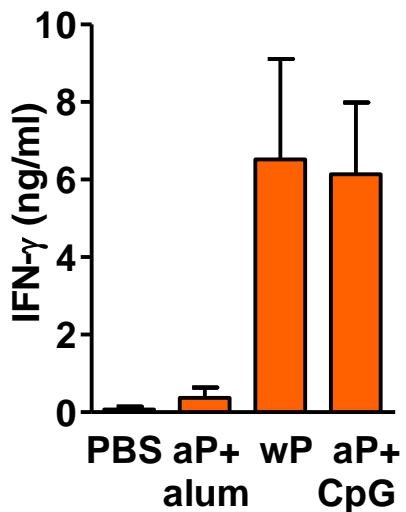
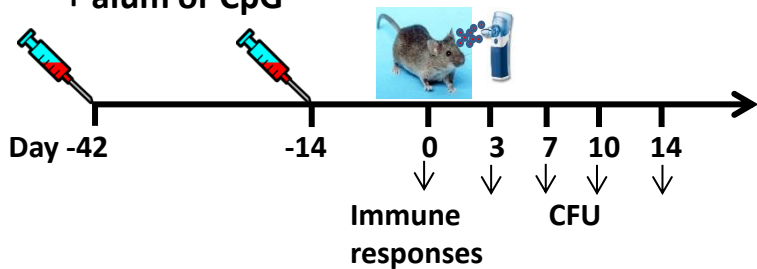


Adjuvants: activate innate immunity

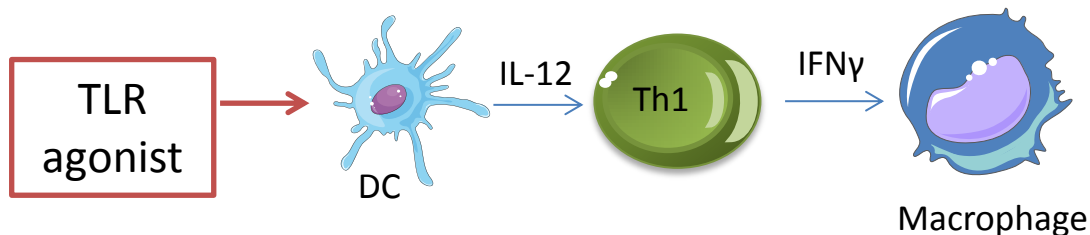
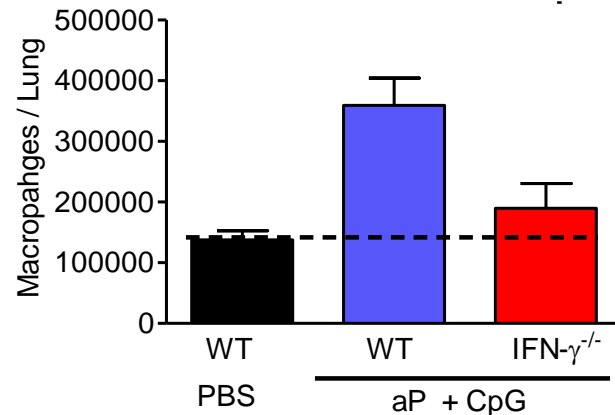
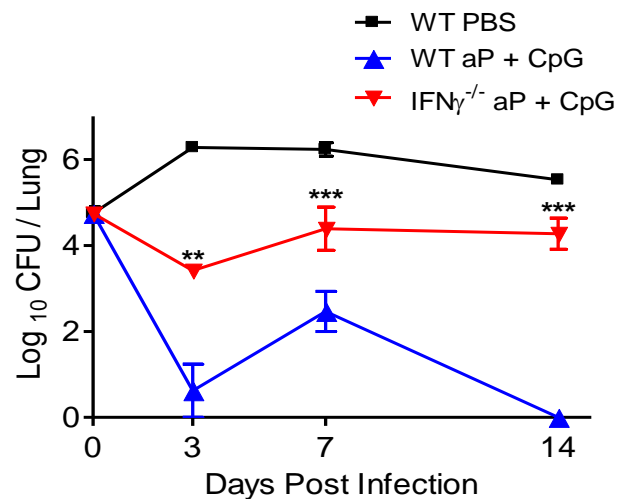


Immunization with an experimental aP + TLR9 agonist, CpG, is as effective as wP against *B. pertussis* challenge

