



היחידה למחלות זיהומיות בילדים - מרכז רפואי וולפסון

New Adjuvants and Their Role in Vaccination

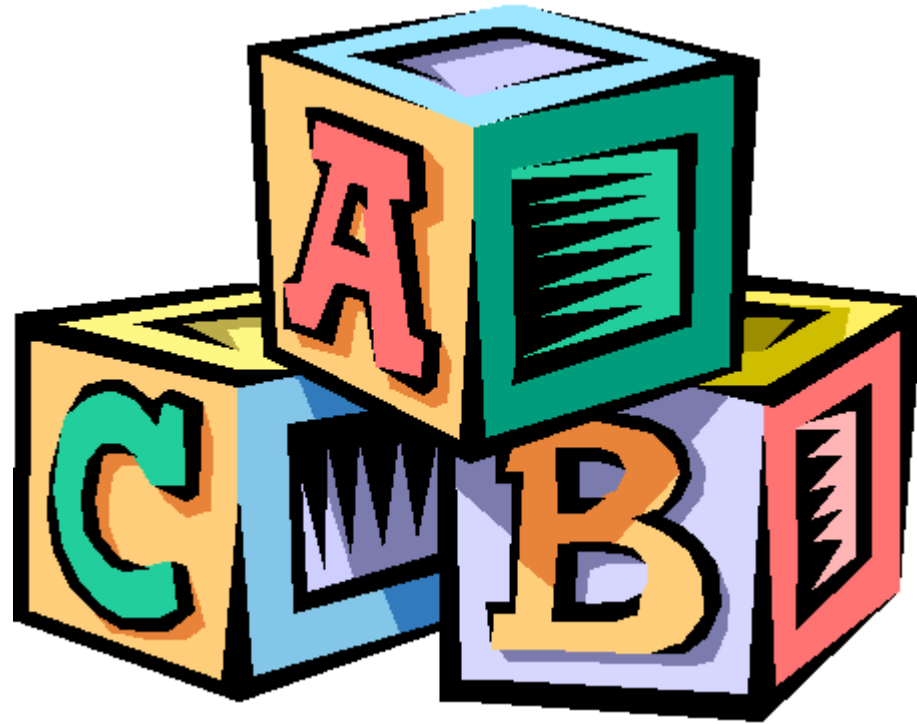
Prof. Eli Somekh
Wolfson Medical Center



האמנם Adjuvant-phobia ??

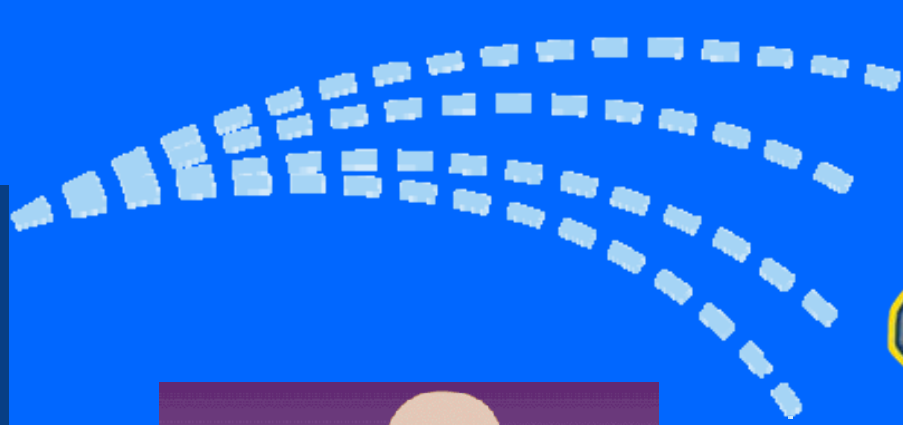
- “כאילו רק החיסונים עצמם אינם מסוכנים דיים, דמיינו חיסונים מחוזקים בטורבו”.
- “תוכנית שמחייבת לחסן חיסון המוני מיליוני ילדים, בתרופה, המכילה אדג'ובנט, הידוע כמחולל מחלות אוטואימוניות רבות, היינה תוכנית זדונית ומסוכנת ביותר”.

HOW VACCINES WORK?



ABCs OF CHILDHOOD VACCINES

“כאשר הגוף נחשף לחיסון הוא יוצר נוגדנים אשר נלחמים בפולש”



האמנם?



אז זהו, שזה לא, זה לא תמיד עובד..

מדוע חלק מהחיסונים אינם עובדים?

Some vaccines, especially subunit vaccines do not always trigger the danger signals required to stimulate the optimum immune response.

המערכת החיסונית "מבינה" כי מדובר באיום סרק ואינה מגיבה בעוצמה לגרוי.

“Adjuvants - The Immunologist's dirty little secret“

(Charles A. Janeway, 1989)



So, What are adjuvants?

- “Adjuvants alert the immune system to the presence of the immunogen”.
- “Without the adjuvant's clear message, the immune system will not wake up, and the vaccine will be ignored”.

מדוע חלק מהחיסונים נכשל?

- הטיטר של הנוגדנים שנוצר הוא נמוך מדי.
- הנוגדנים הנוצרים אינם ב- ISOTYPE הרצוי.
- התגובה נוצרת היא בעיקרה הומורלית (נוגדנים), בעוד שלסילוק מספר מחוללים (בעיקר מחוללים תוך תאיים) יש צורך בתגובת חיסון תאי.

Adjuvant can affect:

