The Westmead Institute
FOR MEDICAL RESEARCH

Progress with Herpesvirus vaccines

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Declarations

- Chair, Publications committee, GSK Shingrix ZoE50 and ZoE70 trials
- Member, Global Adult Vaccine Advisory Board, Merck
- Chair, Zostaxax Advisory Board,Seqirus/ BioCSL

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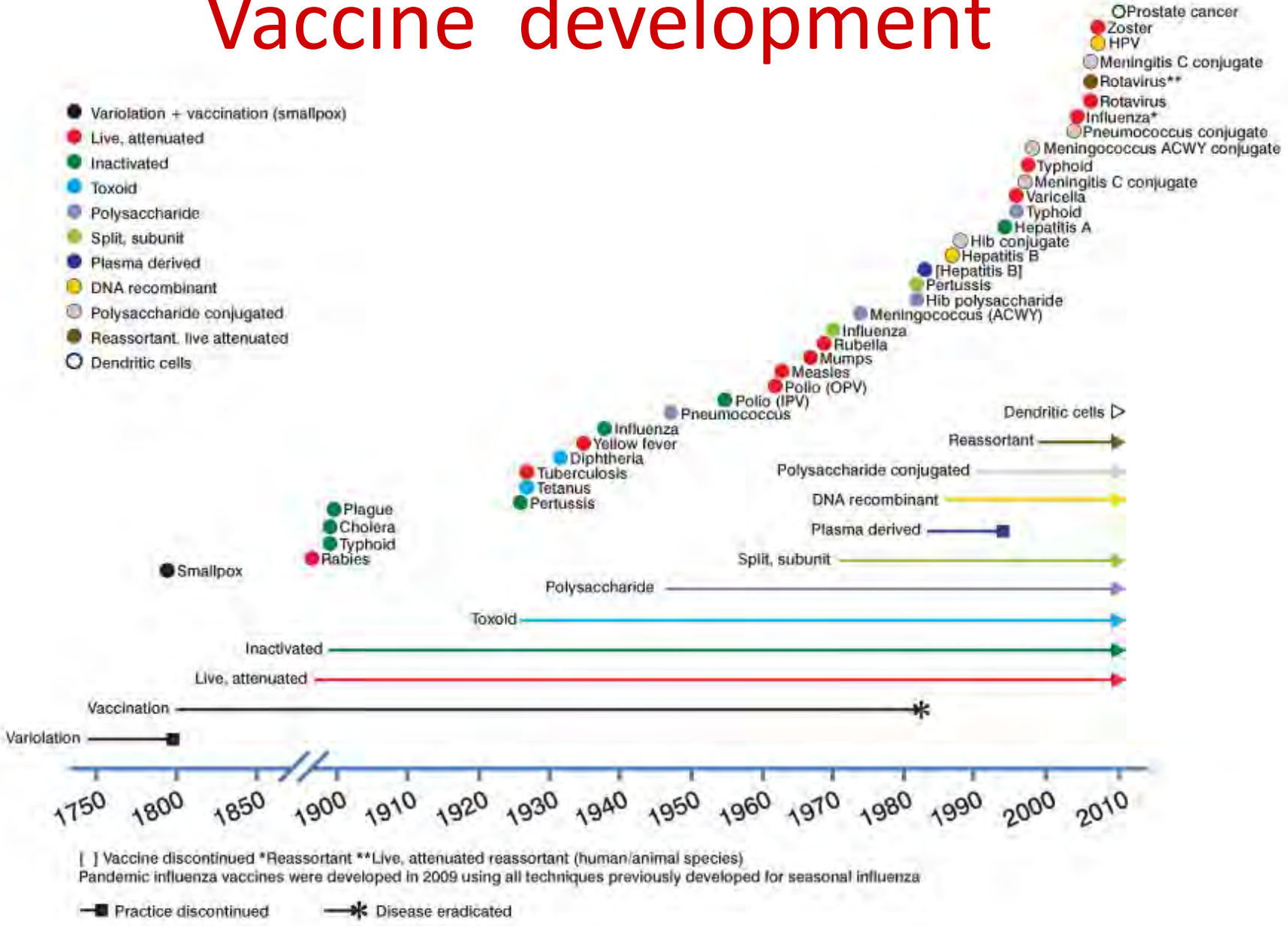
Vaccine development



