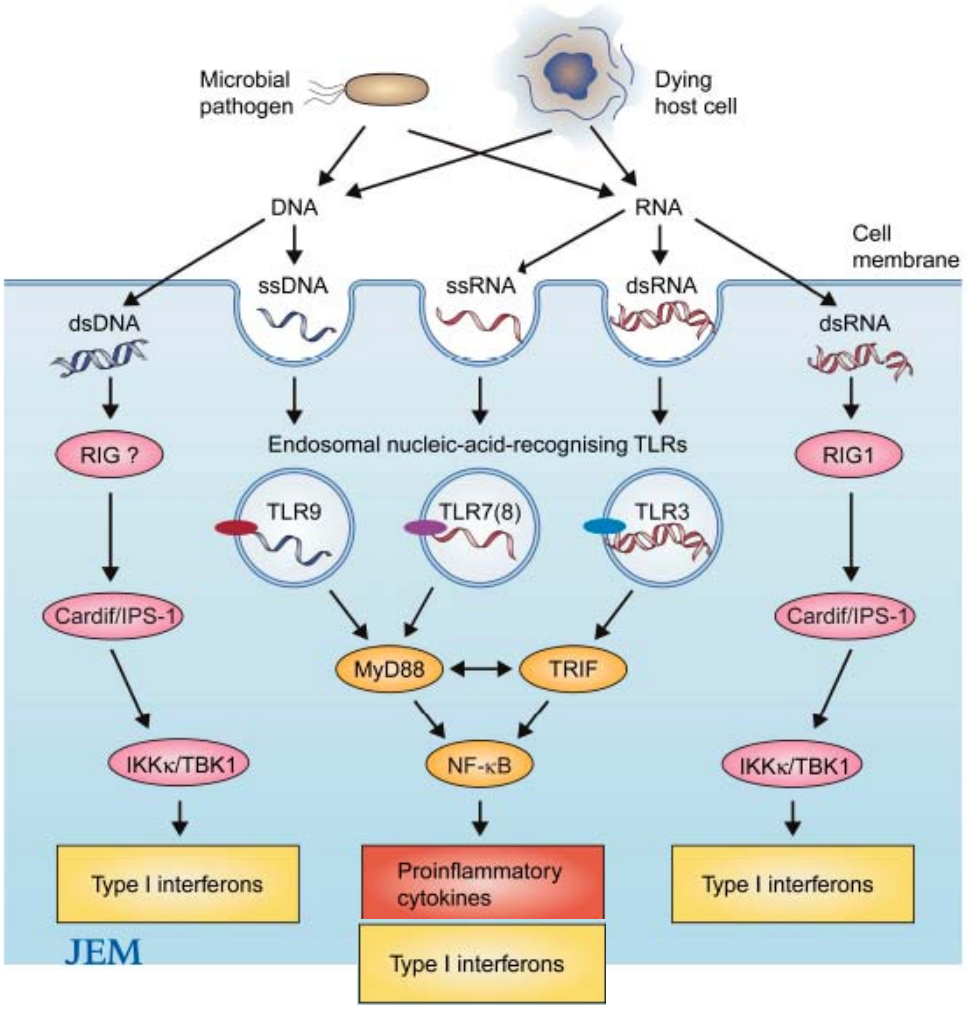
Development of TLR Oligonucleotide Agonists as Vaccine Adjuvants