The amount of antibody

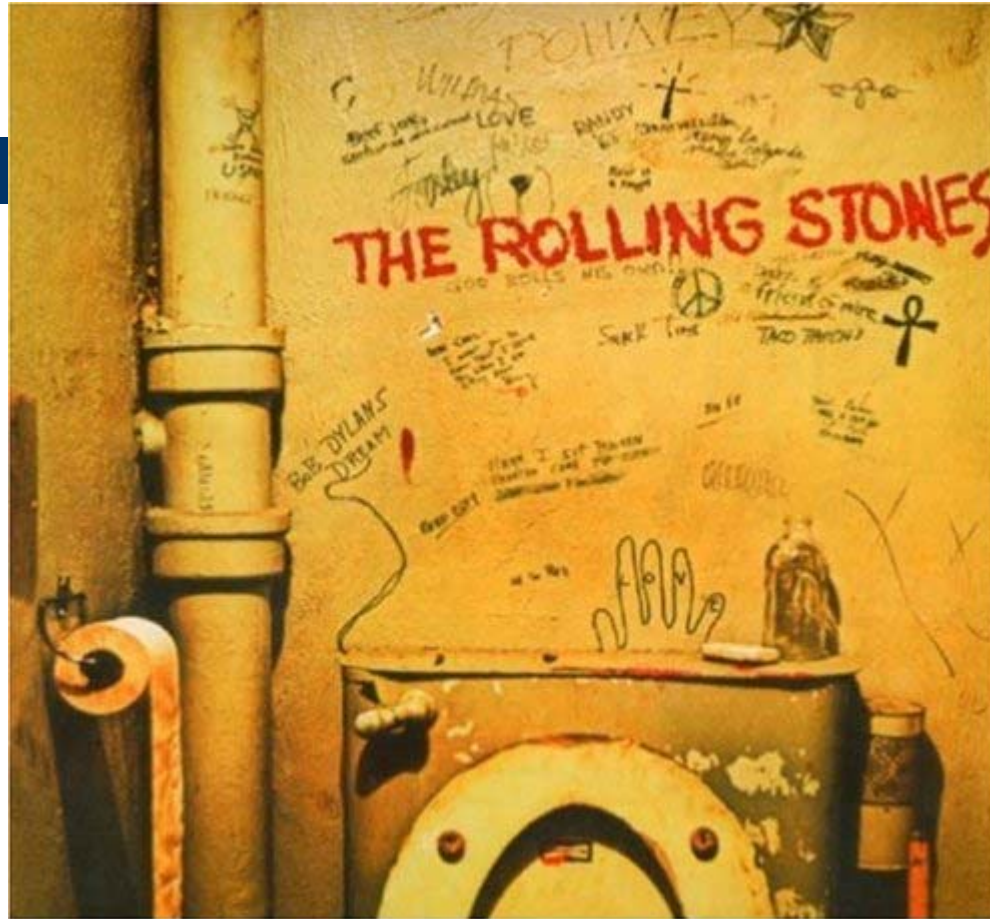
The isotype of antibody

The nature of the T cells produced

לשלוט בגובה הלהבות



"You can't always get what you want"



"But if you try sometimes.. you get what you need".

How do Adjuvants Work?