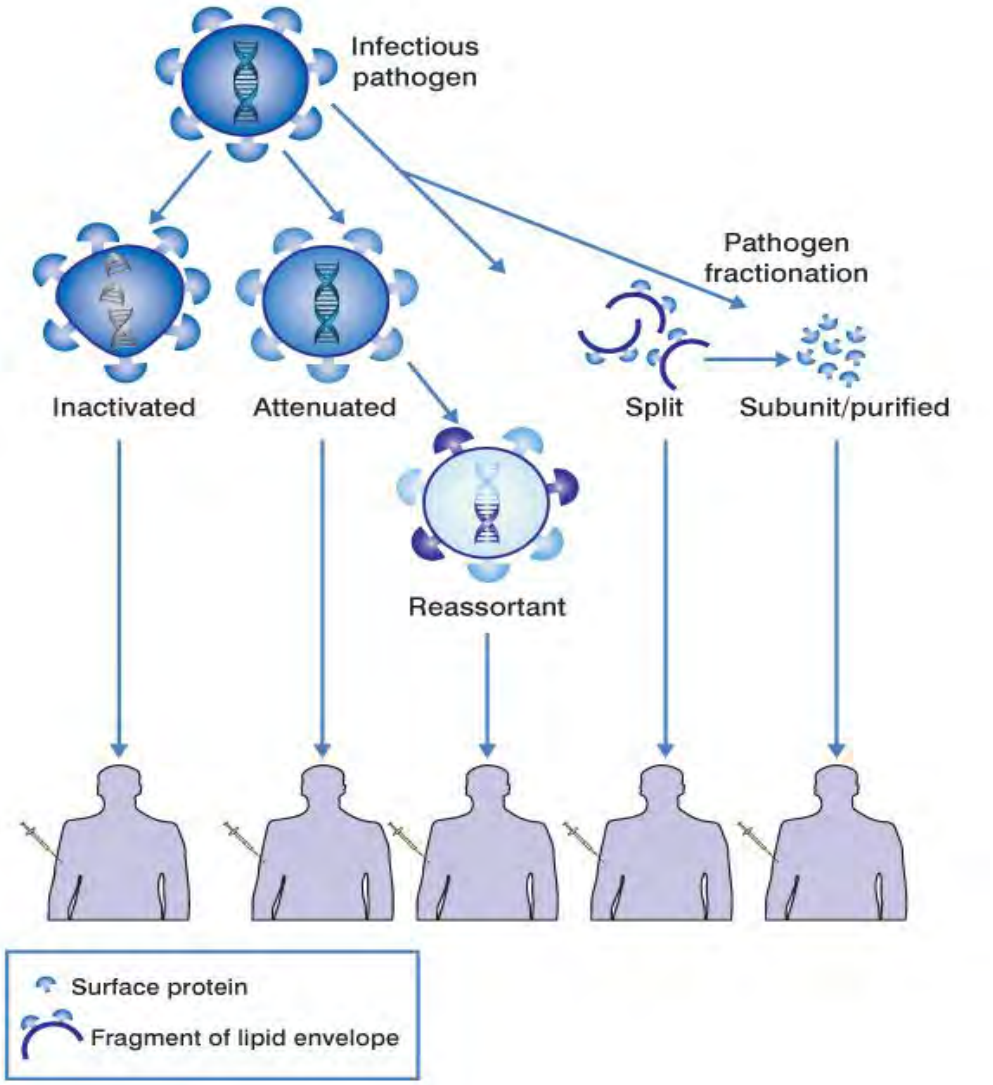
From 'Understanding Modern vaccines' Eds Garcon, Cunningham et al 2011