aP 'vaccine'
rPT (1 μ g) + FHA (2.5 μ g)
+ alum or CpG



protection mediated by Th1 cells



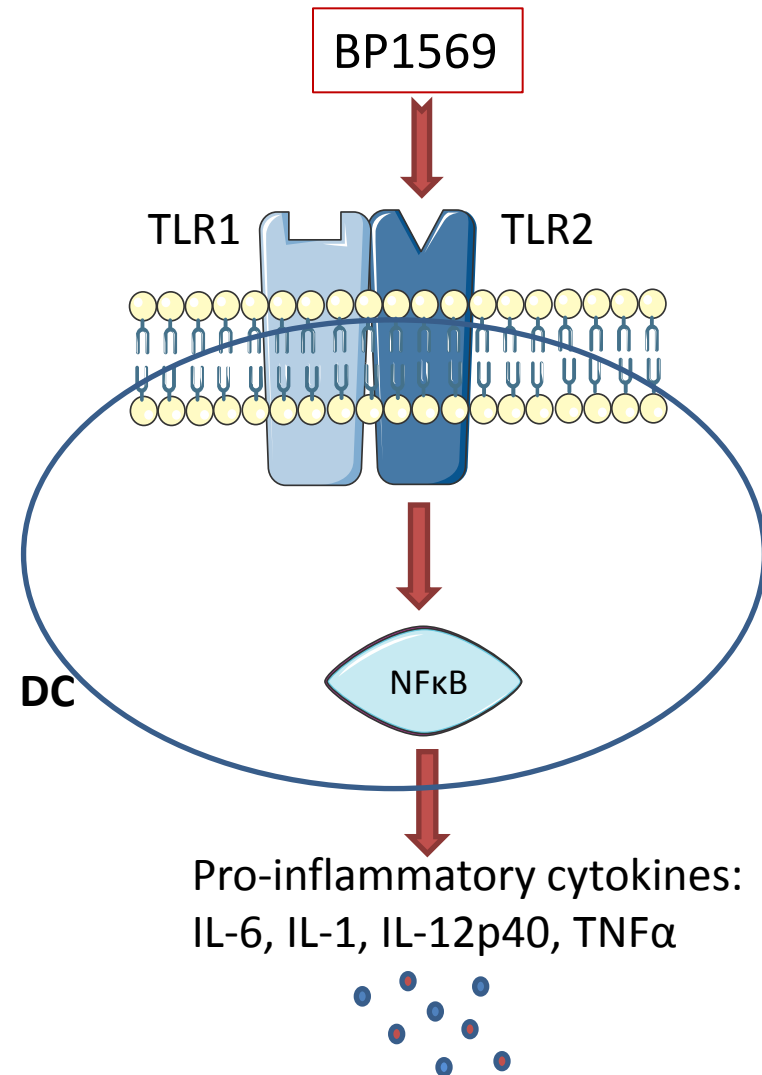
Novel TLR2 agonist and antigen from *B. pertussis*

BP1569

- 40 kDa lipoprotein from *B. pertussis*.
- A TLR2 agonist.
- Immunostimulatory *in vitro* and *in vivo*
- **Antigenic component** of *B. pertussis* – immune responses to Bp1569 in infected mice.

LP1569

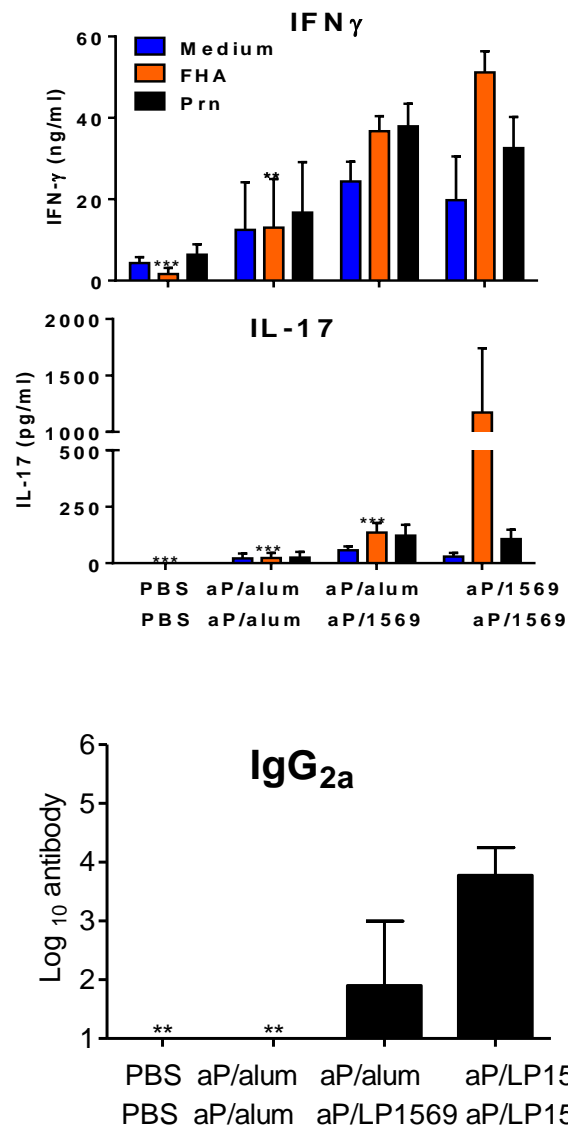
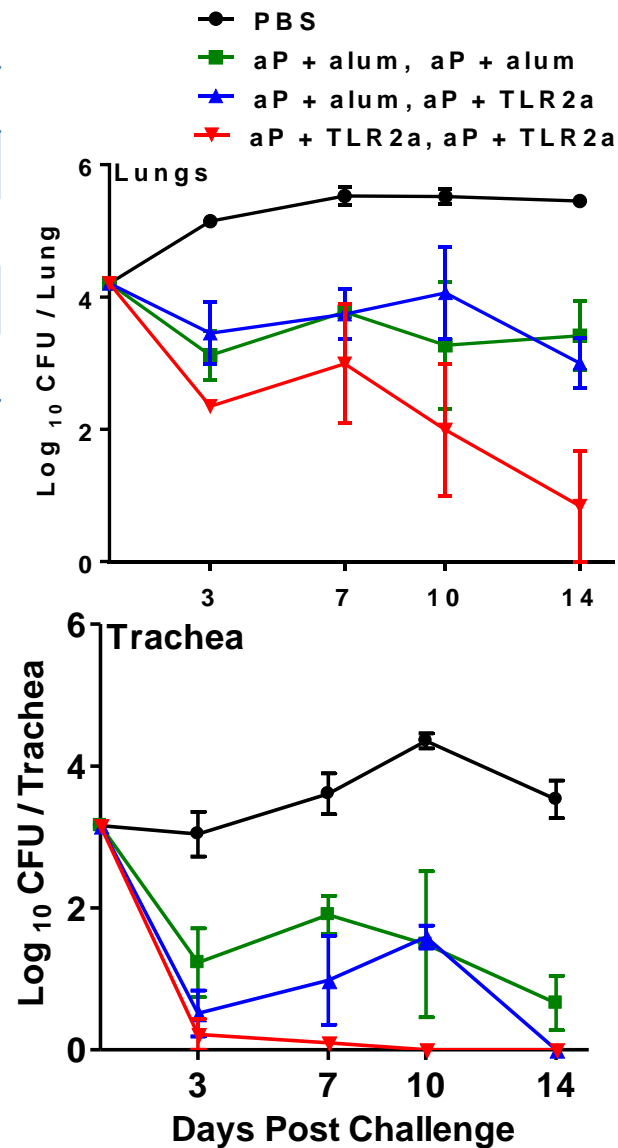
- Synthetic lipopeptide version of BP1569.
- Activates dendritic cells that promote Th1 and Th17 responses.
- Adjuvant activity *in vivo*