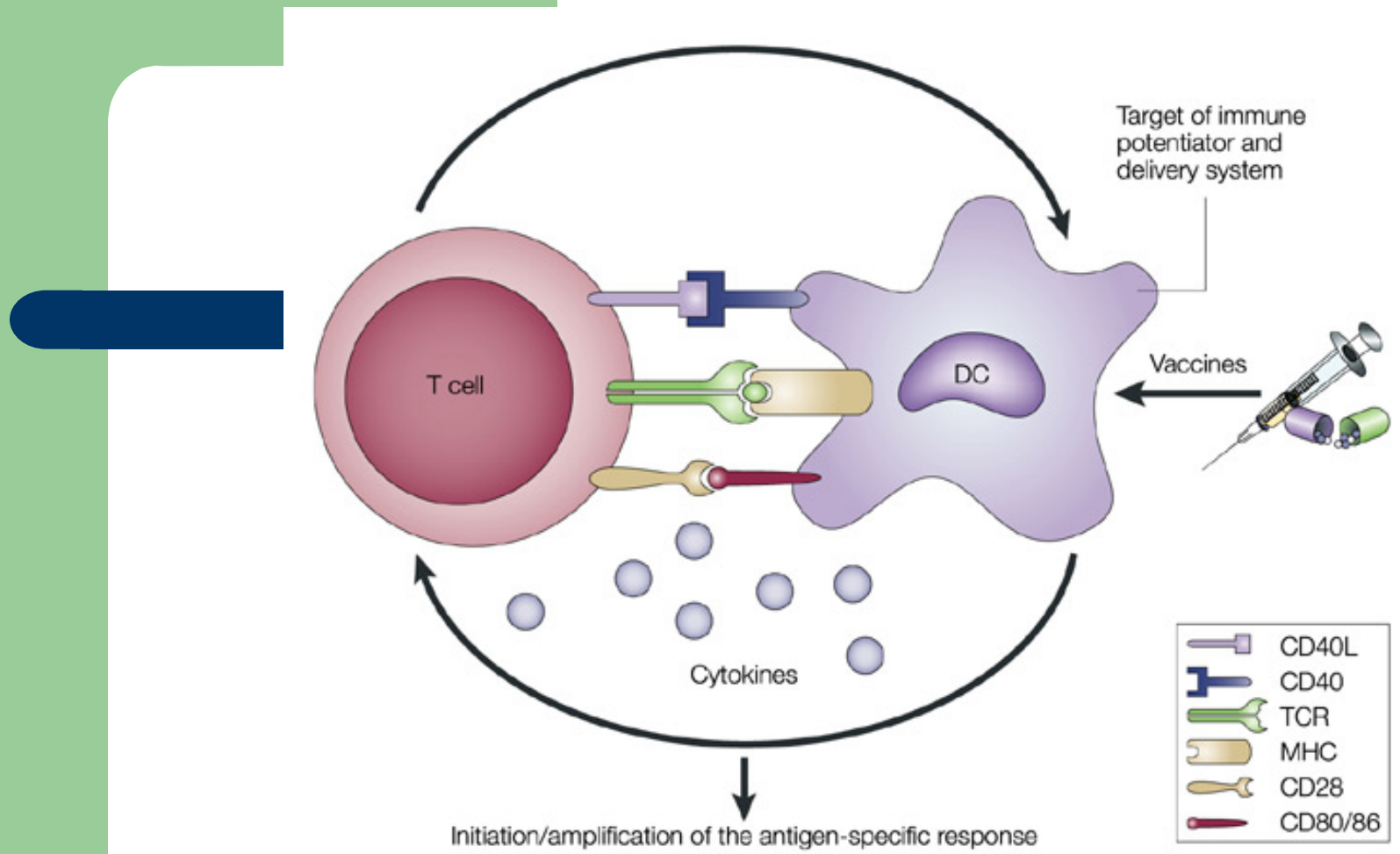


The Innate Immunity

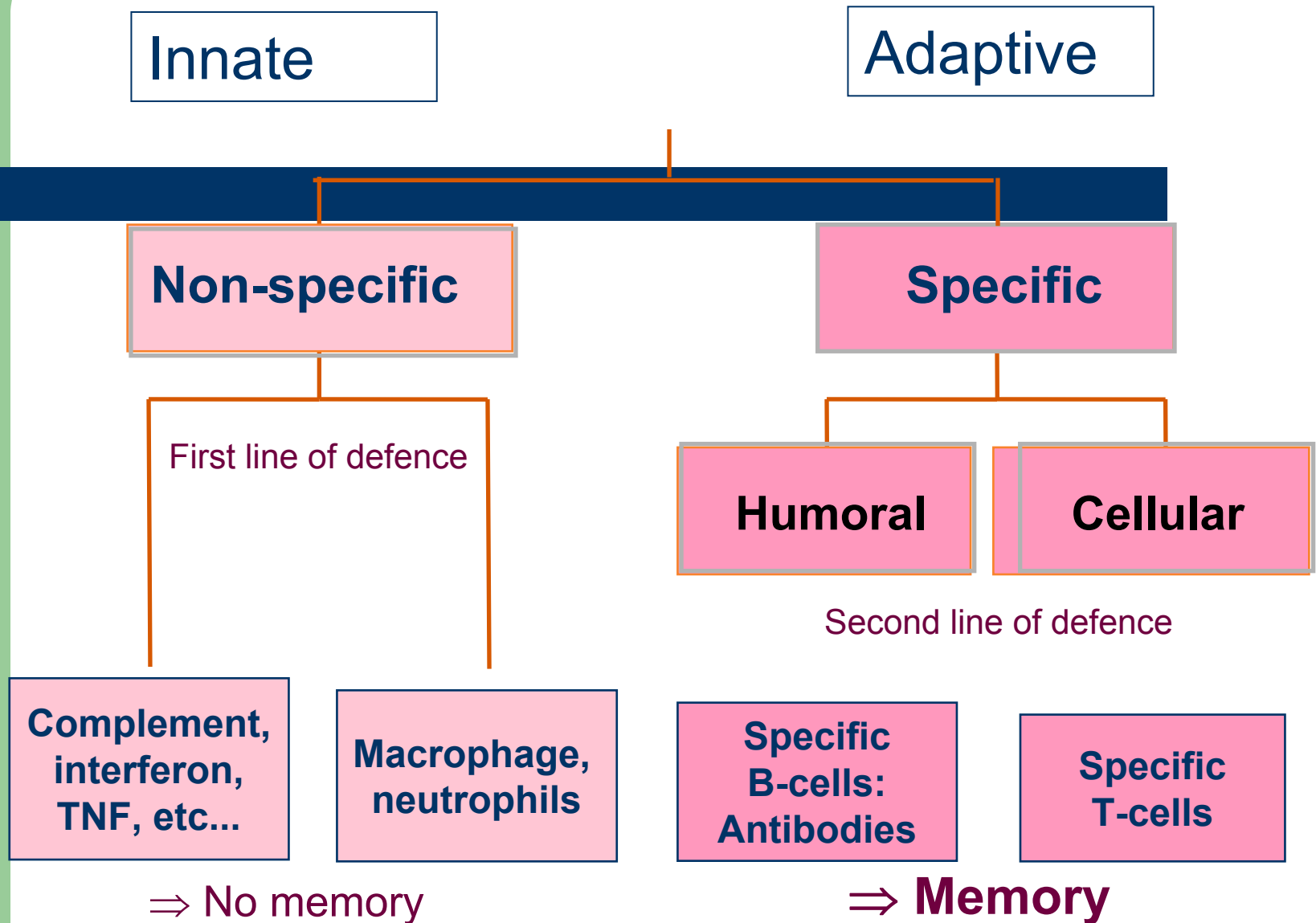
(המערכת המוטבעת)

The Adaptive Immunity

(המערכת הנרכשת)



The immune system: basic response



⇒ No memory

⇒ Memory

Innate Immunity - Cinderella Immunity



- The innate system seems to be dull, crude, uninteresting and simple, but....
- The adaptive system does not work without innate response.
- The innate system not only activates B & T cell response also determine the type of the immune response.

הזנב שמכשכש בכלב..