AIDS Vaccine'07
Seattle WA
August 21, 2007

Heather L. Davis, PhD
SVP Pharmacology R&D
Coley Pharmaceutical Group

COLEY

Nucleic acid TLR agonists



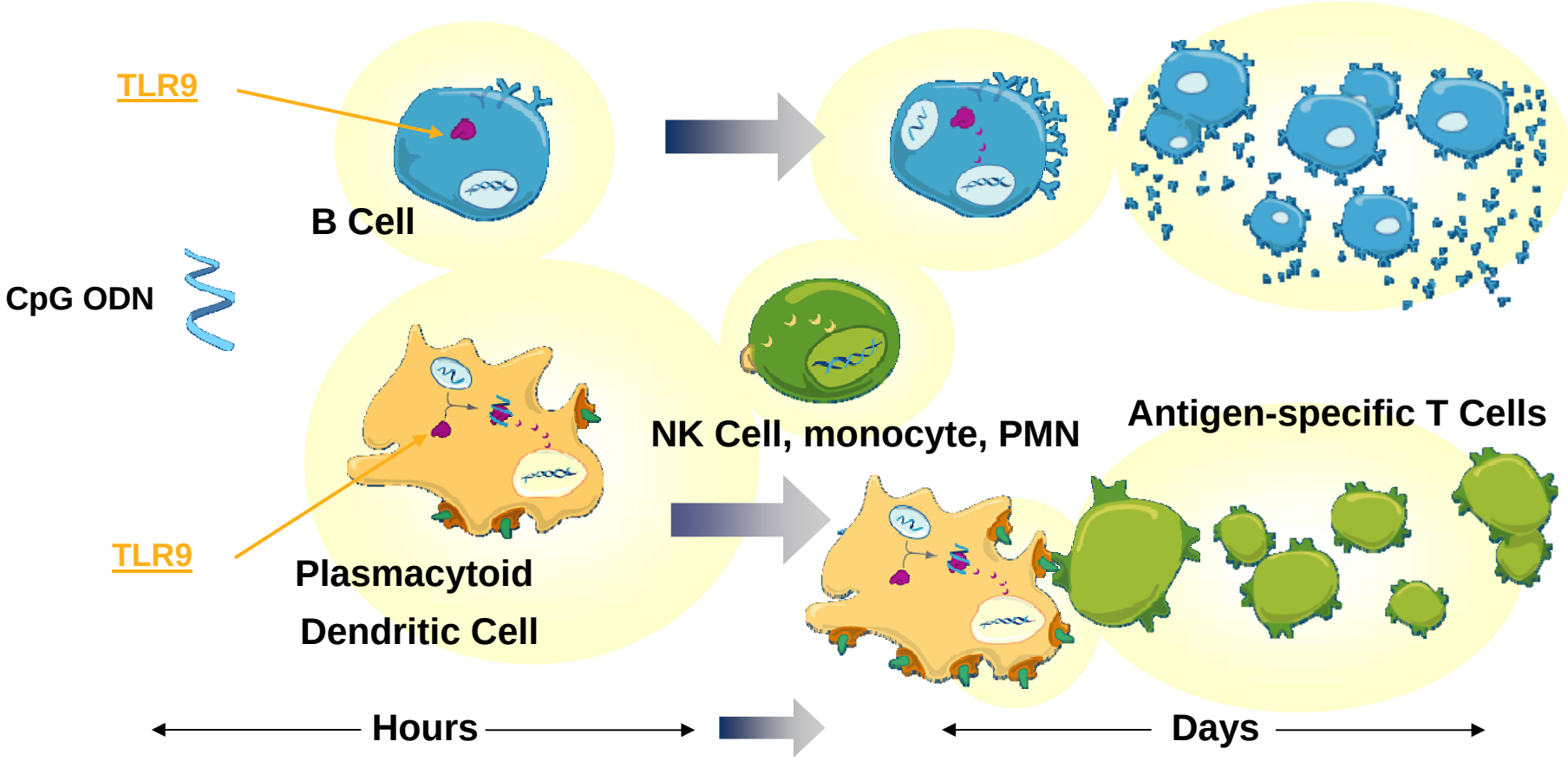
	Natural	Synthetic
TLR 3	dsRNA	Poly rI:rC
RIG1	dsRNA	5'-pppG
TLR7/8	ssRNA	U-rich ORN
TLR9	ssDNA	CpG ODN
RIG?	dsDNA	Poly dA:dT

Modified from Wagner and Bauer JEM 2006

CpG ODN TLR9 Agonists as Vaccine Adjuvants

CpG TLR9 agonist: MOA as vaccine adjuvant

Early innate immune activation leads to later induction or enhancement of adaptive immunity

