Adjuvanted vaccines for the elderly

Arnaud Didierlaurent, PhD

GSK Vaccines, Rixensart, Belgium

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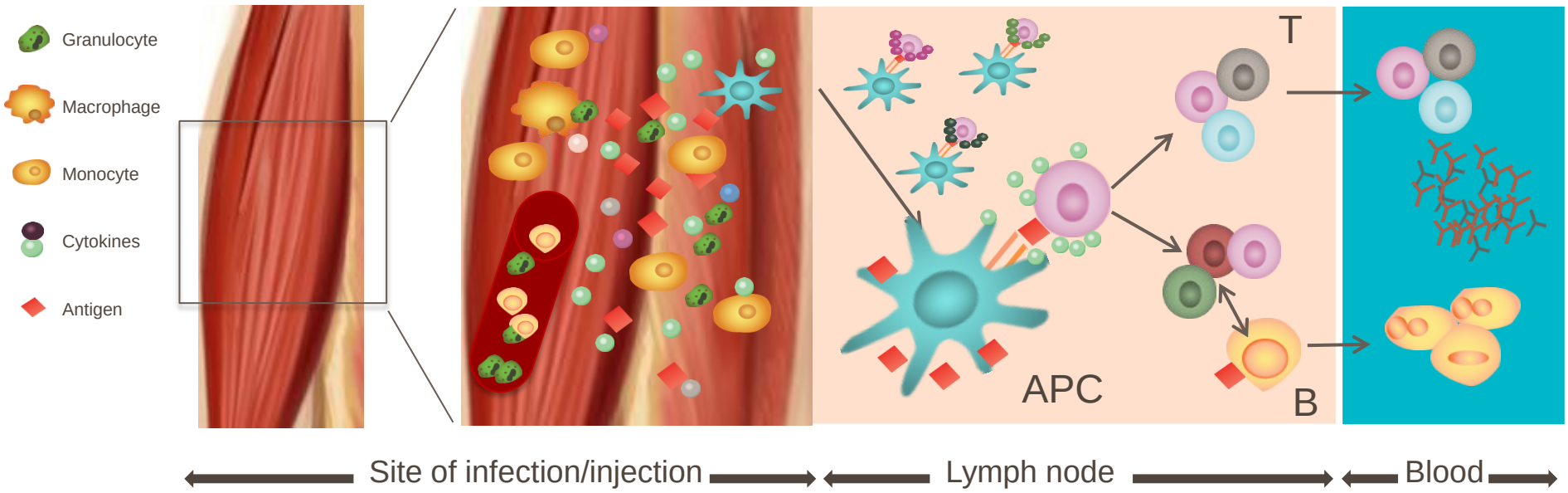
Role of Innate and adaptive immune response in adjuvant response

Innate response (0 – 72h)

Adaptive response (Day 1 to weeks)



Stimulation of the local innate system

Local cytokine response

Recruitment of innate immune cells

Adaptive immune response

Garçon N, *et al.* Understanding Modern Vaccines, *Perspectives in Vaccinology*, Vol 1, Amsterdam: Elsevier; 2011; chapter 4: p89-113

Only few vaccine adjuvants have been evaluated in the Elderly

Adjuvant name	Mechanism or receptor	Clinical phase or licensed product name
dsRNA analogues (for example, poly(I:C))	TLR3	Phase 1
Lipid A analogues (for example, MPL, RC529, GLA, E6020)	TLR4	Cervarix, Supervax, Pollinex Quattro, Melacine
Flagellin	TLR5	Phase 1
Imidazoquinolines (for example, Imiquimod, R848)	TLR7 and TLR8	Aldara
CpG ODN	TLR9	Phase 3
Saponins (for example, QS21)	Unknown	Phase 3
C-type lectin ligands (for example, TDB)	Mincle, Nalp3	Phase 1
CD1d ligands (for example, α- galactosylceramide)	CD1d	Phase 1
Aluminum salts (for example, aluminum oxyhydroxide, aluminum phosphate)	Nalp3, ITAM, Ag delivery	Numerous licensed products
Emulsions (for example, MF59, AS03, AF03, SE)	Immune cell recruitment, ASC, Ag uptake	Fluad, Pandemrix
Virosomes	Ag delivery	Epaxal, Inflexal V
AS01 (MPL,QS21, liposomes)	TLR4	Phase 3
AS02 (MPL,QS21, emulsion)	TLR4	Phase 3
AS04 (MPL, aluminum salt)	TLR4	Cervarix
AS15 (MPL, QS21, CpG, liposomes)	TLR4 and TLR9	Phase 3
GLA-SE (GLA, emulsion)	TLR4	Phase 1
IC31 (CpG, cationic peptide)	TLR9	Phase 1
CAF01 (TDB, cationic liposomes)	Mincle, Ag delivery	Phase 1
ISCOMs (saponin, phospholipid)	Unknown	Phase 2

Adapted from Reed SG et al, *Nature Med* 19: 1597-1608, 2014

Can Adjuvant help? Observed benefits of adjuvants in candidate or licensed vaccines

- Increased and persistent CD4 and antibody response[1]
- Antigen dose sparing effect [2]
- Increase breadth of the antibody response (MF59/AS03-adjuvanted flu)[3]
- Evidence of cross-reactive T-cell response[5]
- AS are being used in vaccines in populations with specific immune status, such as HIV+[7]and other immunocompromised people[6]

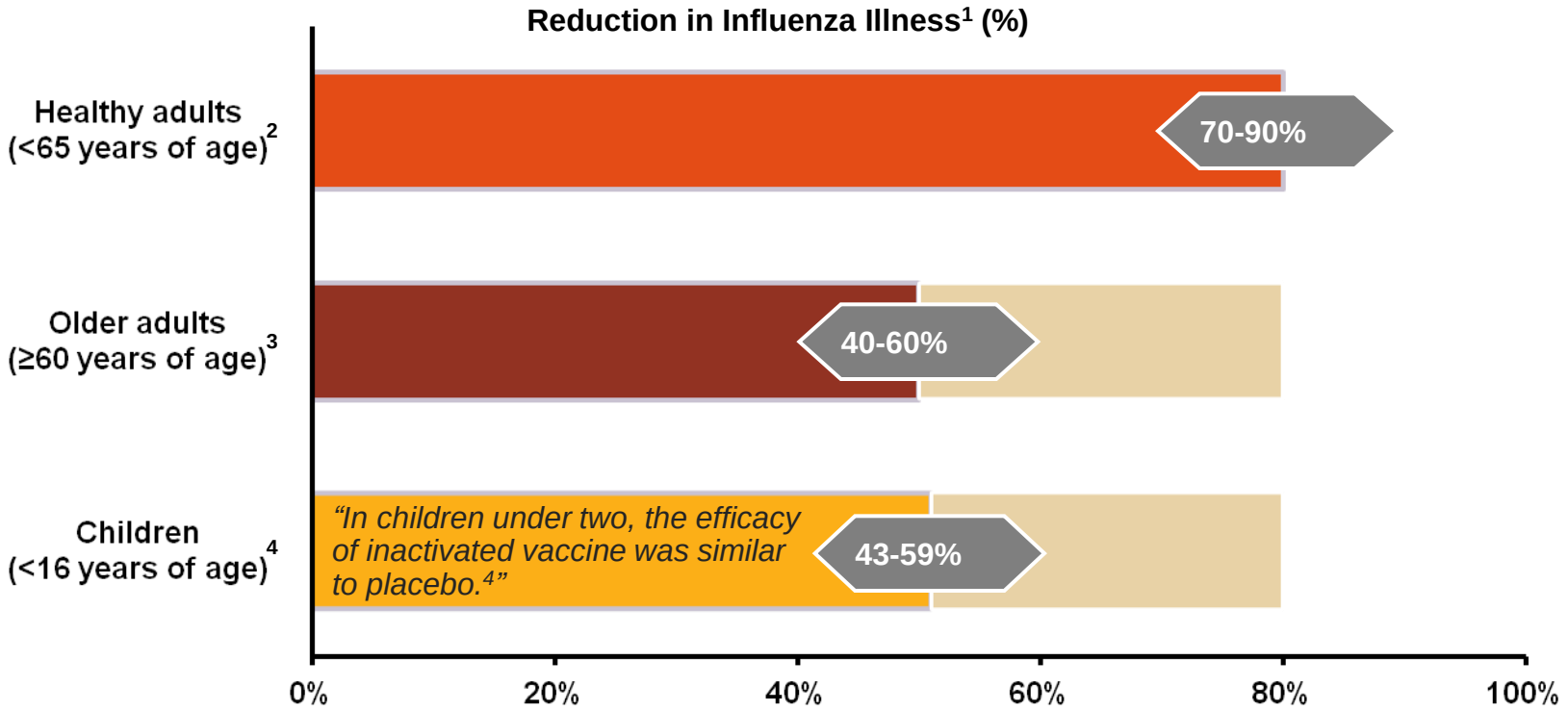
WHAT ISTHE EVIDENCE IN THE ELDERLY POPULATION?