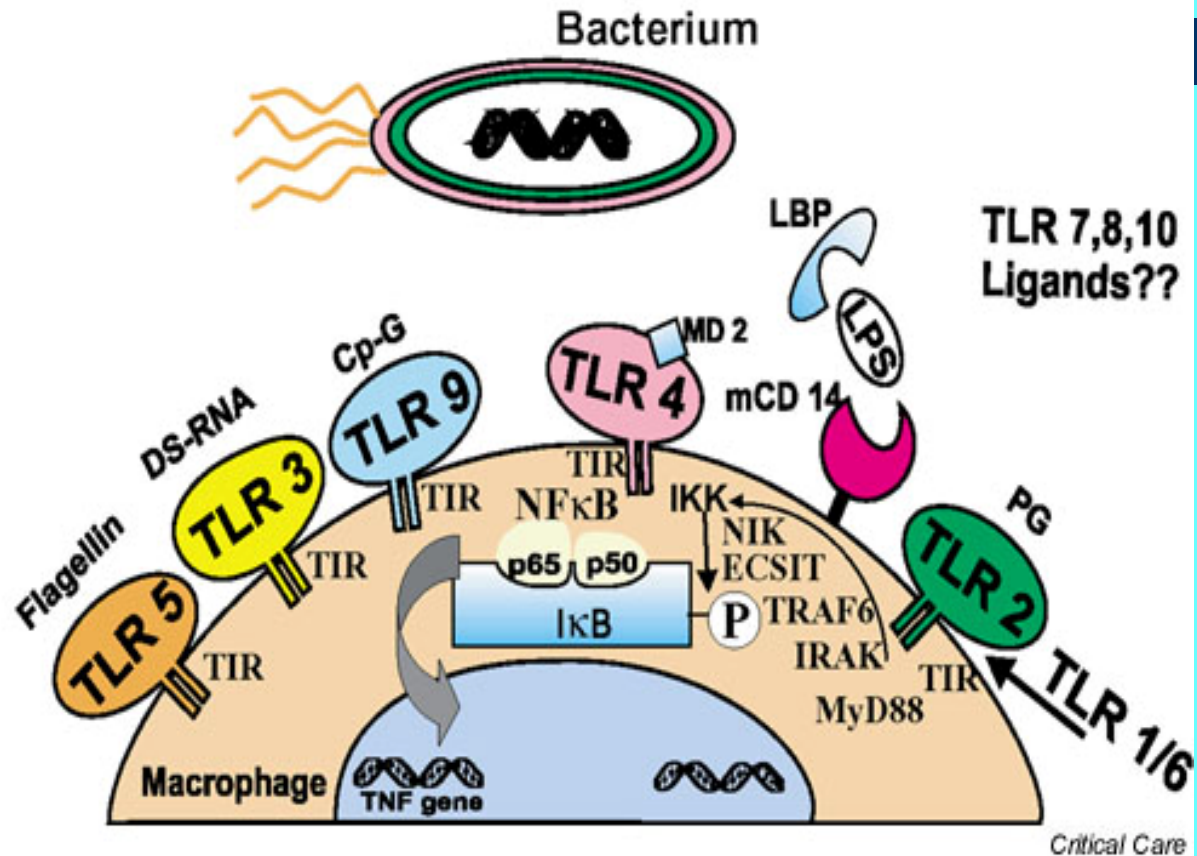
©Linda Silvestri



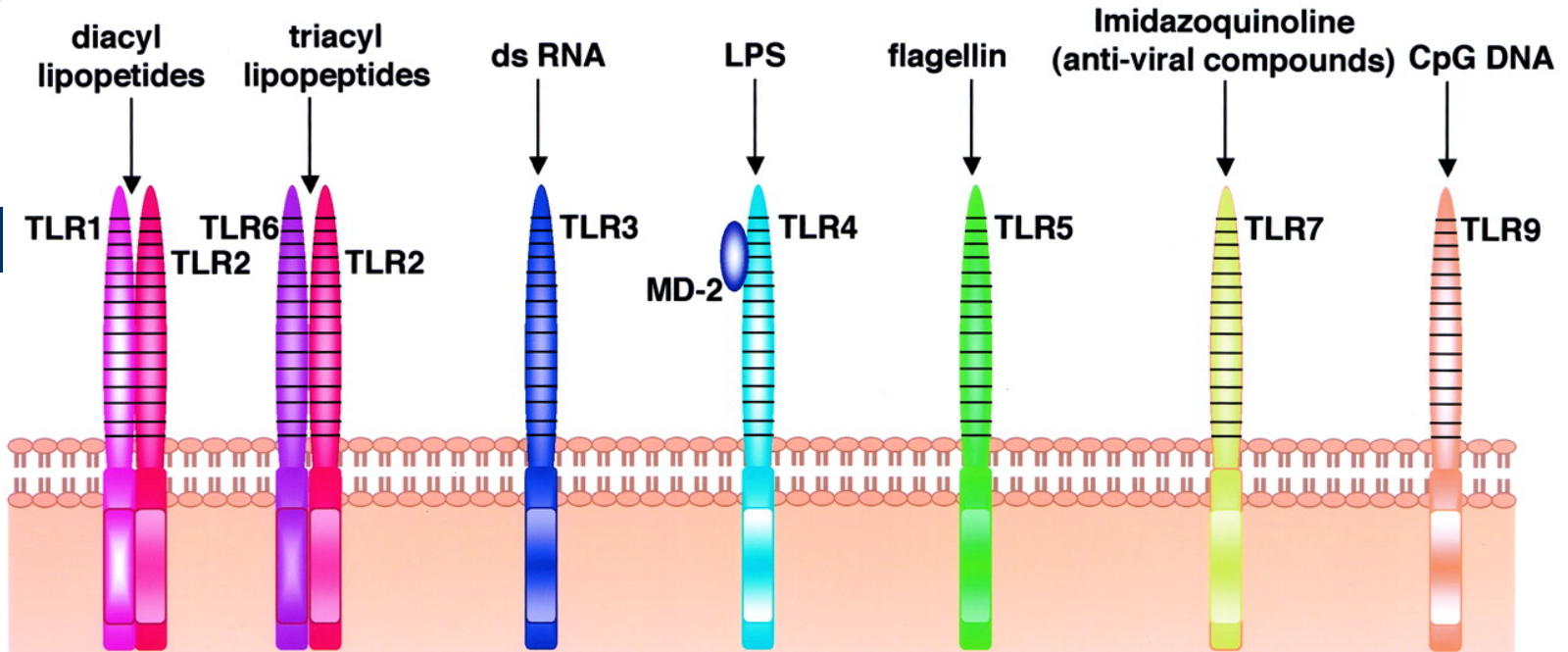
“The man (adaptive immunity) is the head, but the woman (innate immunity) is the neck. And she can turn the head any way she wants”

Toll Like Receptors - The weird Proteins

Signaling Events of the Innate Immune Response

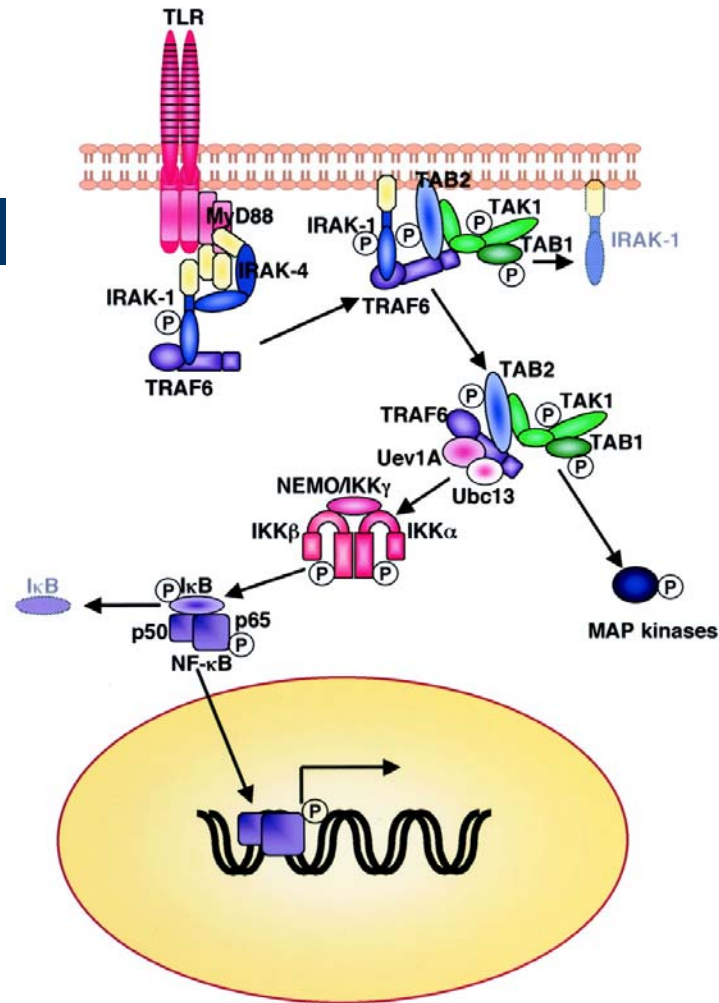


Summary of ligands recognized by TLR family.