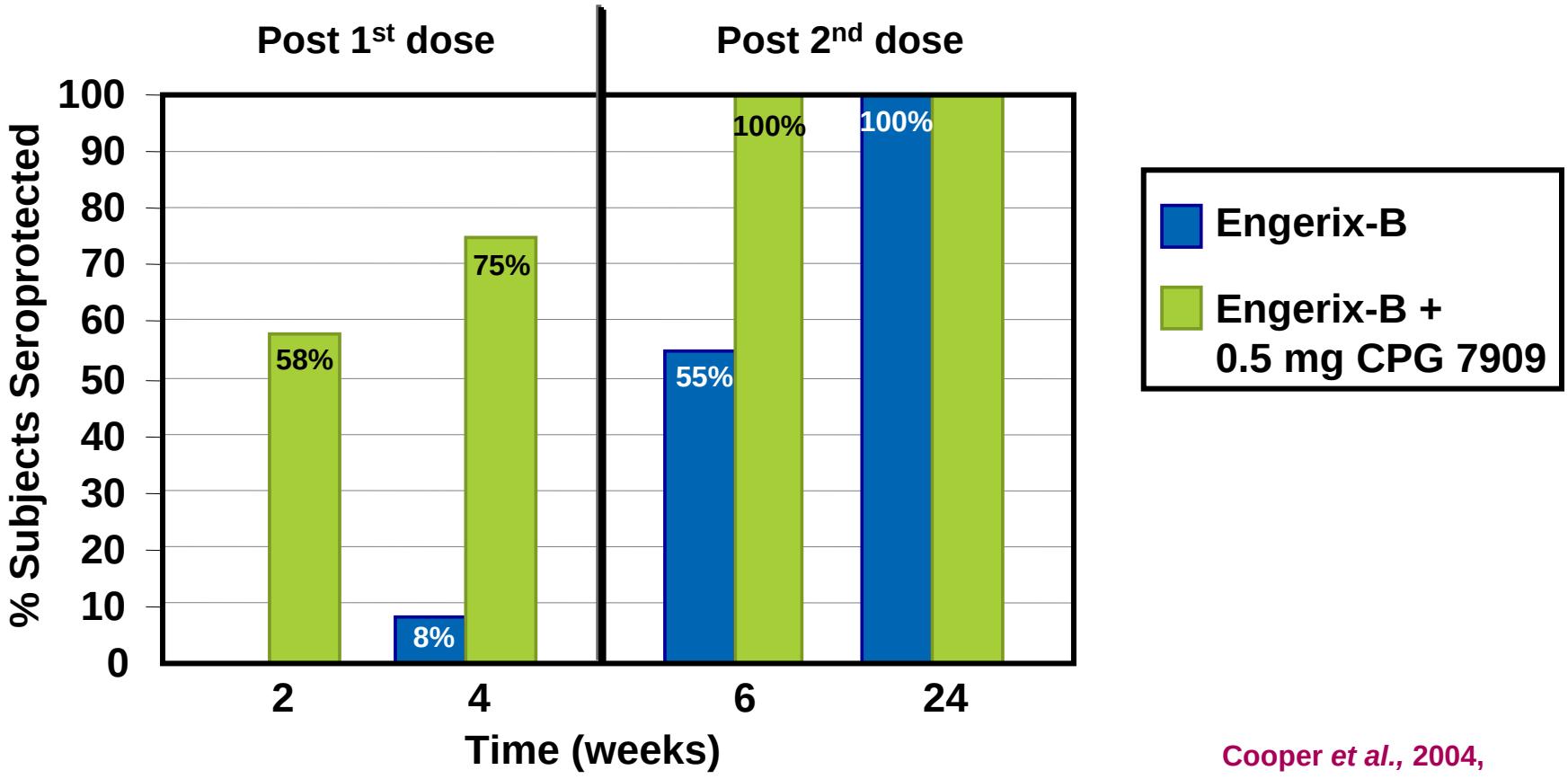


CpG ODN as a Vaccine Adjuvant: Summary of Results from Animal Data

- **Effective with virtually any antigen**
  - Peptides, soluble proteins, VLPs, whole killed, live attenuated
  - Polysaccharides must be formulated or conjugated
  - Weak antigens best co-formulated or conjugated
- **Strong synergy with most other adjuvants / delivery systems**
  - Retains strong Th1 effect of CpG
- **Strong Ab and Th1 CMI responses**
  - Most Th1 of 19 adjuvants compared with tumor antigen in mice
- **Faster seroconversion allows earlier boost**
- **Overcomes hypo-responsiveness**
  - Neonates (even with maternal Ab) and aged animals
  - Genetic hypo-responsiveness (orangutans)
- **Allows reduced antigen doses (10-1000x dose sparing)**
- **Strong mucosal immunity with IN or oral delivery**

V001: Engerix-B + CPG 7909 in normal volunteers

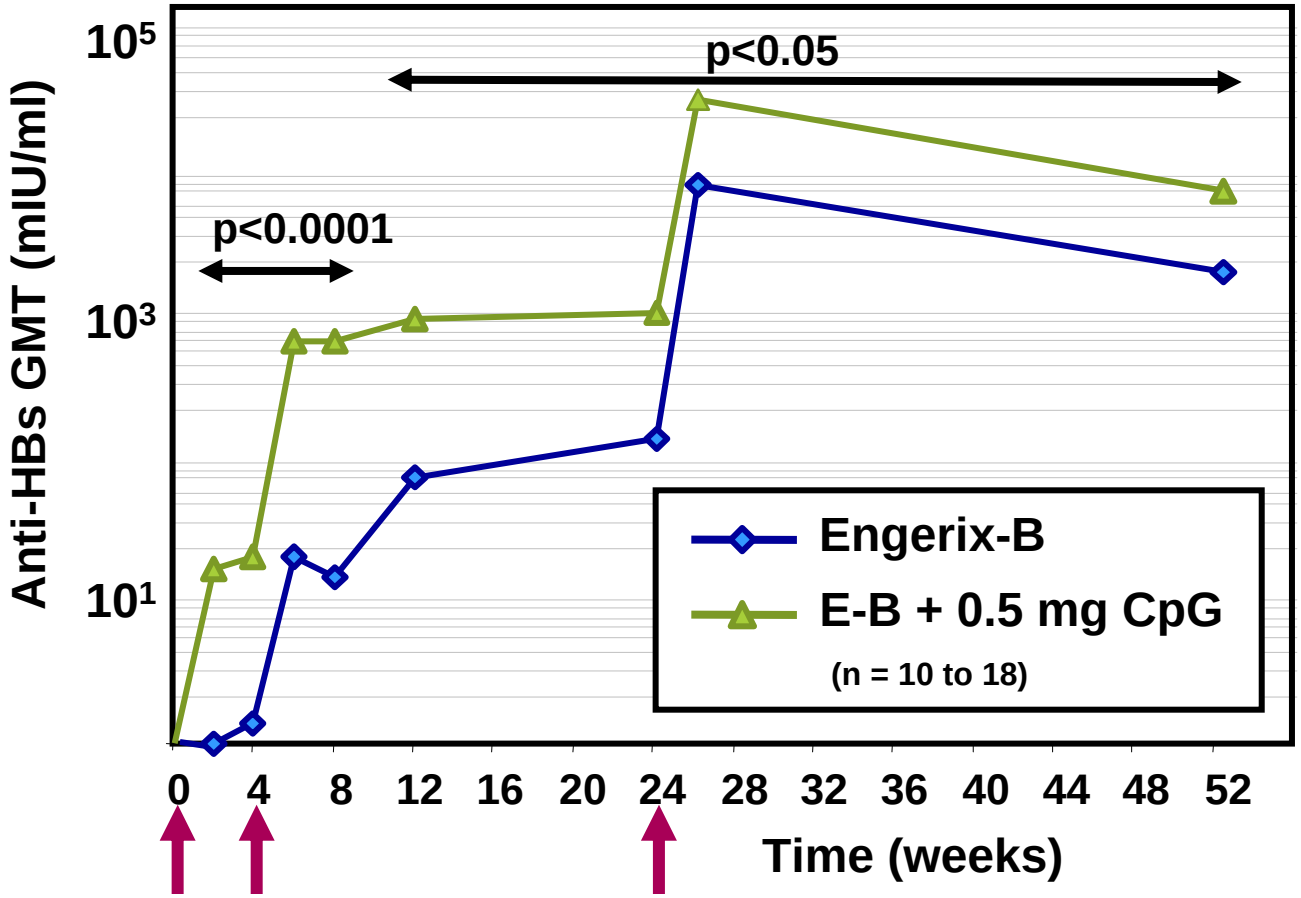
Proportion of subjects with seroprotective titers (≥10mIU/ml)