Five ‘ages’ of vaccines

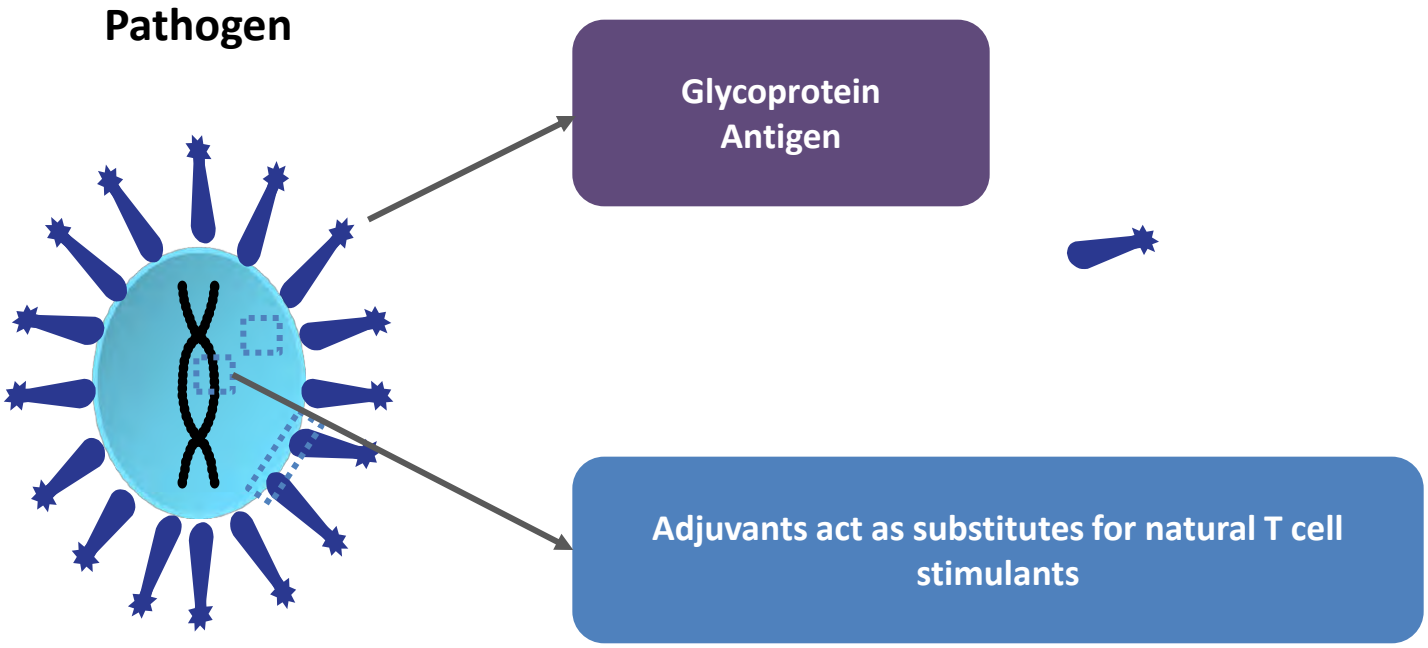
- Infancy: multiple
- Adolescence: papillomavirus, HSV, EBV
- Pregnancy
- Older adults: influenza, pneumococcus, shingles
- Any, Epidemic: influenza, Ebola, Dengue, ?Zika