Prime / boost with an experimental acellular pertussis vaccine + TLR2 agonist induces sterilizing immunity in trachea

Prime	Boost
PBS	PBS
aP + Alum	aP + Alum
aP + Alum	aP + LP1569
aP+ LP1569	aP + LP1569

Ag/adj	Dose
FHA, rPT:	0.2 µg/mouse
LP1569:	50 µg/mouse
Alum:	100 µg/mouse



A rationally designed pertussis vaccine based on established correlates of Immunity?

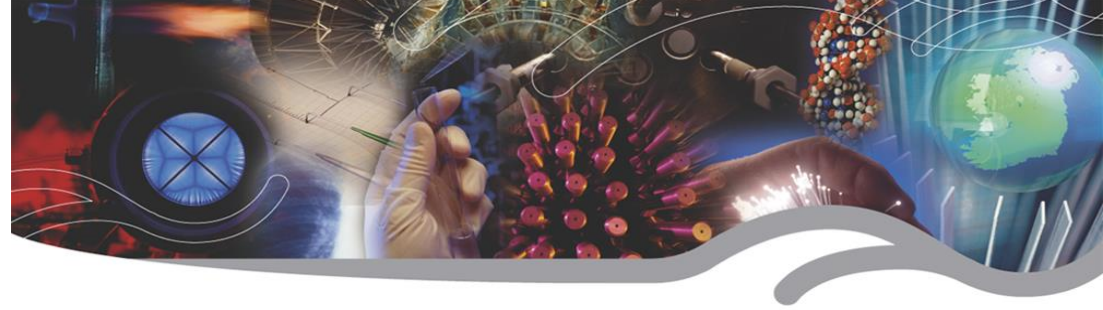
Vaccine/ Infection	Efficacy in Children	Efficacy in mice	IgG (ELISA)	Th2 cells	Th17 cells	Th1 cells	Opson Ab	Memory B cells/ Tfh cells	Memory T cells/ T _{RM} cells
aP	70-85%	Medium	++++	++++	+	-	-	+	-
wP or Infection	90-95%	High	++	-	++	+++	+++	+++	+++
aP + novel adjuvants (PAMPs)	?	High	++++	-	+++	++++	++++	?	?

Conclusions

- Current aP vaccines administered with alum as the adjuvant have suboptimal efficacy and in particular induction of long term immunity
 - Fail to induce appropriate immunological memory
 - Fail to induce appropriate T cell responses, including Th1, circulating Tfh and lung T_{RM} cells
- Possible solutions
 - Booster immunization with a reformulated vaccine (e.g. add new adjuvant to existing Tdap for pre-school/adolescent booster)
 - 3rd generation paediatric aP vaccine with Th1/Tfh/T_{RM} inducing adjuvant (+/- alum) needed to address resurgence of pertussis



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