References:

[1] Leroux-Roels et al. *Vaccine*, 2015 (HBs/AS01); Leroux-Roels et al., *Clin. Vaccine Immunol*. 2014 (F4/AS01); Roteli-Martins *et al*., *Hum Vaccin Immunother* 2012 (HPV/AS04)
[2] Baras et al. *PLoS One* 2008; Leroux-Roels et al. *Lancet* 2007 ; Nolan et al, *J Infect Dis* 2015
[3] Khurana et al. *Sci Transl Med*. 2011 (MF59); unpublished (AS03)
[4] Nolan et al, J Infect Dis 2014
[5] Moris et al. *J. Clin. Immunol.* 2011 (H5N1/AS03); Wheeler et al, *Lancet Oncol* 2012 (HPV/AS04-Cervarix); Einstein et al, *Hum Vaccines* 2011
[6] Stadtmauer et al. *Blood* 2014 (Zoster gE/AS01); Tong et al. *Kidney Int* 2005 (HBs/AS04-Fendrix); Siegrist et al, *Plos One* 2012 (H1N1/AS03)
7 Denny L, *et al*. *Vaccine* 2013 (HPV/AS04Cervarix); Ho J et al. *AIDS* 2011 (H1N1/AS03); Harrer et al. *Vaccine* 2014 (F4/AS01); Berkowitz, et al. J. Inf. Dis. 2014. (VZV gE/AS01)

Observation 1: limited efficacy of conventional non-adjuvanted Influenza vaccines in older adults

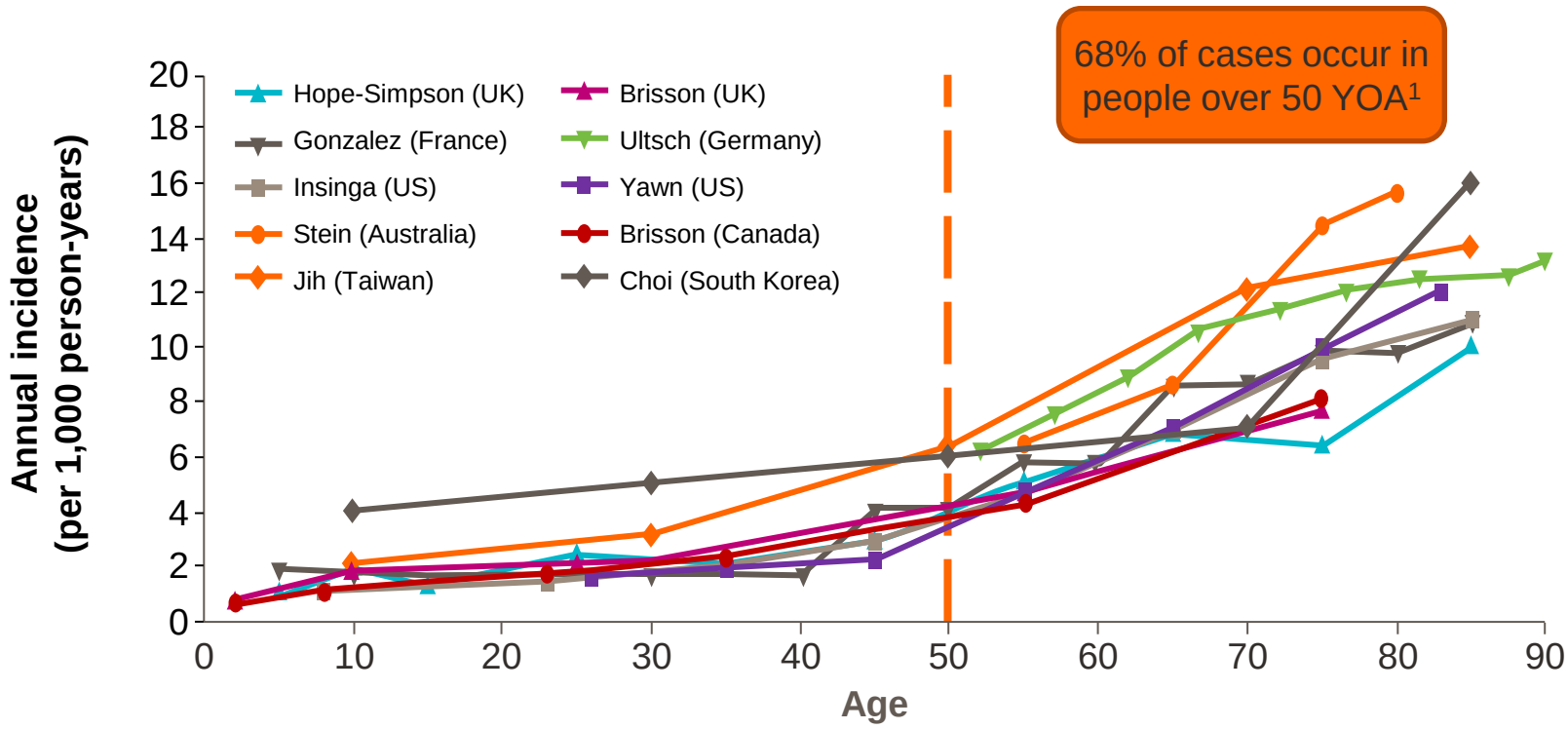
Estimated reduction in Influenza Illness[1] Following Administration of Non-adjuvanted TIVs to Healthy Adults (<65 Years), Older Adults (≥60 Years) and Children (<16 Years)



Data shown are taken from different studies and definition of influenza illness endpoints can vary by study

[1]. Please refer to source references for more details;
[2] CDC available at http://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm;
[3] McElhaney JE. *Aging health*. 2008; 4:603-613
[4] Jefferson T, et al. *Cochrane Database of Systematic Reviews* 2008. Issue 2. Art. No.: CD004879

Observation 2: Herpes zoster incidence rate increases with age (regardless of geography)



Several studies have shown that the incidence of HZ increases substantially with age[1,2]

HZ, herpes zoster; YOA, years of age

1. Yawn and Gilden. *Neurology* 2013; 81: 928930; 2. Harpaz *et al. MMWR Recomm Rep* 2008; 57: 1–30

Impact on efficacy- Adjuvanted *vs* plain seasonal split flu

Number of participants infected and relative efficacy by influenza strain during the year 1 surveillance period in the year 1 efficacy cohort

	Participants infected		Relative efficacy
	AS03-adjuvanted TIV (n=21 573)	Non-adjuvanted TIV (n=21 482)	
Primary endpoint*			
Influenza A or B, or both	274 (1·27%, 1·12 to 1·43)	310 (1·44%, 1·29 to 1·61)	12·11% (−3·40 to 25·29)
Exploratory analysis*†			
Influenza A	224 (1·04%, 0·91 to 1·18)	270 (1·26%, 1·11 to 1·41)	17·53% (1·55 to 30·92)
Influenza A H3N2	170 (0·79%, 0·67 to 0·92)	205 (0·95%, 0·83 to 1·09)	17·54% (−1·05 to 32·71)
Influenza A H1N1	17 (0·08%, 0·05 to 0·13)	12 (0·06%, 0·03 to 0·10)	−41·61% (−196·50 to 32·37)
Post-hoc analyses‡			
Influenza A H3N2	190 (0·88%, 0·76 to 1·01)	242 (1·31%, 0·99 to 1·28)	22·0% (5·68 to 35·49)
Influenza B Yamagata	12 (0·06%, 0·03 to 0·10)	11 (0·05%, 0·03 to 0·09)	−8·71% (−146·36 to 52·03)
Influenza B Victoria	37 (0·17%, 0·12 to 0·24)	29 (0·13%, 0·09 to 0·19)	−27·16% (−106·75 to 21·80)

Data are n (%, 95% CI) or % (95% CI). Excluding A H1N1 pdm09 strains. TIV=inactivated trivalent influenza vaccine. *Real-time PCR. †No subtype was identified with real-time PCR for 37 samples in the group given AS03-adjuvanted TIV and 53 samples in that given non-adjuvanted TIV; these samples were further analysed with multiplex RT-PCR. ‡Multiplex RT-PCR.