Cooper *et al.*, 2004, J Clin Immunol 24: 693-701

V001: Engerix-B + CPG 7909 in normal volunteers

Anti-HBs GMT (ITT/Attrition population)

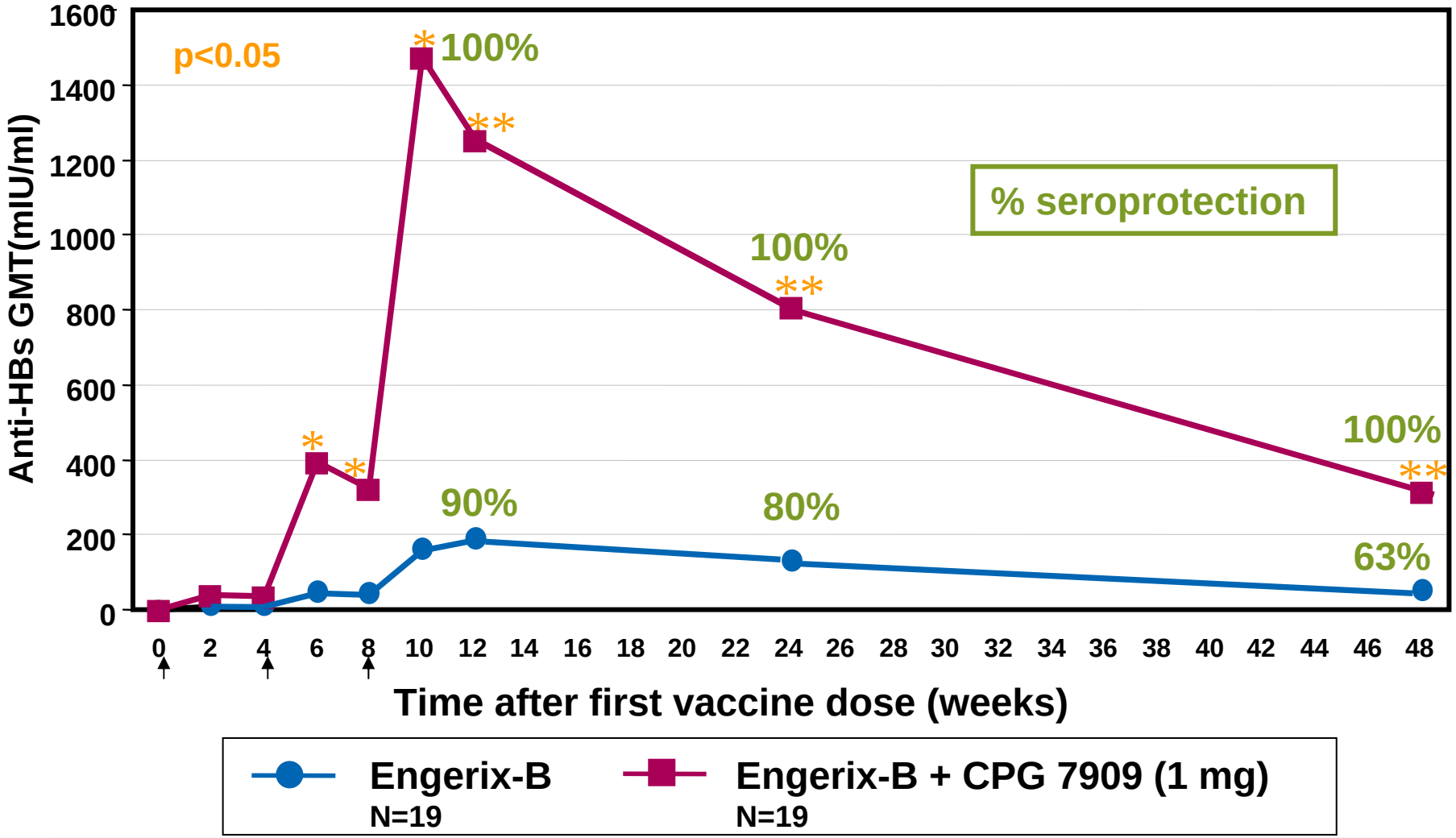


Antibodies also had significantly greater avidity for HBsAg in subjects receiving 0.5 mg CPG 7909

[Siegrist et al., Vaccine 2004, 23: 615-22]