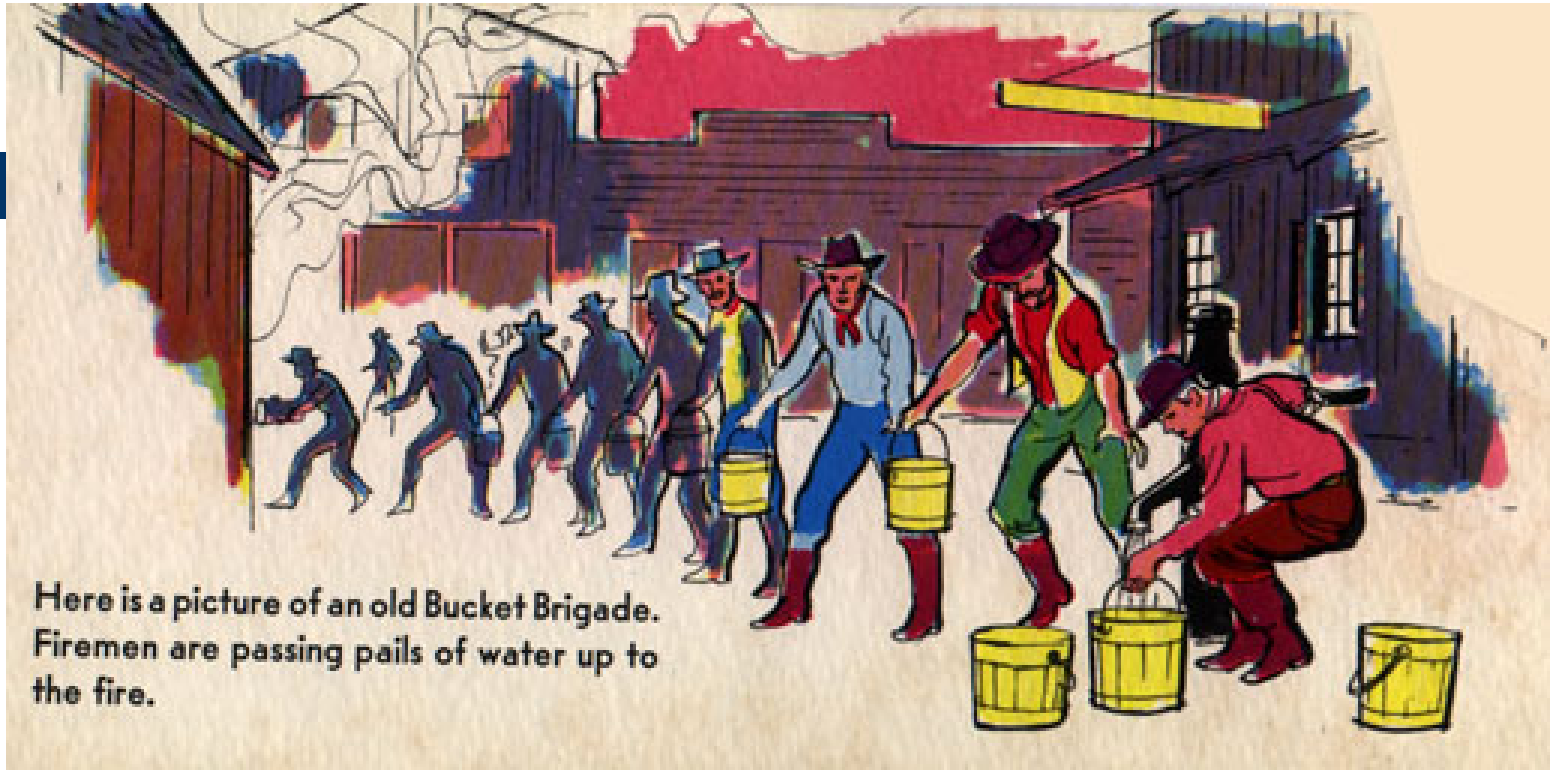


Akira S J. Biol. Chem. 2003;278:38105-38108

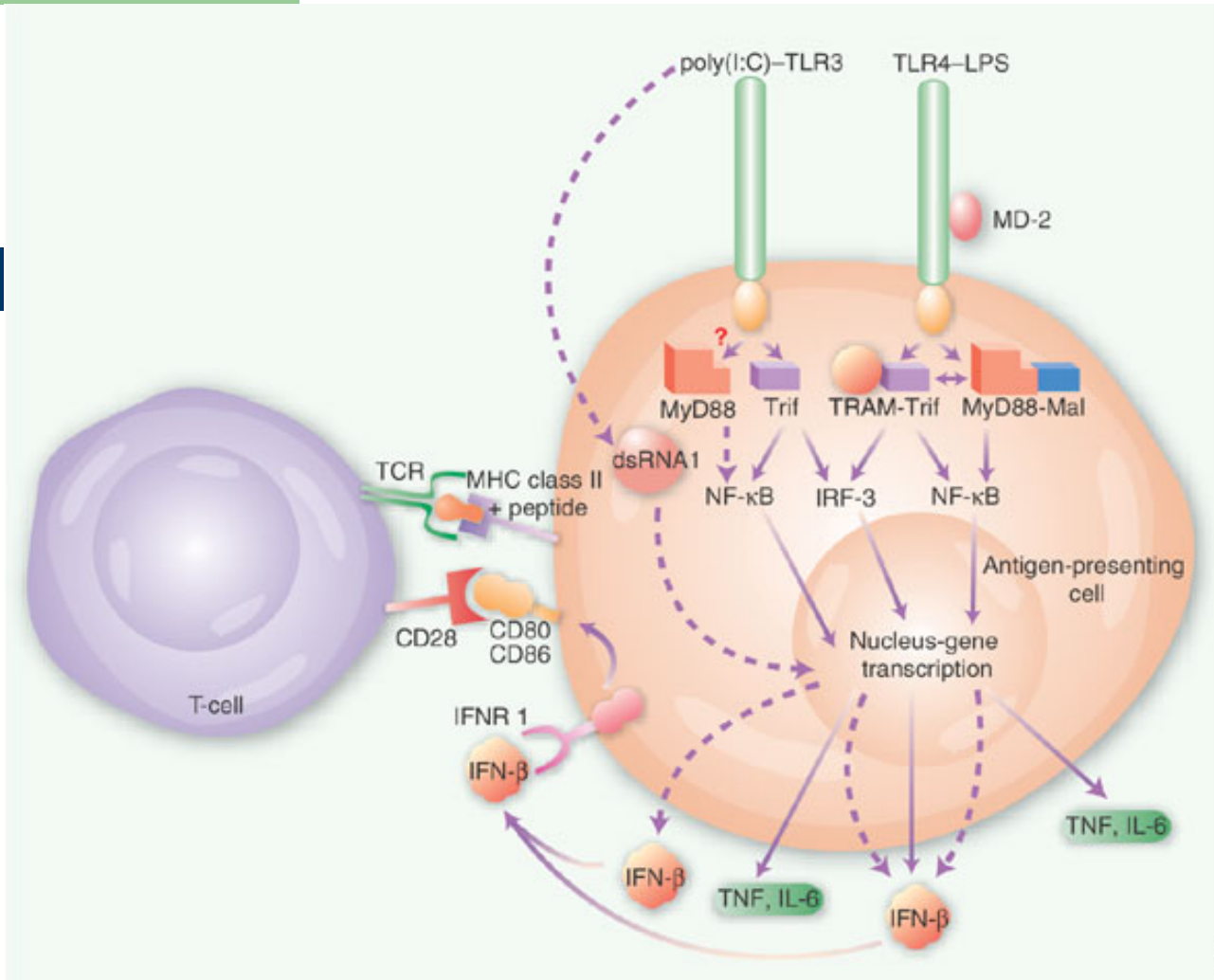
TLR signaling pathways



Akira S J. Biol. Chem. 2003;278:38105-38108



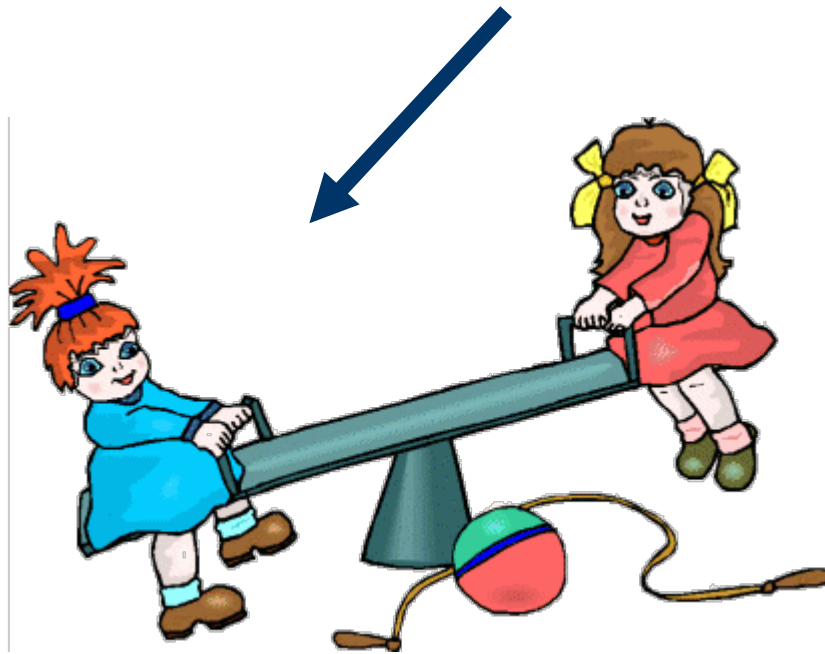
Here is a picture of an old Bucket Brigade.
Firemen are passing pails of water up to
the fire.





TLR TLR TLR TLR TLR TLR TLR TLR

Th1 / Th2 response



Types of Adjuvants



Aluminium Hydroxide (Alum).

Most widely used: >80% of vaccines contain alum.
Proposed way - ~~Depot effect.~~

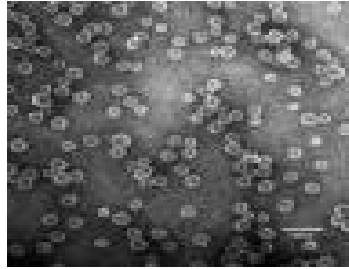
Alum activates the 'inflammasome'. (*Nature* **453**,
1122–1126; 2008).

Cells damaged by alum release uric acid, a known trigger of the
inflammasome (*J. Exp. Med.* **4**, 869–882; 2008).