Types of vaccines

- Whole virus
- Live attenuated
- Inactivated
- Split
- Sub-unit



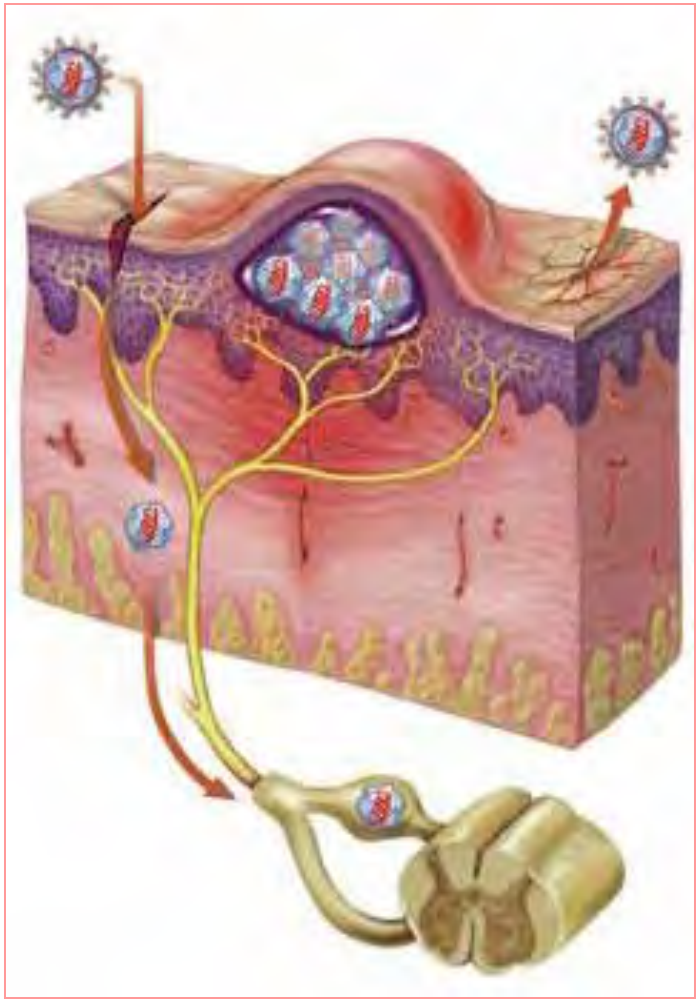
Recombinant VZV/HSV glycoprotein + T cell adjuvant