Cooper *et al.*, 2004,
J Clin Immunol 24: 693-701

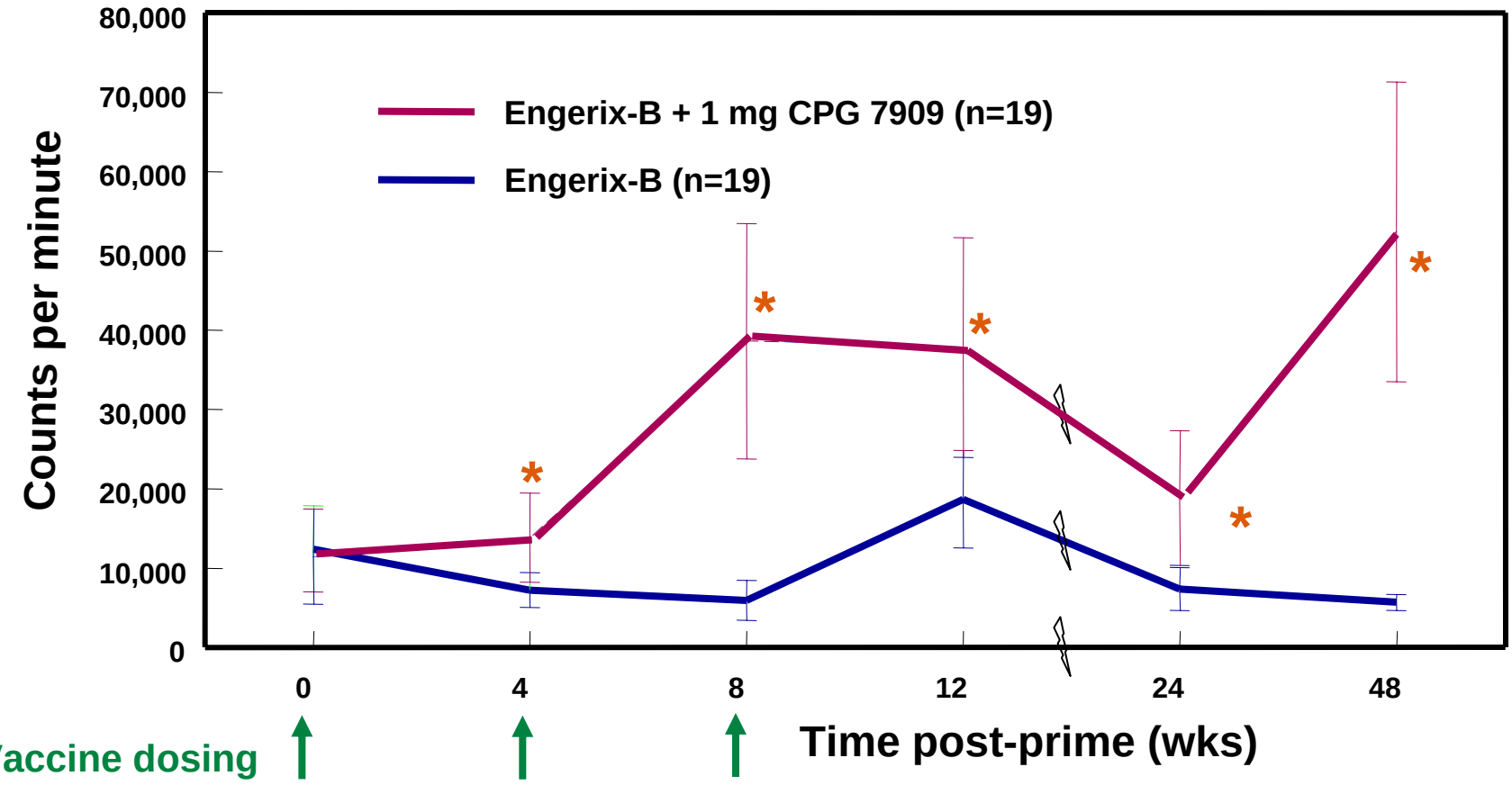
V004: VaxImmune enhances anti-HBs Ab responses in HIV-infected subjects