Independent of TLR's signaling

Stimulate Th2 response

MF59:



- Oil based emulsion (including squalene).
- Taken by antigen presenting cells (DCs) and stimulate cytokine production.
- Induce Th2 response

MPL - monophosphoryl lipid A

- MPL is derived from the bacterial cell wall.
- Detoxified form of LPS
- TLR4 agonist
- Stimulate Th1 response

CpG *Motifs*

(3'-cytidine 5'-guanosine dinucleotide)

- Unmethylated
- Common in bacterial or viral DNA
- TLR9 Agonists

Saponins (glycosides)

QS21

Derived from the bark of a Chilean tree *Quillaja saponaria*.

Induce IL-2 and gamma IFN secretion and TH1 response.

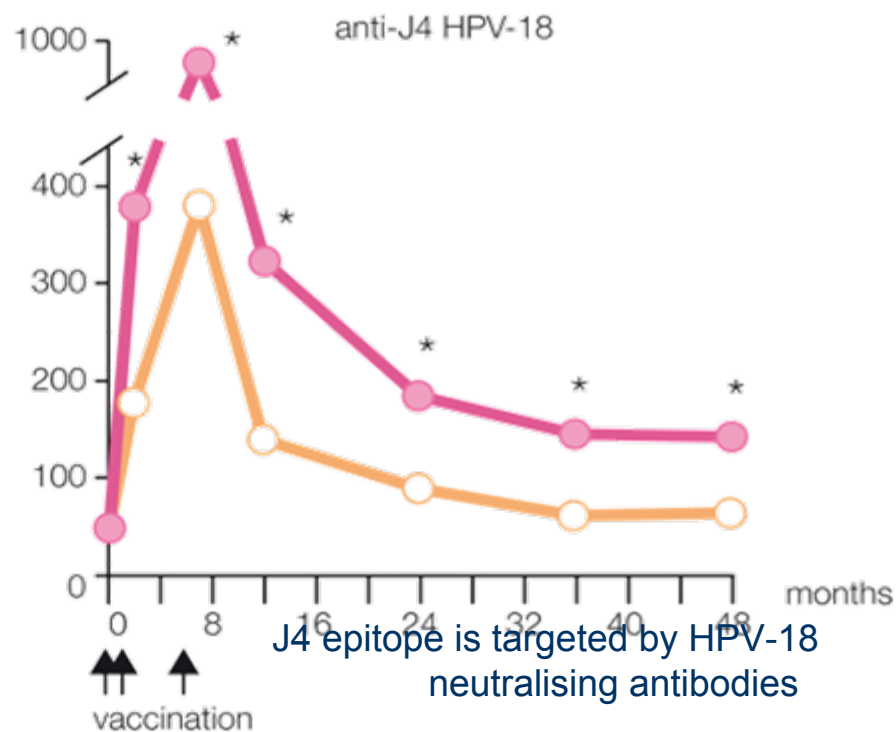
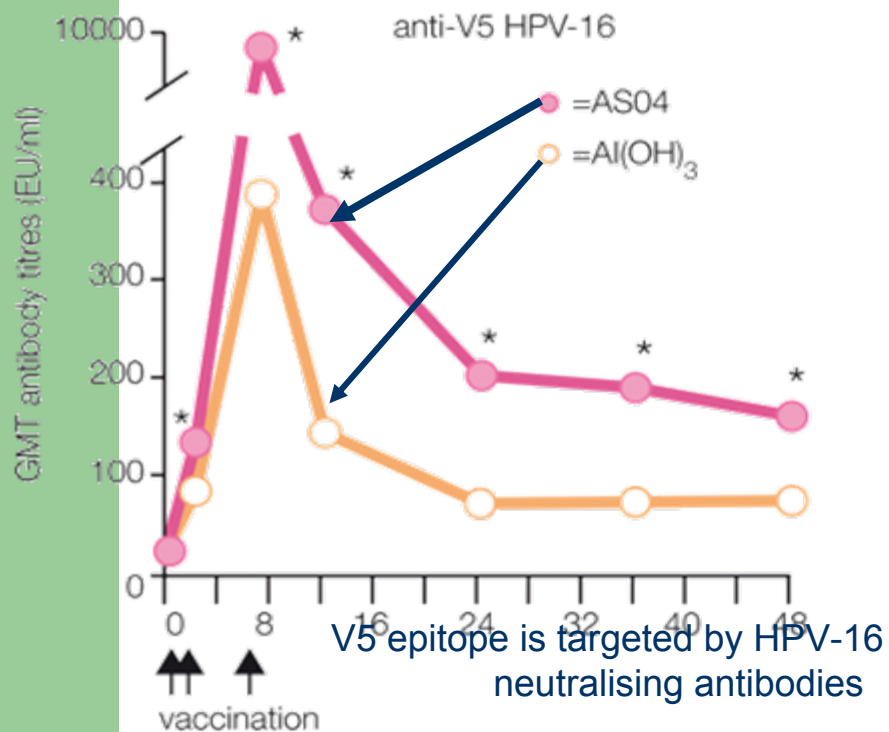
Combination Adjuvants