N= 43,800 aged 65 years and older

Similar data with MF59-TIV with a reduced "pneumonia/influenza" hospitalizations by 23% over TIV*

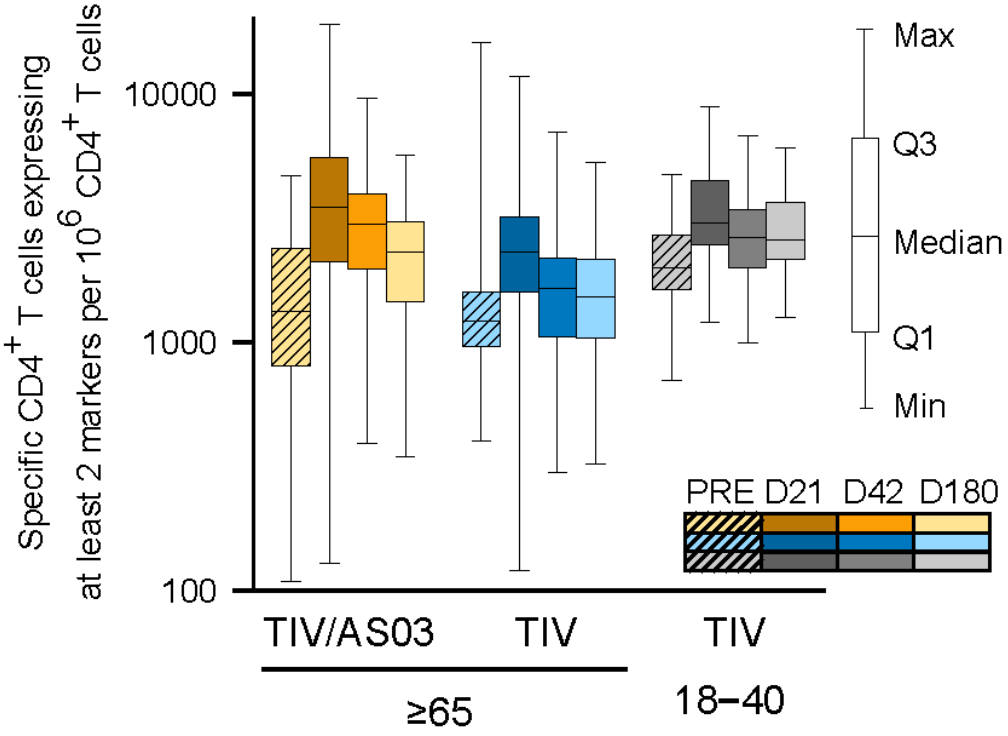
Clinical outcomes during peak season in year 1 in the year 1 peak season efficacy cohort

	AS03-adjuvanted TIV (n=21 394)	Non-adjuvanted TIV (n=21 337)	Relative efficacy*
Pneumonia or clinical influenza	202 (0·94%, 0·82 to 1·08)	225 (1·05%, 0·92 to 1·20)	10·70% (−7·99 to 26·15)
All-cause death	63 (0·29%, 0·23 to 0·38)	88 (0·41%, 0·33 to 0·51)	28·59% (1·32 to 48·33)
Admission to hospital because of respiratory diseases	84 (0·39%, 0·31 to 0·49)	89 (0·42%, 0·34 to 0·51)	5·95% (−26·72 to 30·20)
Pneumonia only†	32 (0·15%, 0·10 to 0·21)	56 (0·26%, 0·20 to 0·34)	43·08% (12·13 to 63·14)

Data are n (%, 95% CI) or % (95% CI). TIV=inactivated trivalent influenza vaccine. *Descriptive estimates. †Post-hoc analysis with adjustment for regional differences in attack rates in the group given non-adjuvanted TIV.

McElhaney J et al., *Lancet Infect Dis* 2013;13:485-96
*Mannino et al, *Am J Epidemiol* 2012; 176:527-33

Adjuvant (AS03) enhanced T cell response against seasonal split flu in individuals >65 YOA



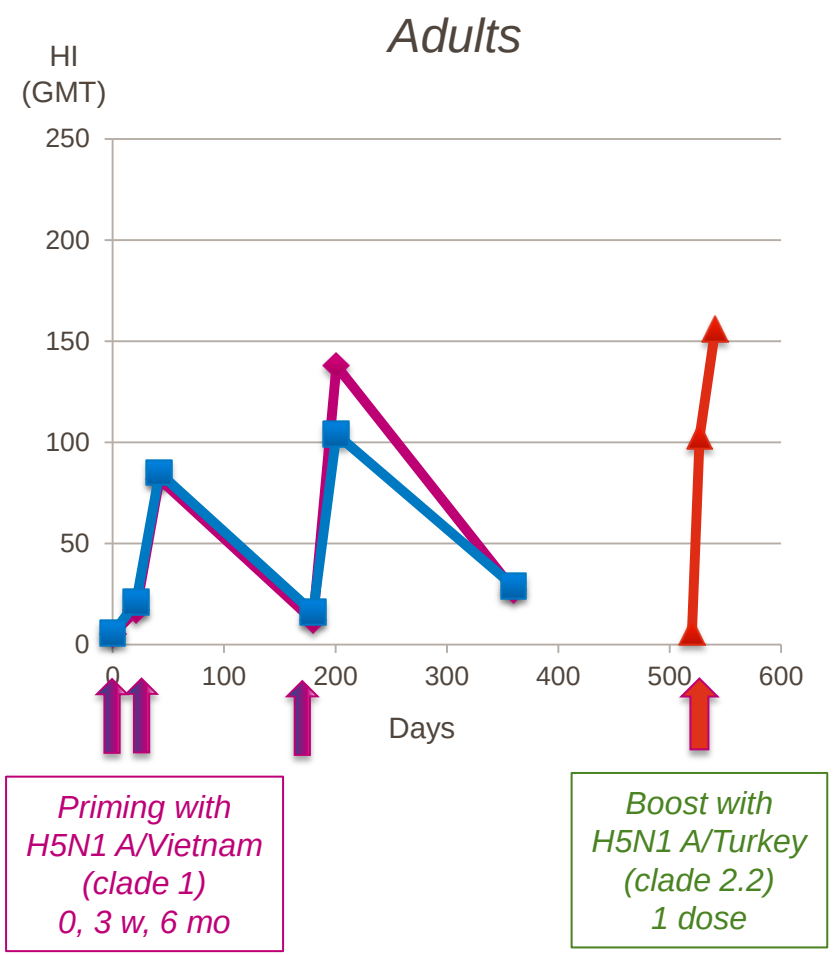
	TIV/AS03 (≥65), TIV (≥65)
21	1.64 (1.35-1.99; *p*<0.001)
42	1.70 (1.44-2.00; *p*<0.001)
180	1.40 (1.21-1.61 ; *p*<0.001)

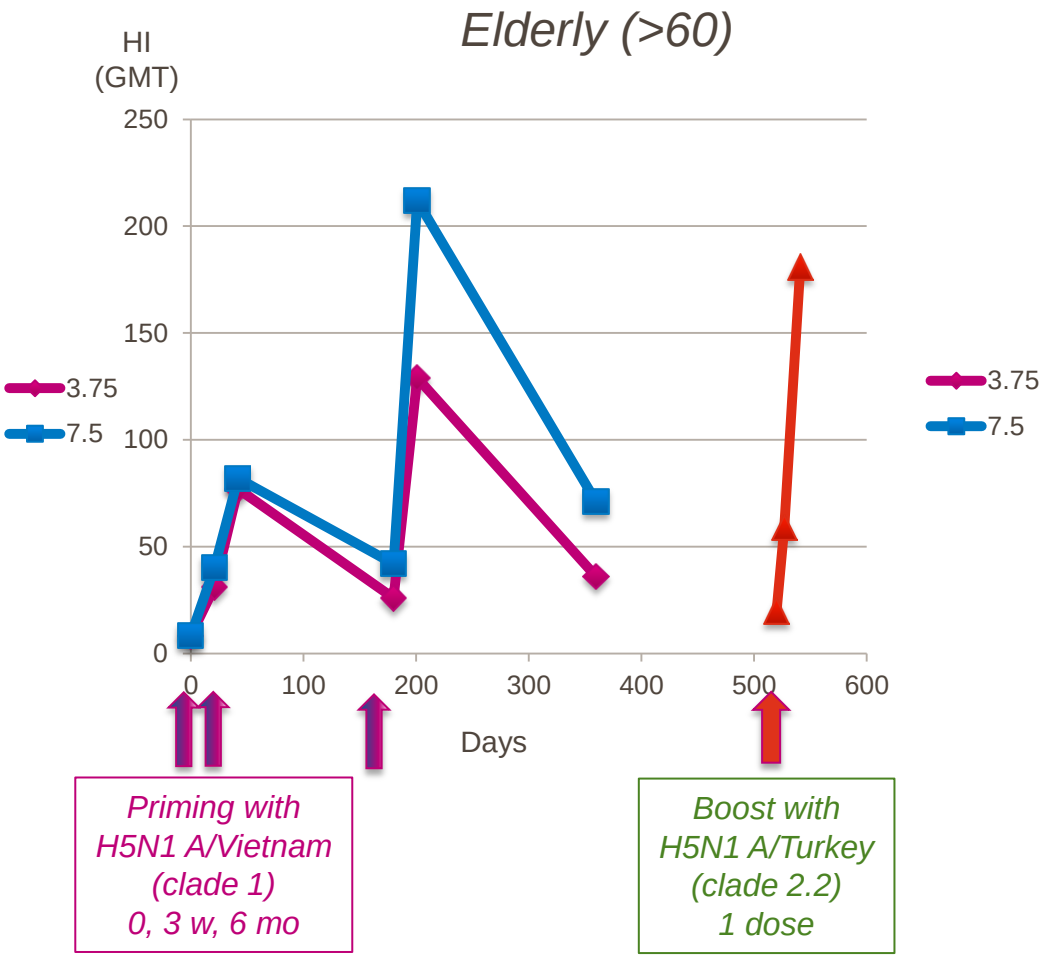
The level of T cell response in > 65y approaches the one observed in younger adults