Cooper et al. AIDS 2005

V004: Engerix-B + CPG 7909 in HIV+

CPG 7909 enhances HBsAg-specific lymphoproliferative responses



* Repeat Measures ANOVA week 4, 8, 12 p=0.0039, n=38
week 24, 48 p=0.0271, n=38

Other clinical results with CPG 7909 as vaccine adjuvant

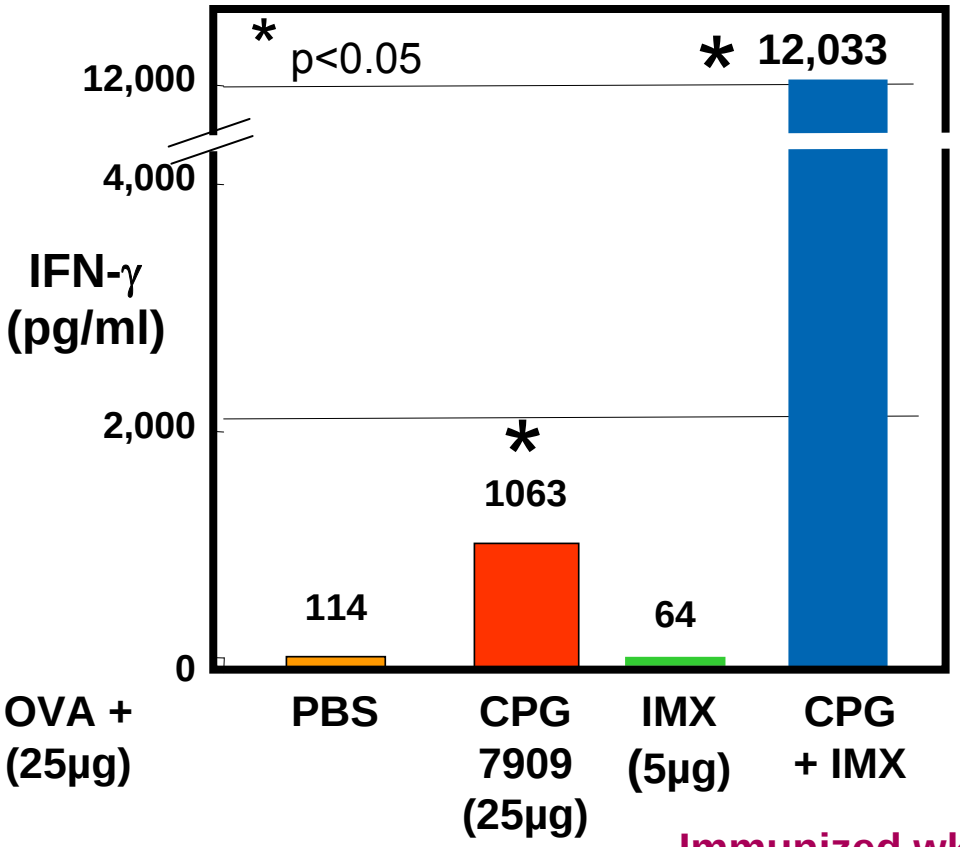
- **Anthrax vaccine (Phase I, NHV)**
  - 3 doses of AVA (alum absorbed) + CPG 7909
  - ~10-fold higher titers IgG and neutralizing Ab
- **Candidate malaria antigens (2 x Phase I, NHV)**
  - *P. falciparum* AMA-C1 or MSP-1_{42} + alum + CPG 7909
  - 5-10-fold higher Ab and enhanced *in vitro* parasite Growth Inhibition Assay (GIA)
- **Tumor antigens**
  - A number of pilot or Phase I studies with peptides or recombinant antigens showed potent T cell responses with CPG-containing formulations

Summary: Potential of CpG ODN TLR9 agonists as adjuvants to HIV vaccines

- **Clinical data with several antigens shows enhanced antigen-specific immunity**
  - **Humoral: kinetics, magnitude, avidity and longevity**
    - **All vaccines also included alum**
  - **Cell-mediated: induces potent CD4+ and CD8+ T cell responses with tumor antigens**
    - **Best results with more complex formulations**
- **Overcomes hyporesponse in HIV+ patients**
- **Well tolerated**
- **Formulation optimization could further enhance responses**
- **>35 ongoing clinical trials**
  - **2 phase III vaccines: HBV prophylactic, MAGE-3 for NSCLC**

OVA/CpG/IMX vaccine in mouse B16-OVA melanoma model

Improved anti-tumor responses correlate with T cell responses



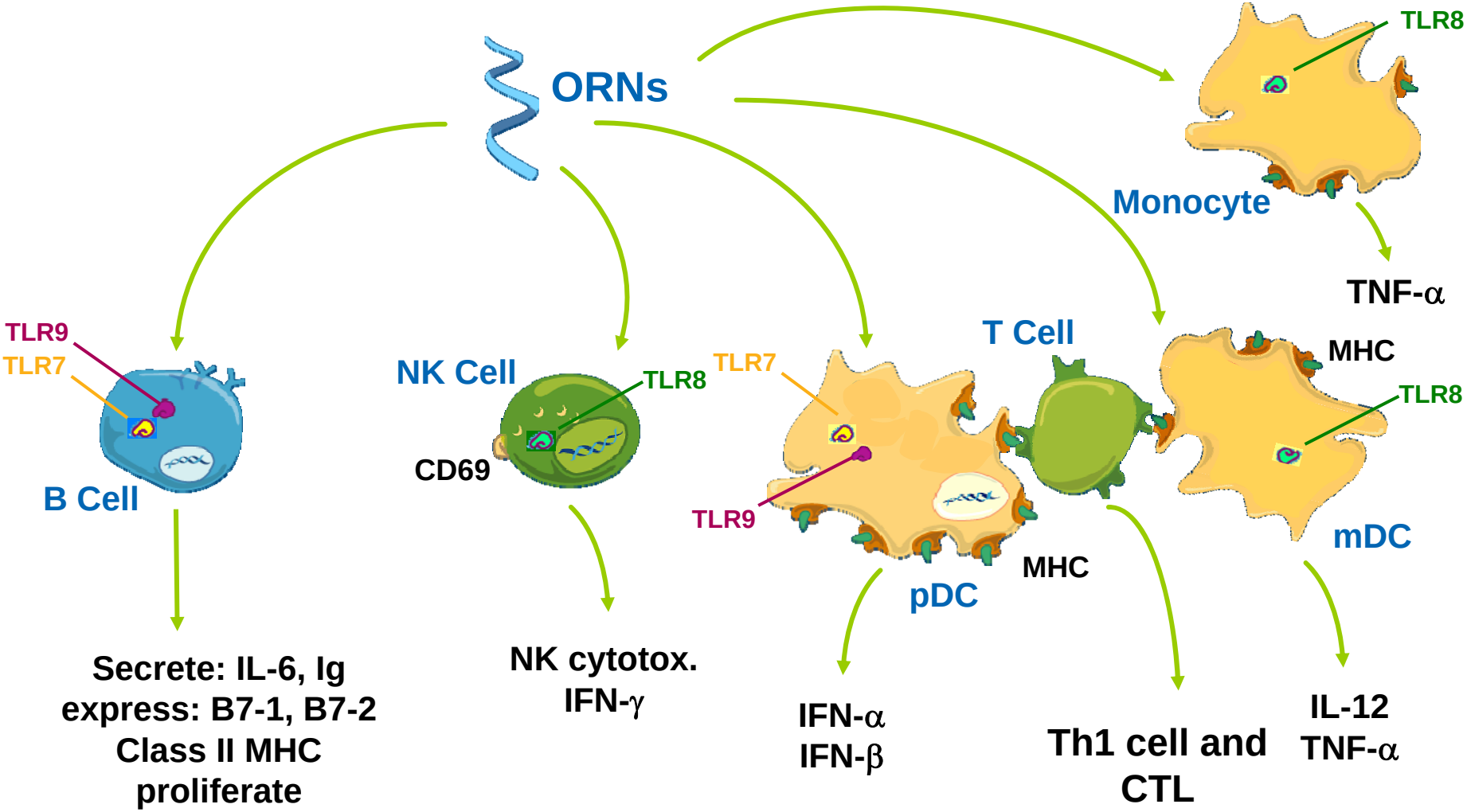
Adjuvant (n=5)	Controlled disease (<500 mets)
PBS	0%
CpG	60%
IMX	40%
CpG + IMX	80%