- ASO4 : Alum + MPL
- ASO2 : MPL + QS21 + oil/water emulsion.



Usage of Newer Adjuvants

AS04 in GSK cervical cancer candidate vaccine Human data: Antibodies



* Wilcoxon's non-parametric ($p < 0.05$)
Giannini SL, et al. Vaccine 2006; 24: 5937-49

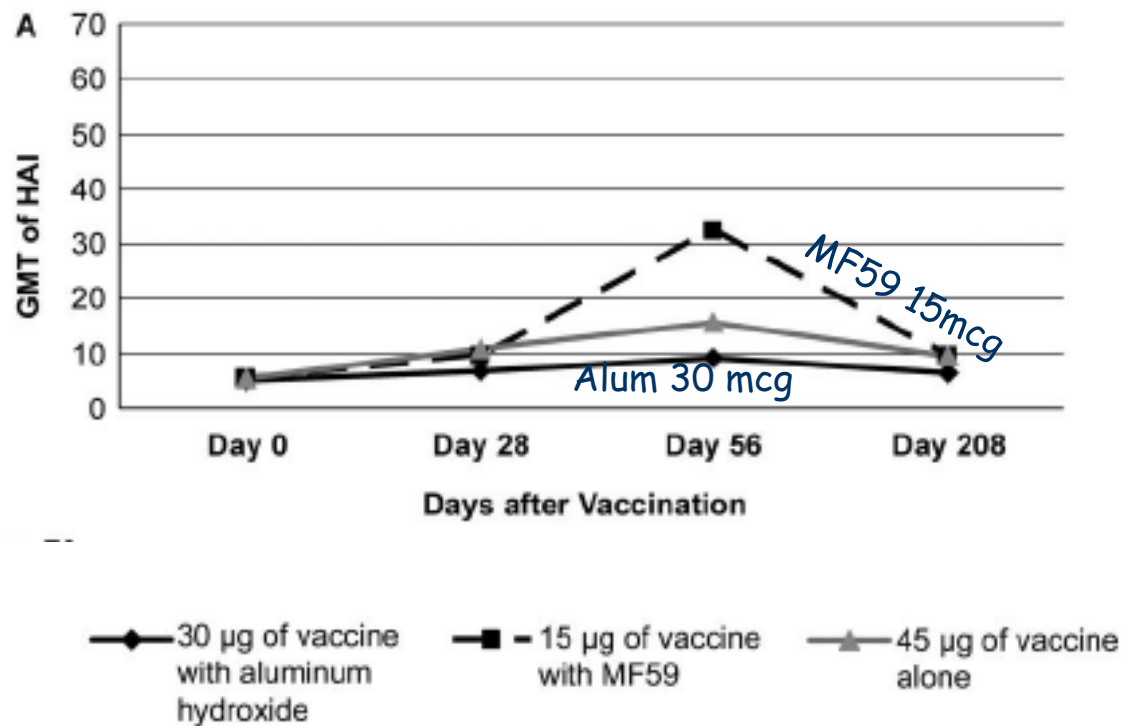
Pandemic H5N1 Influenza Vaccine development

High dosages of influenza virus hemagglutinin are needed to elicit a protective antibody titer.

Antigen dosage may be reduced and immunogenicity improved with the use of MF59 adjuvant.

Expert Rev Vaccines. 2008;7:241-247

MF59 adjuvant Boosts Immunogenicity of H5N1 (*J Infect Dis* 2008;197:667-675)



Adjuvant and Other Novel Vaccines

1. HBV vaccines (ASO4, CPG)
2. CMV Vaccine (MF59)
3. HSV (ASO4)

Malaria Vaccine in Children

- More than 1 million deaths are attributable to malaria every year!
- Emergence of widespread resistance to previously highly effective drugs.
- Vaccines with malaria antigen (RTS,S) alone, or with alum are **not effective!**
- Studies with new adjuvants are promising:
 - AS02 (MPL + QS21 + oil in water)
 - AS01E (MPL + QS21 + liposomes)

*Alonso PL, Lancet 2004; 364:1411-20
Alonso PL, Lancet 2005; 366:2012-8.*

Efficacy of RTS,S/AS01E Vaccine against Malaria in Children 5 to 17 Months of Age