specific for the three (pooled) influenza vaccine strains

Couch et al, *BMC Infect Dis*, 2014; 14:425

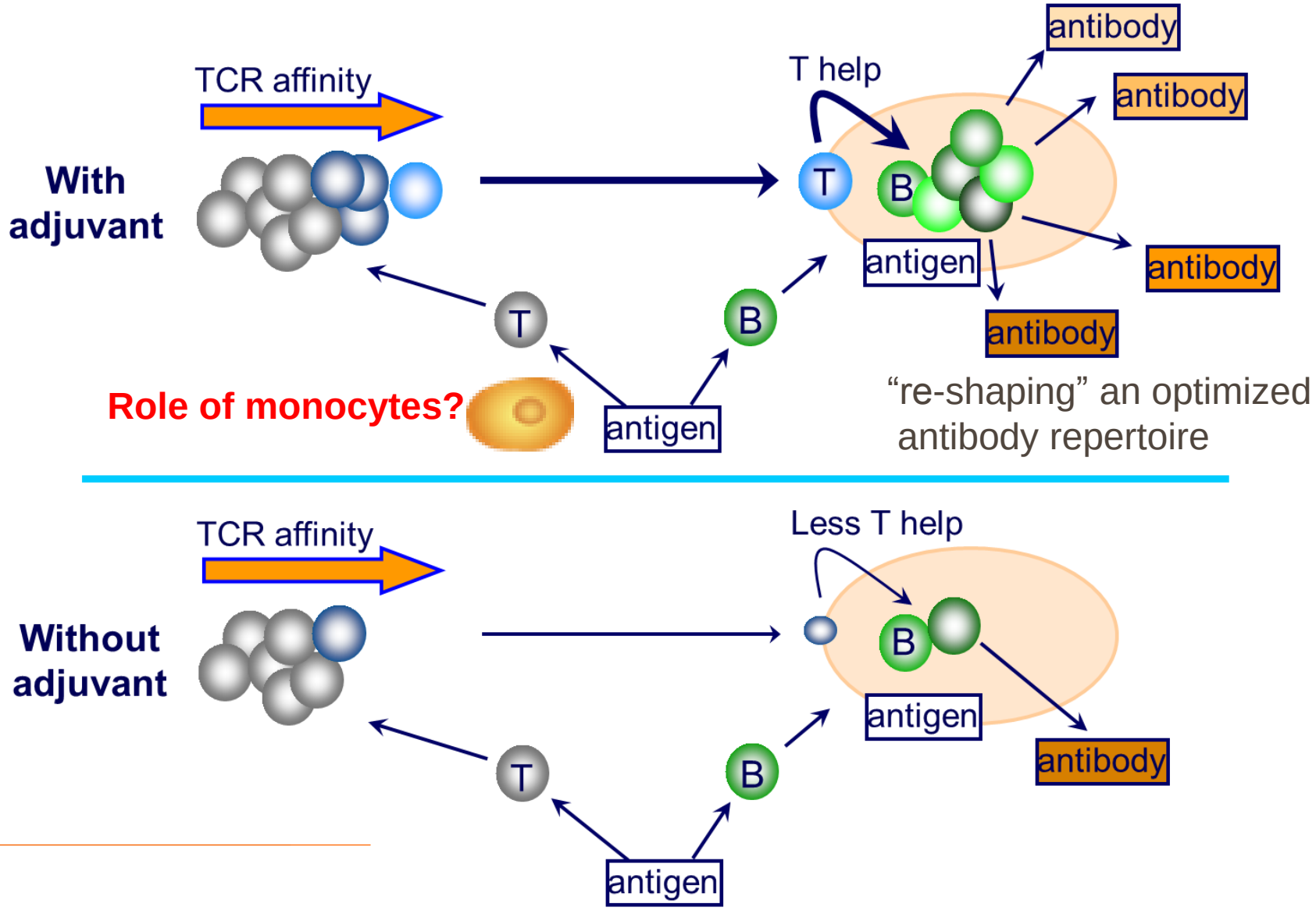
Priming in the Elderly with MF59-adjuvanted H5N1 vaccine and boostability with heterovariant strain





Data from Banzhoff et al, *PLoS ONE* 2009, and Fragapane et al, *Clin Vaccine Immunol 2010*

Potential role of T cell induced by the adjuvanted vaccine in B cell “adaptibility”



Reactogenicity induced by adjuvanted Flu vaccine is generally of lower intensity in the Elderly than in younger adults

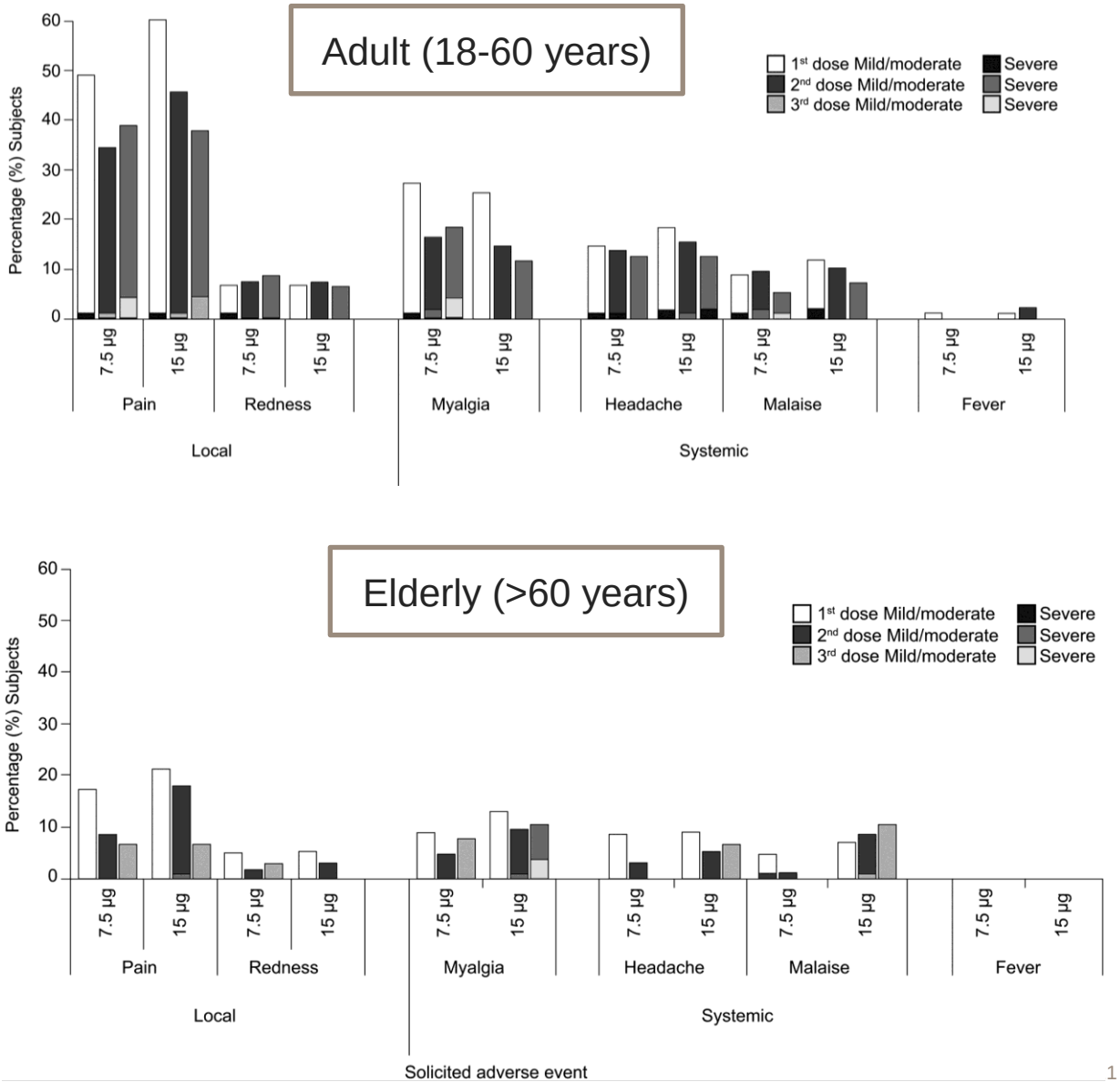
MF59-adjuvanted H5N1 A/Vietnam

If reactogenicity considers as a proxy for "innate activation" :

Due to lower innate stimulation by adjuvant

or

reduced fitness of innate effectors?