Immunized wks 0&3, challenge wk4
Splenocytes @ wk8 restimulated with OVA @ 500 µg/ml
No IFN-gamma detected in non-vaccinated animals

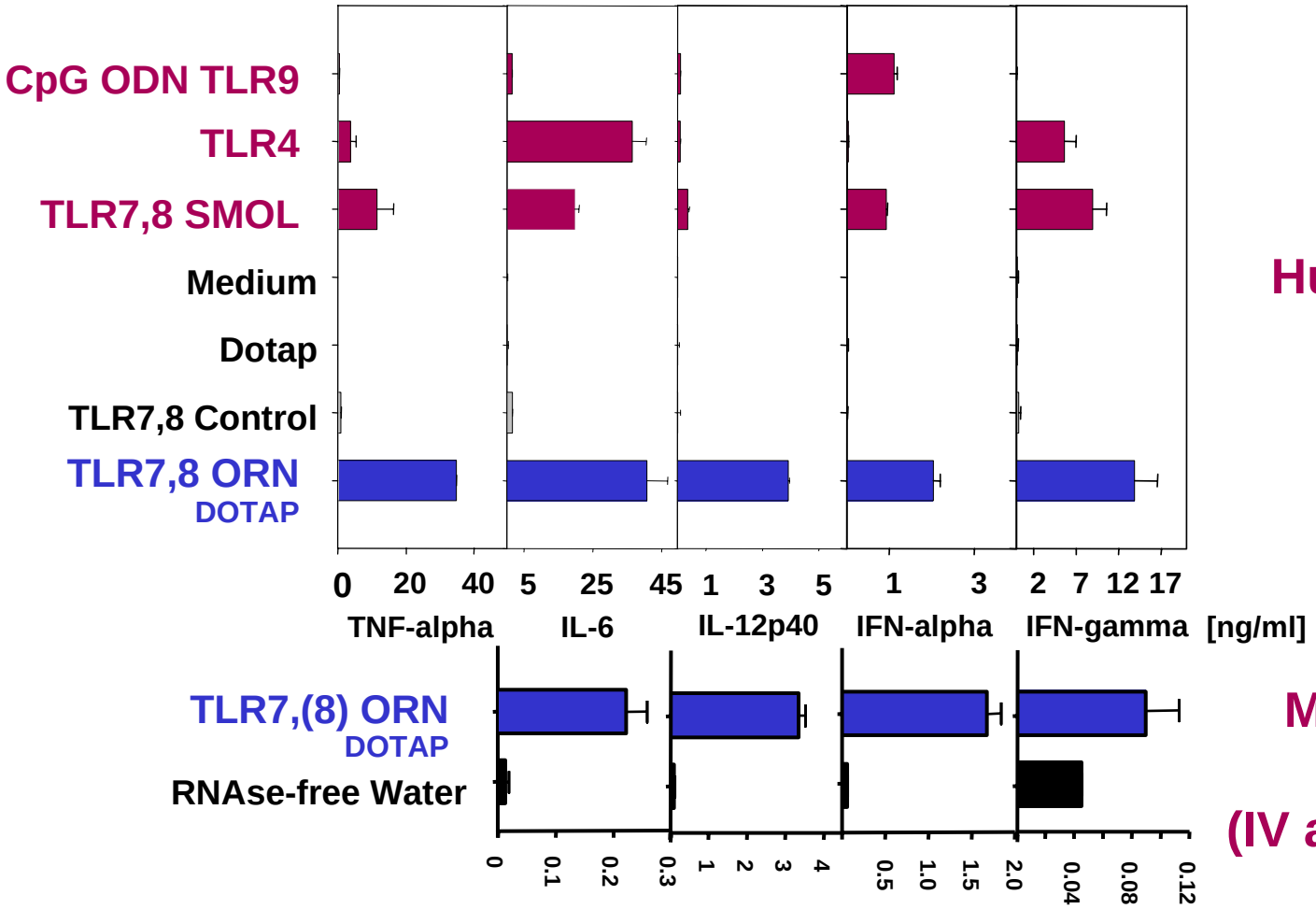
ORN TLR7, TLR8 Agonists as Vaccine Adjuvants