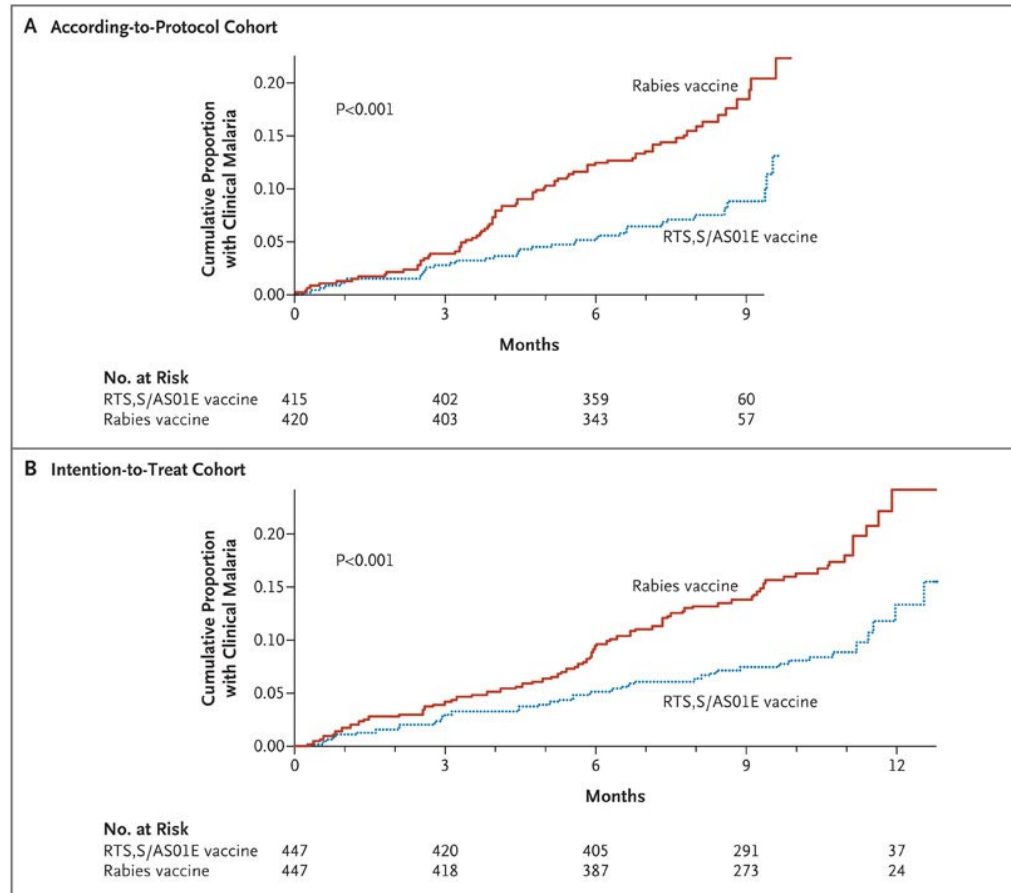
Children were randomly assigned to receive:
Malaria vaccine - 402 children)
or
Control vaccine (rabies) - 407 children.

Malaria episodes:
Recipients of Malaria vaccine -38 episodes
as compared with
Recipients of the rabies vaccine - 86 episodes.

Efficacy - 56% (95% CI, 31 to 72; $P < 0.001$).

Bejon et al. NEJM. 2008 ;359: 2521

Kaplan-Meier Estimates of the Time to the First or Only Episode of Clinical Malaria.



Bejon et al. 2008 ;359: 2521

Safety

- **A** higher incidence in local and general AEs was observed.
- Stimulation of TLRs is not without risk. Theoretically it could leave one susceptible to autoimmune disease.

SPECIAL ARTICLE:

Adjuvants and autoimmunity

E Israeli, N Agmon-Levin, M Blank,
Y Shoenfeld.

Lupus (2009) 18, 1217–1225

Table 2 Adjuvants involvement in autoimmune manifestation

<i>Adjuvant involved</i>	<i>Manifestations/disease/Ab</i>	<i>Species</i>	<i>References</i>
MDP;LPS;Gram + CoxackieB3,IL1 β ,TNF α	Experimental thyroiditis; Myocarditis	Mice	Rose ⁴⁸
Mineral oils	Sclerosing lipogranulomas	Mice human?	Di Benedetto ³³
Pristane, mineral oils	Plasmacytomas	Mice	Anderson and Potter ³⁴
Pristane, squalene, IFA	Chronic arthritis	Mice, rats	Cannon <i>et al.</i> ³⁵ Carlson <i>et al.</i> ⁴⁹
Pristane, squalene, IFA	Lupus-related anti nRNP/Sm/Su antibodies	Mice	Satoh <i>et al.</i> ^{37,38}
Pristane, squalene, IFA, mineral oils	Anticytoplasmic Ab, anti ssDNA/chromatin Ab	Mice	Kuroda <i>et al.</i> ³⁹
Pristane, squalene, IFA	Lupus-related anti nRNP/Sm/Su antibodies	Mice	Kuroda <i>et al.</i> ^{39,40}
Silicone	Human adjuvant disease connective tissue diseases	Human	Hennekens <i>et al.</i> ⁵⁰
Silicone	Scleroderma, SLE, RA	Human	Spiers <i>et al.</i> ⁴¹
Alum in vaccines (HBV, HAV, tetanus)	MS, Chronic fatigue syndrome, polymyalgia rheumatica	Human	Gherardi ⁴⁴
Aluminium hydroxide, squalene	Gulf War syndrome, antibodies to squalene	Human	Asa <i>et al.</i> ⁴⁵

“...to bypass the TLR signaling pathway completely in order to circumvent common side effects of adjuvant-activated TLRs such as local inflammation and the general malaise”.

MF59 - adjuvanted versus non- adjuvanted influenza vaccines

Vaccine 2009; 6959–6965

Methods:

Safety data were pooled from 64 clinical trials involving (+)MF59 seasonal and pandemic influenza vaccines.

Events of potential autoimmune origin occurring during the trial

	Overall population		Adjusted RR (95% CI)
	Subjects with any AE, n (per 1000)		
	(+)MF59	(-)MF59	
All trials (n)	11,243	2969	
Predefined MedDRA terms	8 (0.71)	2 (0.67)	2.26 (0.44–11.47)
Cases confirmed by blinded experts	5 (0.44)	2 (0.67)	1.28 (0.22–7.53)
MedDRA terms as defined by Verstraeten et al. [18]	39 (3.47)	18 (6.06)	0.87 (0.47–1.61)
Controlled trials (n)	4000	2969	
Predefined MedDRA terms	4 (1.00)	2 (0.67)	1.91 (0.35–10.43)
Cases confirmed by blinded experts	2 (0.50)	2 (0.67)	0.96 (0.13–6.79)
MedDRA terms as defined by Verstraeten et al. [18]	21 (5.25)	18 (6.06)	1.01 (0.54–1.90)

Analysis of adverse events of potential autoimmune aetiology of AS04 adjuvanted vaccines

Vaccine 26 (2008) 6630–6638

Methods:

All randomized, controlled trials of HPV, HSV and HBV vaccines were analyzed (N = 68,512).

The relative risk (AS04/control) of experiencing any autoimmune event was:

0.98 (95% CI : 0.80 - 1.21)

Summary

- Adjuvants are highly valuable additions to vaccines.
- Adjuvants may modulate *the quality and quantity of the response* following vaccination.
- Licensure of new vaccines containing new adjuvants should be expected in the near future.





THE END