Banzhoff et al, *PLoS ONE* **4**:e4384, 2009

Some lessons from adjuvanted flu vaccine studies in the elderly

- Accumulating evidence that adjuvants - mainly o/w emulsions - can increase immunogenicity and efficacy of influenza vaccines in the elderly, across strains

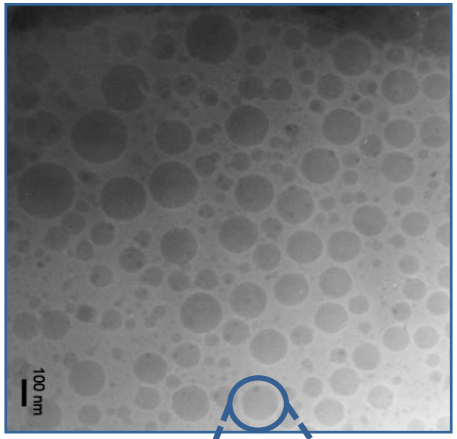
- Efficiency tends to be higher for pandemic *vs* seasonal strains-> highest benefit is when there is a limited established repertoire?

- A potential mechanism involving T_{FH} may overcome this limitation by providing adaptability features to the established repertoire-> Increased breadth of antibody response ? Role of other T cells?

- Activation of innate immunity by adjuvant may be reduced in the elderly (to be confirmed) but nevertheless sufficient to promote T/B-cell activation

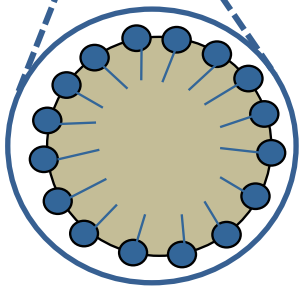
From one adjuvant to another….

Emulsions

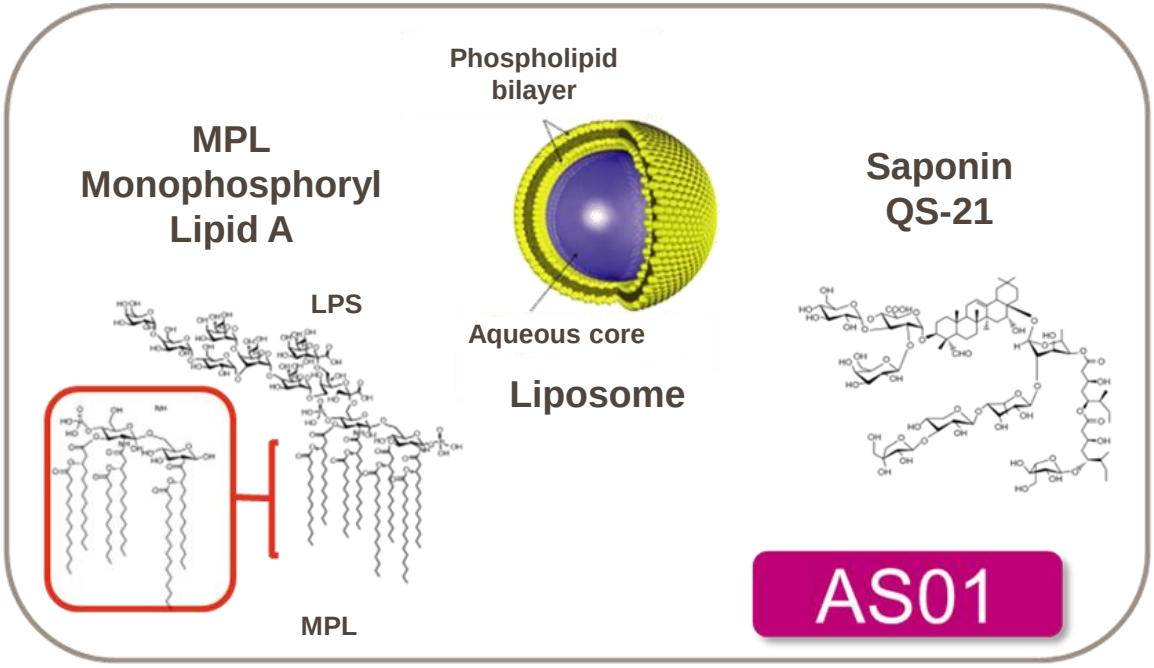


Oil

Surfactant



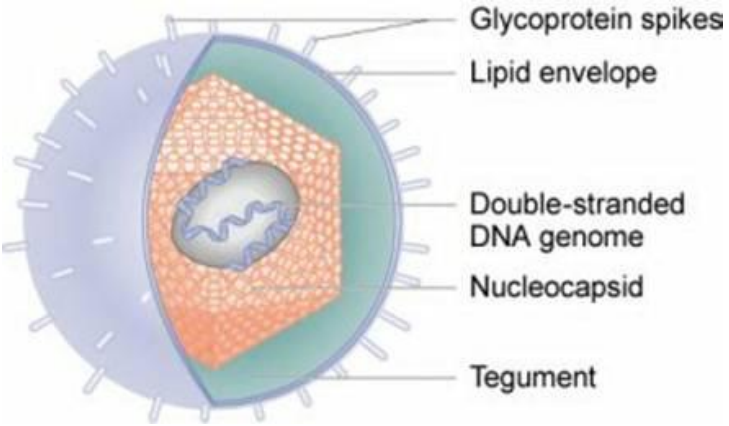
AS01



GSK’s candidate Zoster vaccine antigen

VZV glycoprotein E (gE)

- Highly abundant VZV glycoprotein
- Central role in VZV infection – Essential for virus entry and cell–cell spread
- Expressed in skin lesions and ganglia during HZ episodes
- Target of both humoral and cellular responses



VZV

Results of the HZ/su Ph III efficacy studies

Age range (years)	HZ/su group		Placebo group		VE (95% CI)*
	HZ cases	Incidence (per 1000 person-yrs)	HZ cases	Incidence (per 1000 person-yrs)	
Overall (≥50)	**6**	**0.3**	**210**	**9.1**	**97.2** (93.7-99.0)
50-59	**3**	**0.3**	**87**	**7.8**	**96.6** (89.6-99.3)
60-69	**2**	**0.3**	**75**	**10.8**	**97.4** (90.1-99.7)
≥70	**1**	**0.2**	**48**	**9.4**	**97.9** (87.9-100)

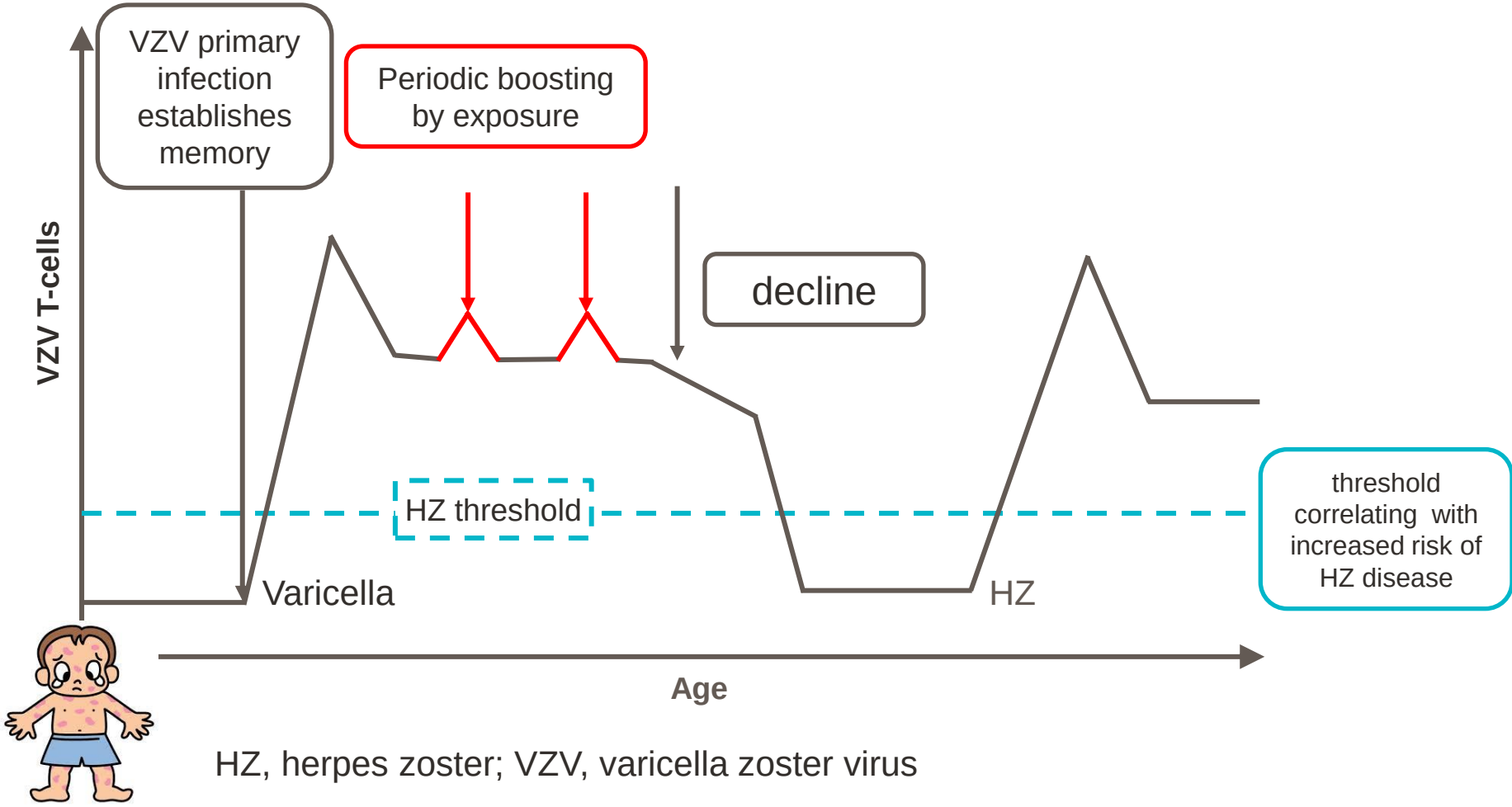
*VE = % vaccine efficacy (Poisson method); CI, confidence interval; p-value = Two sided exact p-value conditional to number of cases, p-value for all comparisons <0.0001