Immunological effects of ORN

Broad cellular expression of TLR7 + TLR8



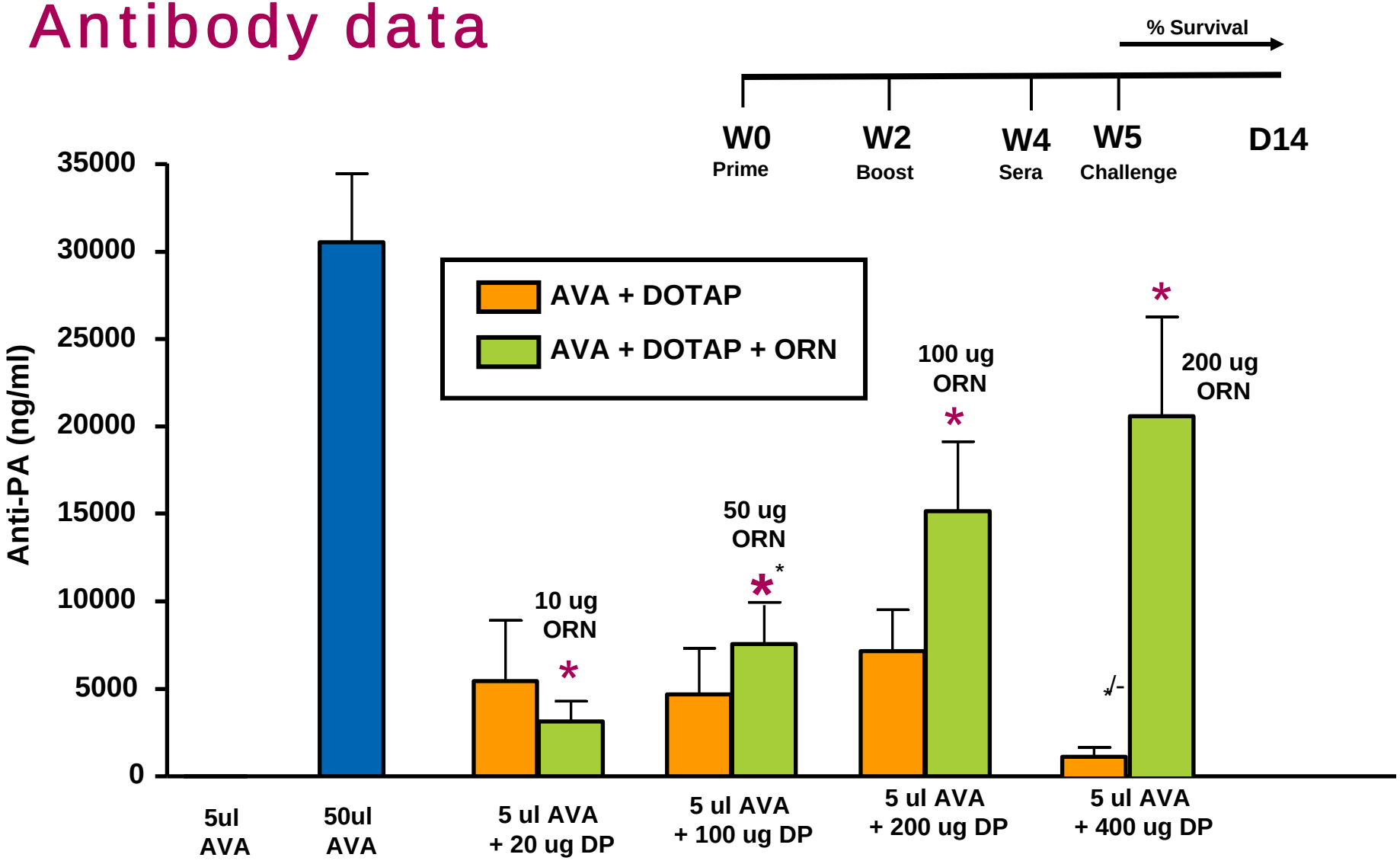
TLR7,8 ORN agonists stimulate broad immune modulatory profile



Human PBMC
In vitro

Mouse serum
In vivo
(IV administration)

TLR 7,8 ORN with anthrax vaccine
Antibody data



Development of TLR Oligonucleotide Agonists as Vaccine Adjuvants

AIDS Vaccine'07
Seattle WA
August 21, 2007

Heather L. Davis, PhD
SVP Pharmacology R&D
Coley Pharmaceutical Group

COLEY