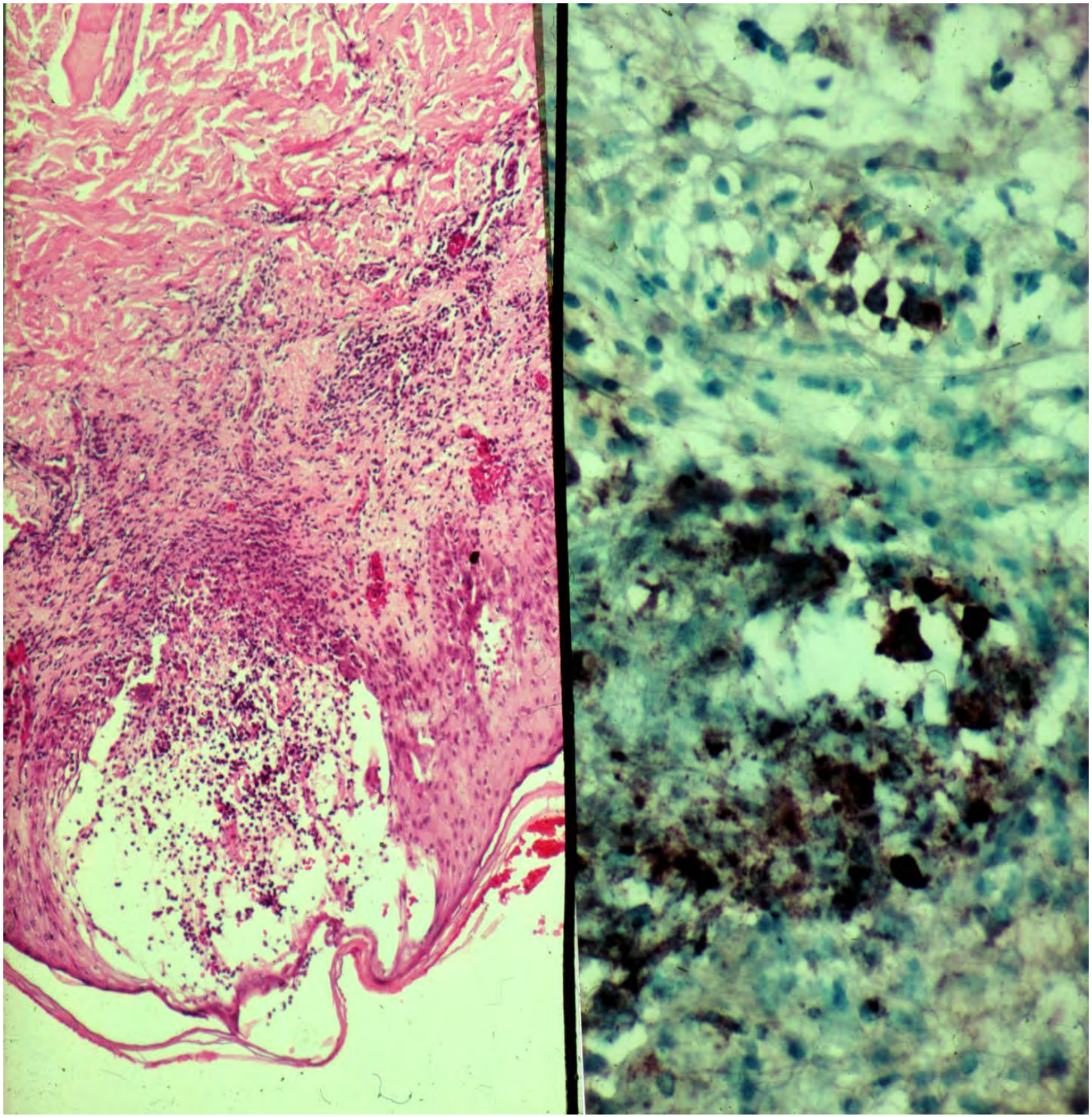
- Viral proteins alone may be insufficiently immunogenic
- Adjuvants act as substitutes for viral immune stimulants enhancing and directing the immune response