- **HZ/su efficacy appeared to be age-independent (even in people ≥70 years) and did not wane during the study period**

- **No imbalance in the incidence of safety endpoints observed between the HZ/su and placebo groups. Local and systemic reactions to HZ/su are common, large majority being mild-moderate and of short duration.**

Lal H et al. *N Engl J Med* **2015;372:2087-2096.**

HZ risk correlates with a decline in VZV-specific T-cell levels

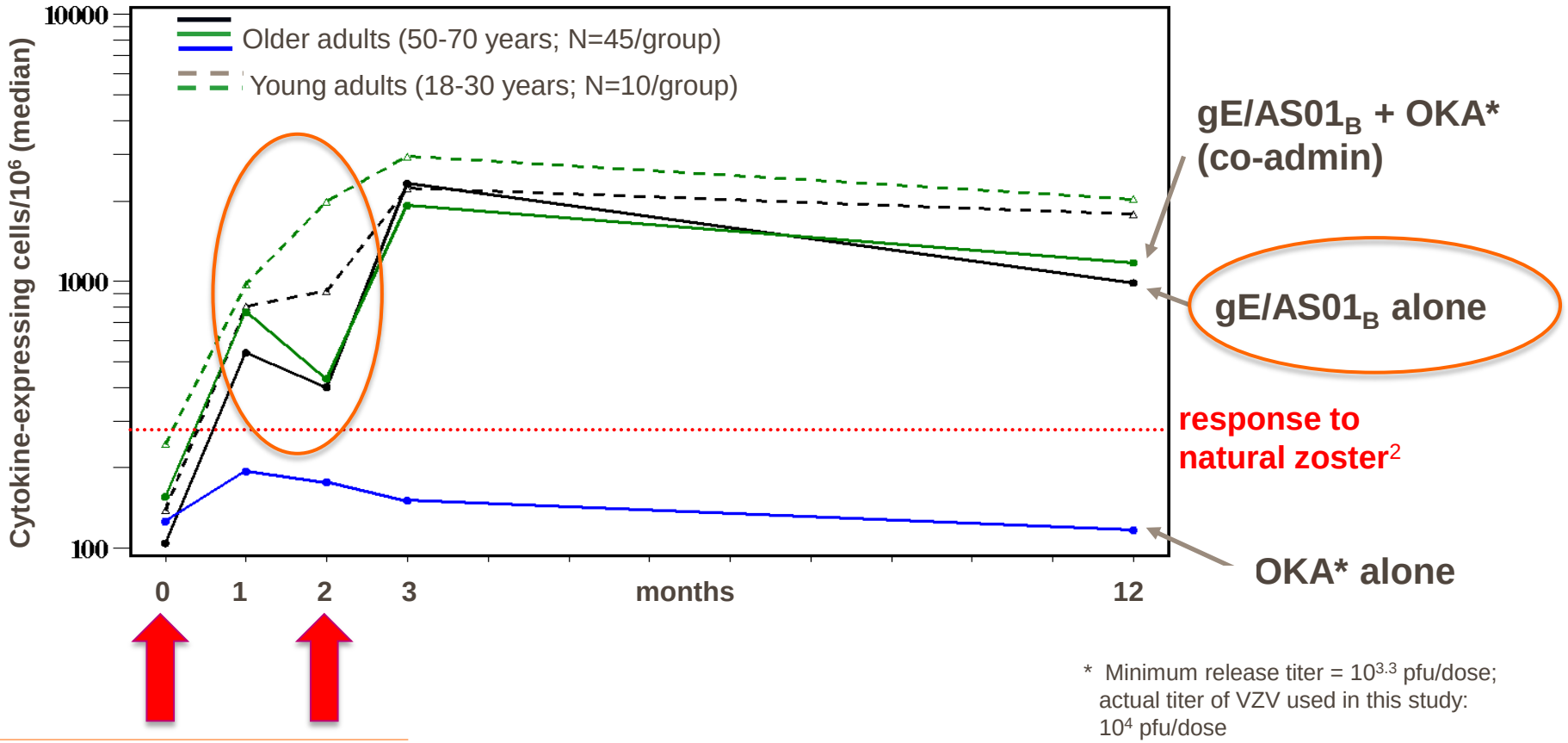


HZ, herpes zoster; VZV, varicella zoster virus

Kimberlin and Whitley. *N Engl J Med* 2007; 356: 1338-43

The ability of AS01 to improve cellular response in the elderly as the basis for its selection for the zoster program

- Immuno PoC study[1]. Open-label, randomized; N=155
- gE/AS01$_B$ and/or VZV live attenuated (OKA) vaccine* administered separately or concomitantly
- 2 doses, Months 0, 2



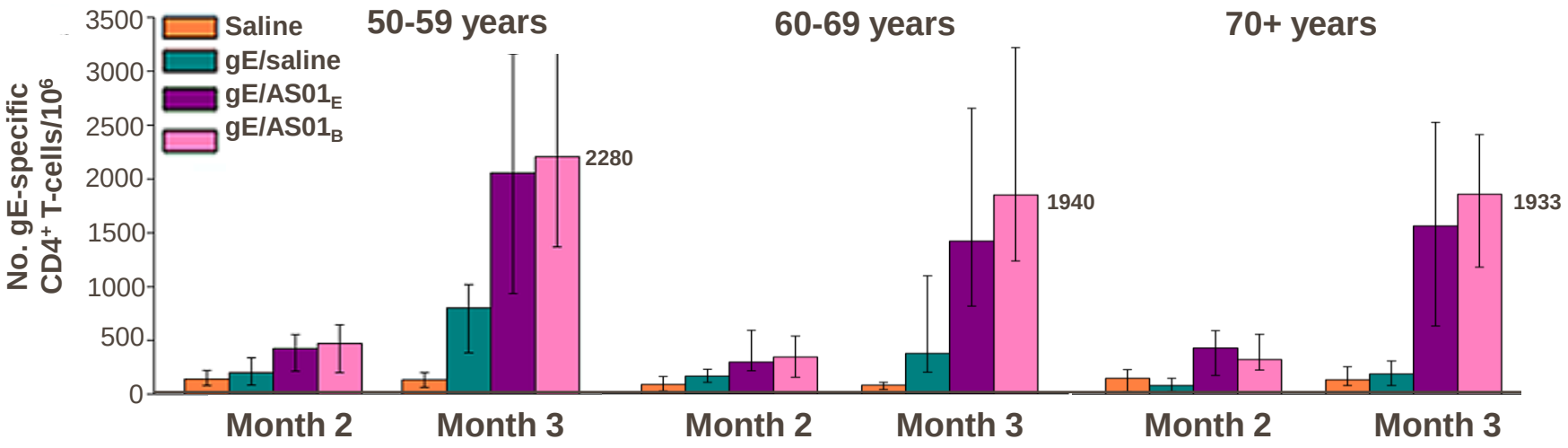
* Minimum release titer = $10^{3.3}$ pfu/dose; actual titer of VZV used in this study: 10^4 pfu/dose