Herpes Simplex Viruses (HSV) 1& 2 and Herpes zoster

- HSV infects genital skin and enters cutaneous nerves
- Establishes a lifelong dormant infection in DRG that reactivates intermittently back to the epidermis
- Herpes zoster (shingles) similar
- HSV infection is restricted to the epidermis, (keratinocytes and LCs) but varicella extends into the dermis
- HSV-1 causes oral and initial genital infection
- HSV-2 causes genital infection
- Genital herpes increases the risk of acquiring HIV >3 fold
- **There is no effective HSV vaccine currently available**

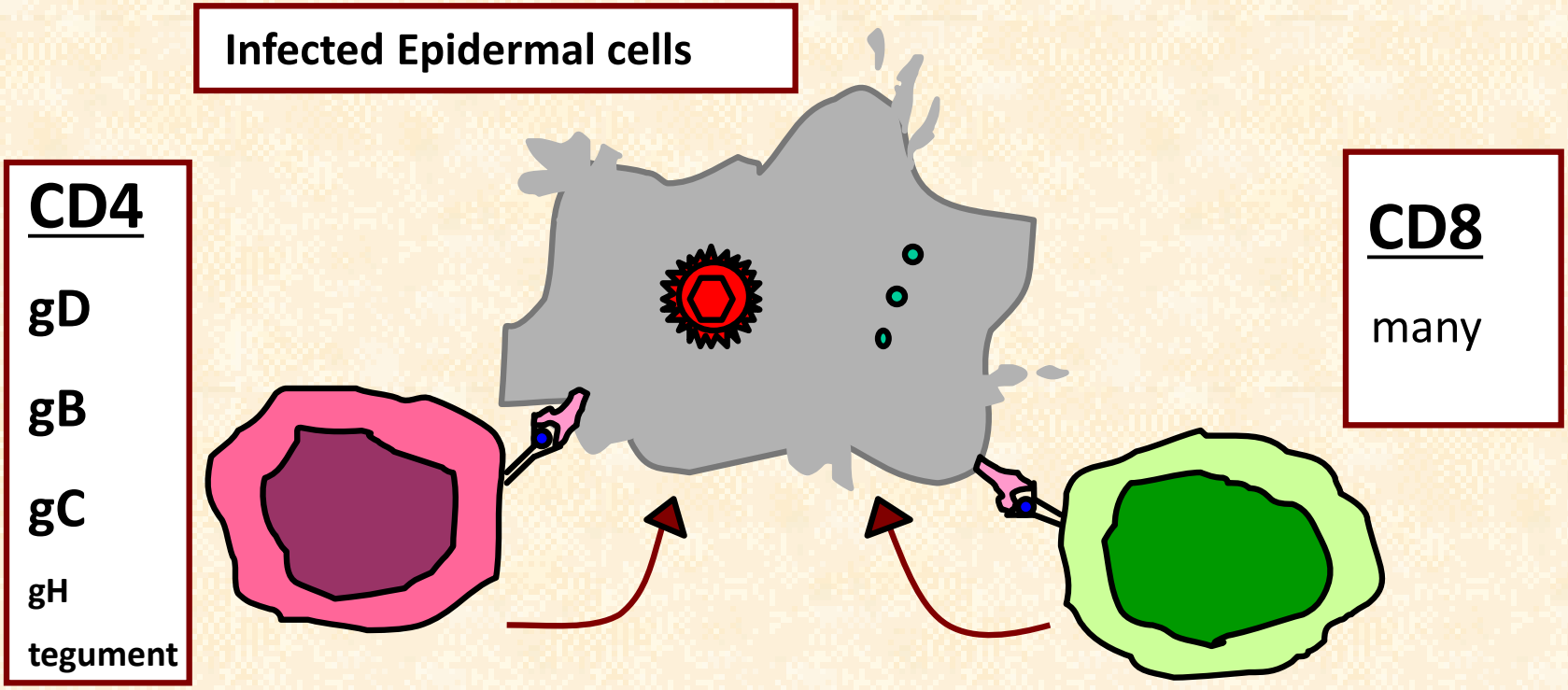


www.3dscience.com/3D_Images/Biology/Viral/Herpes



HSV Vaccine Candidates

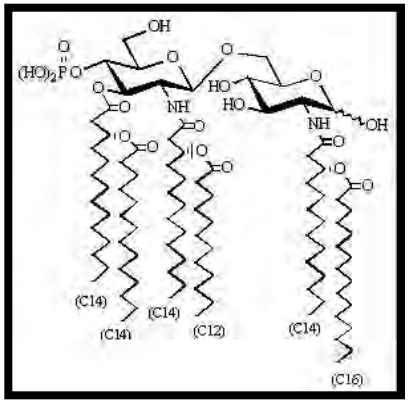
HSV1/2 protein targets for CD4 and CD8 lymphocytes



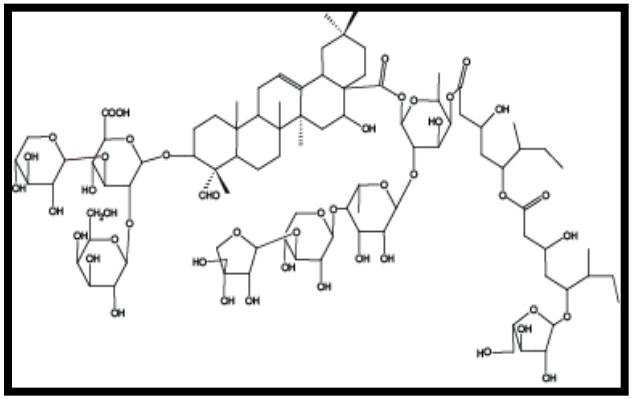
Cunningham/Koelle 1983 - 2000

T cell stimulating adjuvant Systems

- Combinations of:
  - Classical adjuvants: aluminum salts, emulsion, liposomes
  - Immunostimulants: MPL, QS21, (CpG),