[1] Leroux-Roels G, et al., *J Infect Dis* 2012; 206: 1280-1290

[2] from Mols J et al, J Virol Method 2013

Adjuvant dose selection study

Median gE-specific CD4+ T-cell responses by age



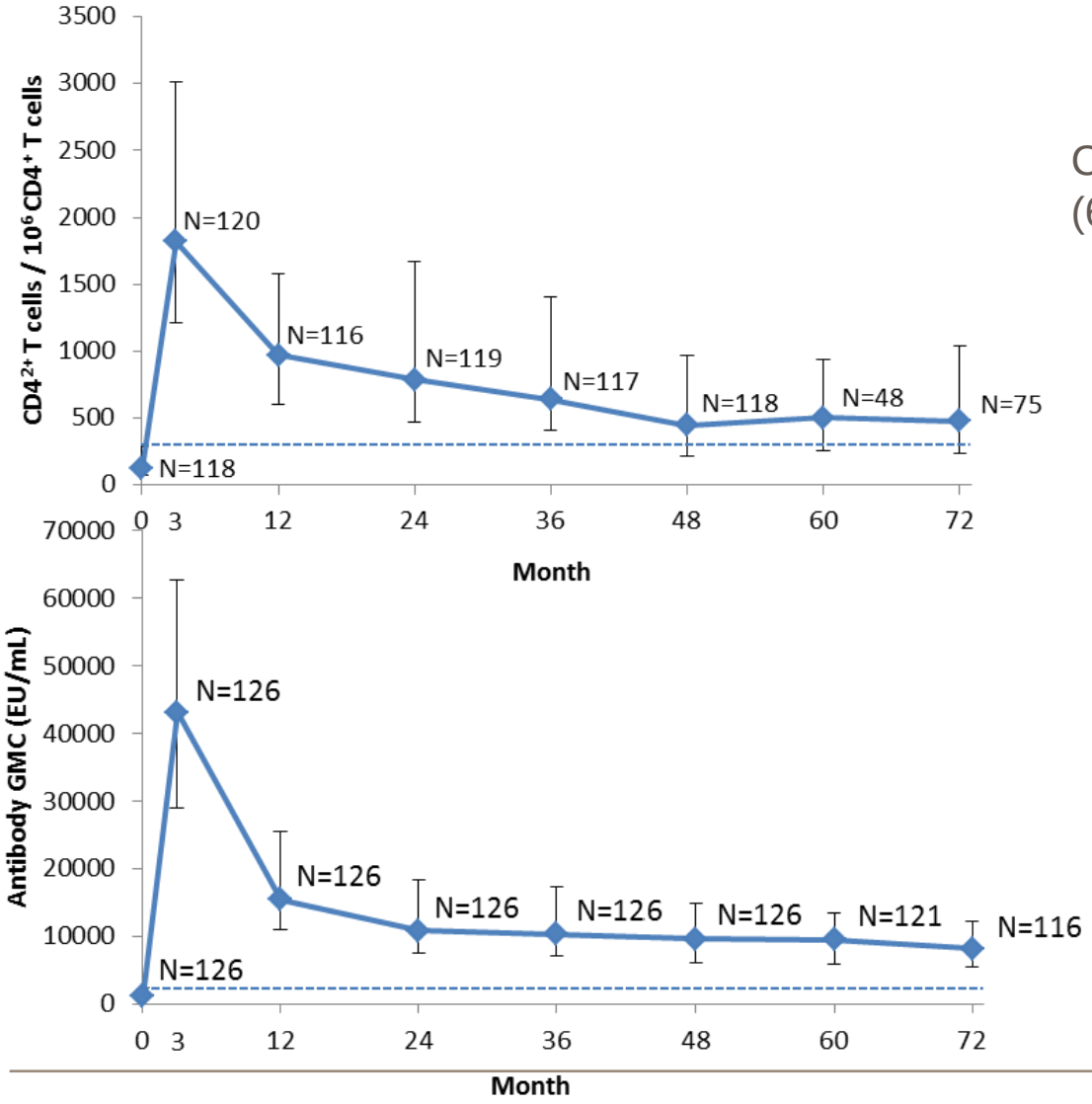
Overall ages: $AS01_B$ induced higher CD4+ T cells than AS01E*
(also true for antibody levels)

AS01B contains 50µg of MPL and QS-21
AS01E contains 25µg of MPL and QS-21

Chlibek et al. *J Infect Dis* 2013; 208:1953-61

***True for separate age strata although statistically significant only for the 60-69y.**

Long-term persistence (6 years) of gE-specific T cells and antibodies



Comparable in the two age groups (60-69 and >70years)

Phase II long-term follow-up:
- >60 yo elderly
- 50 μg gE/AS01$_B$

Chlibek et al. *Vaccine* 2015

Dashed lines: Q3 pre-vaccination value

Chlibek et al. *Vaccine* 2015

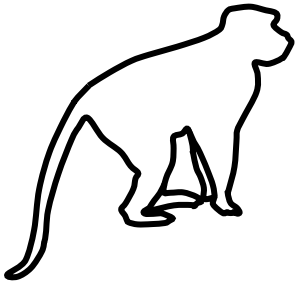
Understanding the mode of action of AS01

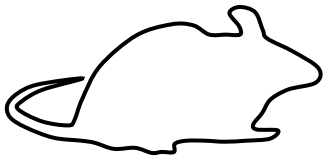
The right model for the right question!

IMPROVE
rational choice/design

Hypothesis generation

Hypothesis validation

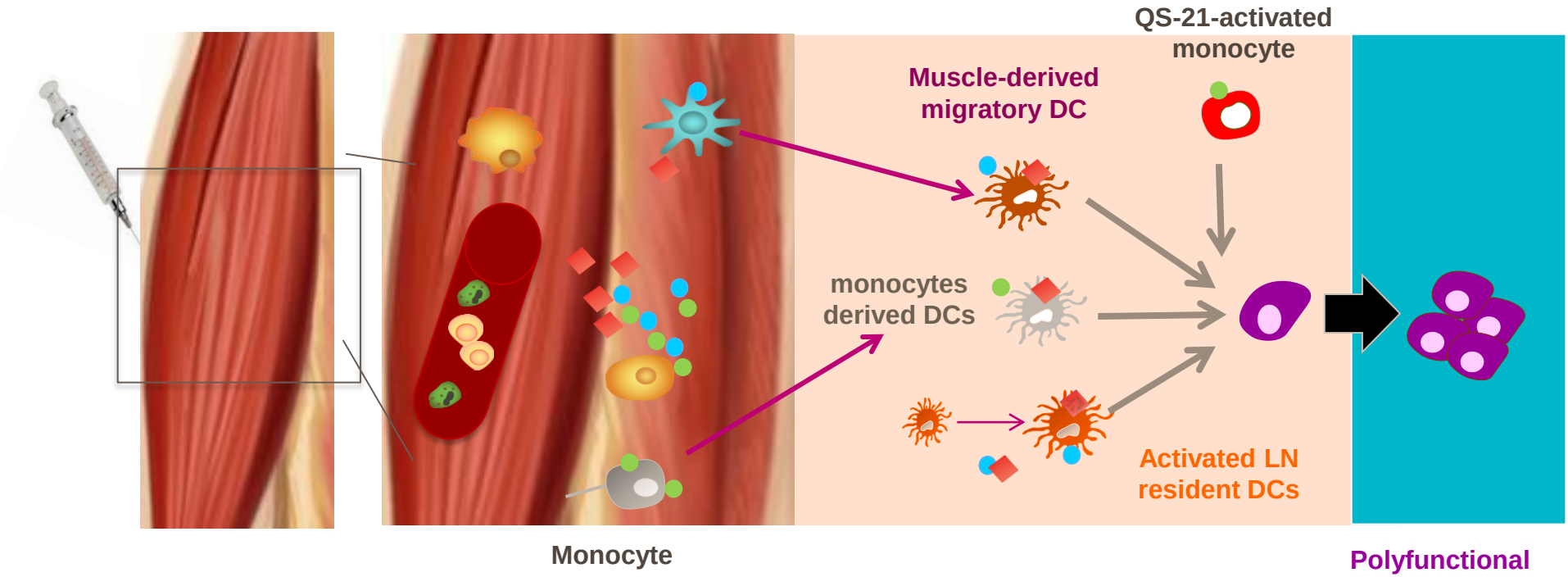




Descriptive work	Mainly Descriptive work	Mechanistic work
Mainly limited to blood signature	Bridge blood signature to local response	Validate cellular and molecular mechanisms

MPL acts on DCs and QS-21 acts on monocytes, broadening the APC population in the LN

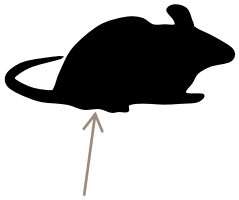
AS01
(MPL + QS-21)



All three types of DCs and activated monocytes may ultimately cooperate to improve the quality of the Ag-specific T-cell response

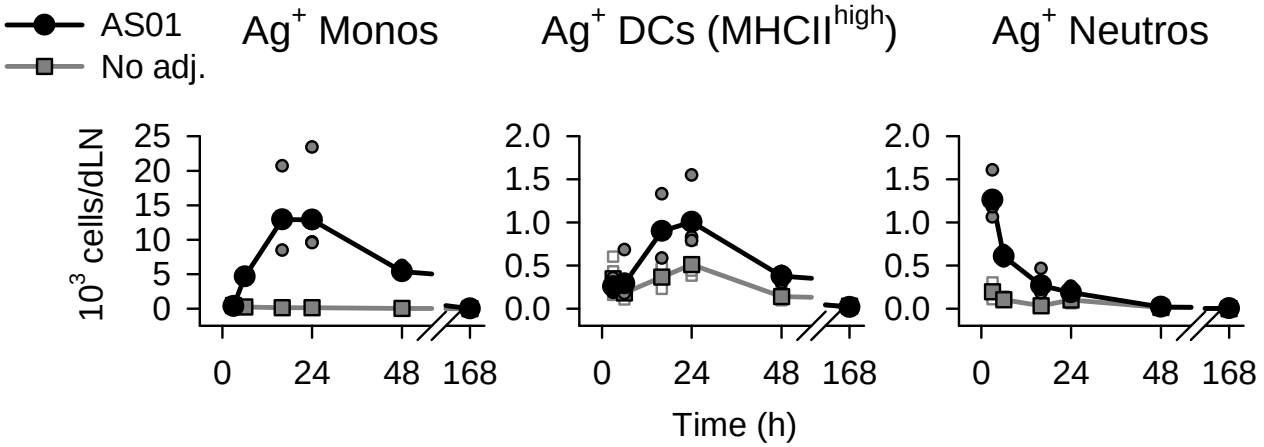
Didierlaurent et al. *J. Immunol* 2014; 193:1920-30

AS01 increases the number of innate cells bearing antigen but does not increase antigen uptake intrinsically

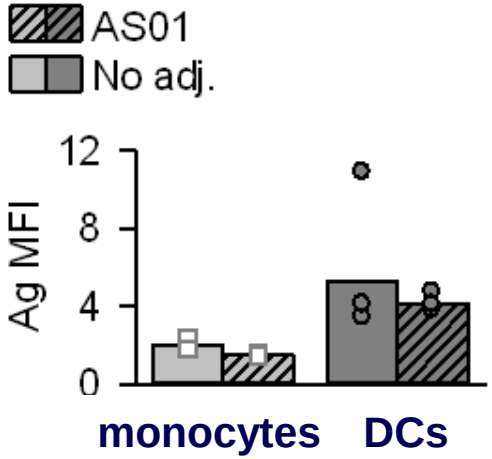


Fluorescent gE
+
AS01

Number of Ag+ cells in the LN



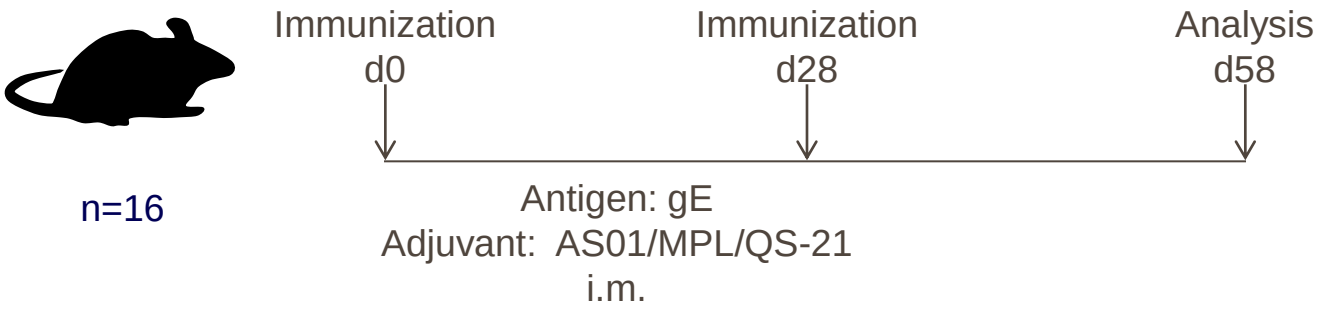
AS01 does not increase antigen uptake in APCs

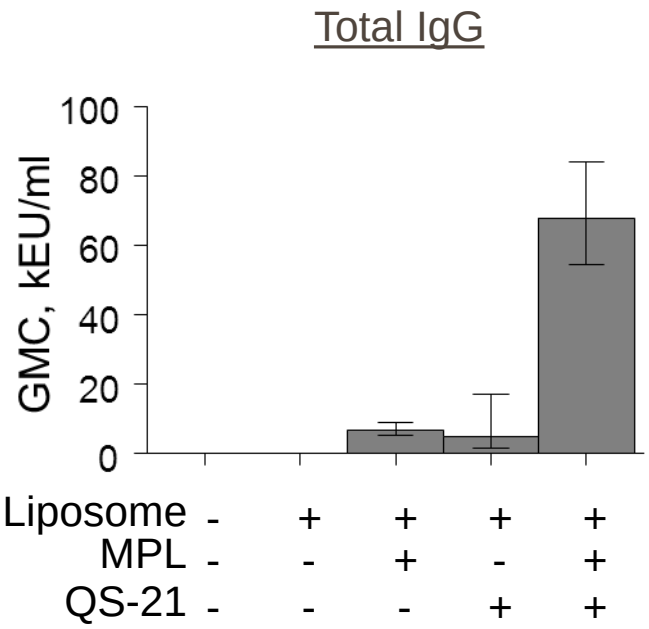


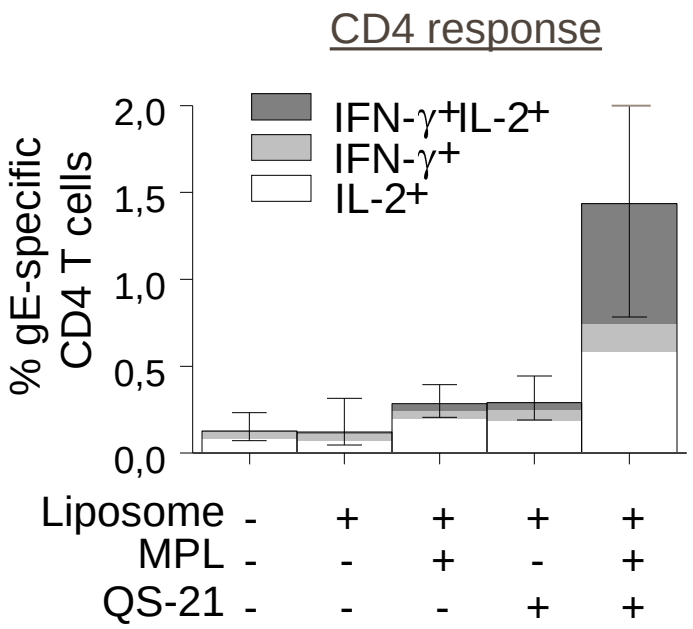
Quantity of antigen per cell

Didierlaurent et al. *J. Immunol*, 2014

Combination of MPL and QS-21 is critical for optimal gE-specific CD4+ T cell response







Dendouga et al, Vaccine 2012; 30:3126-35

Perspectives

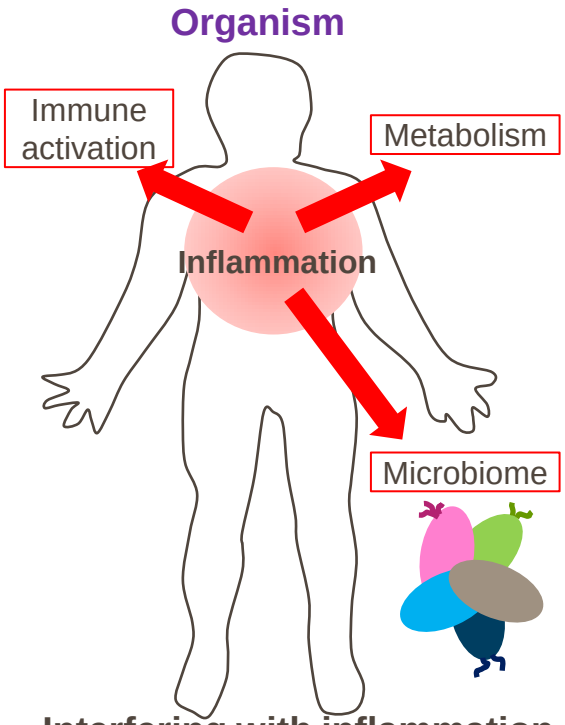
- Understanding the mode of action of adjuvanted vaccines in older adults and potential differences with younger individuals will help to:
  - ❑ Define key elements of innate response involved and whether some should be preferentially targeted (monocytes, NK?)
  - ❑ Ability of adjuvant to genuinely prime de novo response or restore/boost quality/fitness of pre-existing pool of antigen-specific T and B cells
  - ❑ Extend use of adjuvants to target other diseases in the elderly population (Strep, Nosocomial, RSV…)- Zoster-related specificities?

- “Elderly prone” Adjuvants with specific features, targeting of specific innate cells? Need for new adjuvants?

- Combination with other vaccine delivery or other approaches (mTor)?

Vaccine responsiveness and adjuvants….

- BOTH properties antigen-specific memory response AND <u>inflammatory status</u> may condition vaccine responsiveness, in particular to adjuvanted vaccines
- Adjuvant are likely dependent on “innate responsiveness/fitness” in the elderly considering their known mode of action



Some level of inflammation may be needed to overcome hypo-responsiveness (not enough with alum-based vaccine, achieved with AS01)

<u>Or</u>

Baseline dysregulated pathways (inflammaging) should be modulated to alleviate hyporesponsiveness

From Alter and Sekaly, Vaccine 2015; 33supp2: B55-9

Acknowledgments

AS01 MOA work
Margherita Coccia
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Bruce Innis
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