dMPL



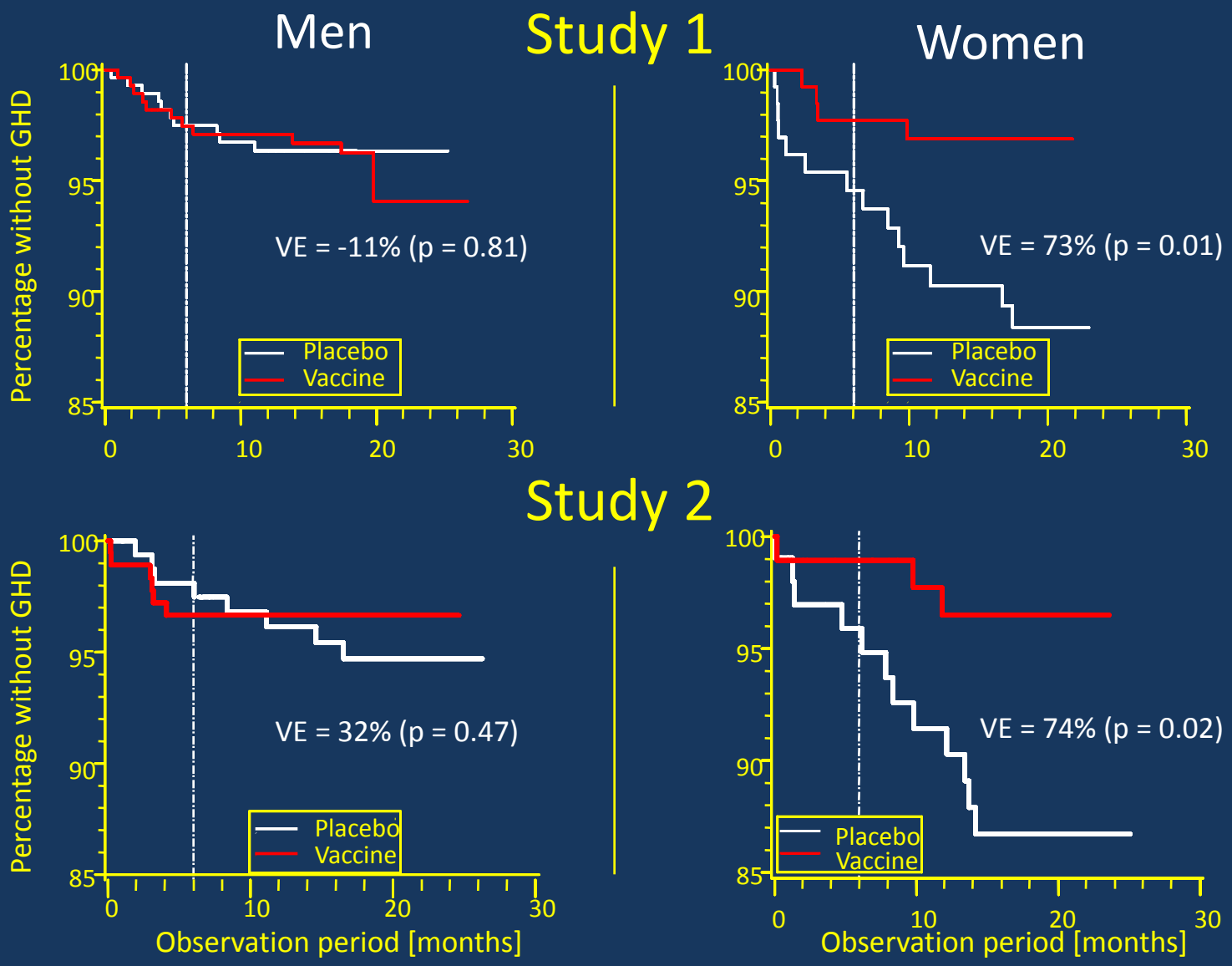
QS21

HSV2 gD/dMPL vaccine - the first (partially) successful vaccine candidate for genital herpes

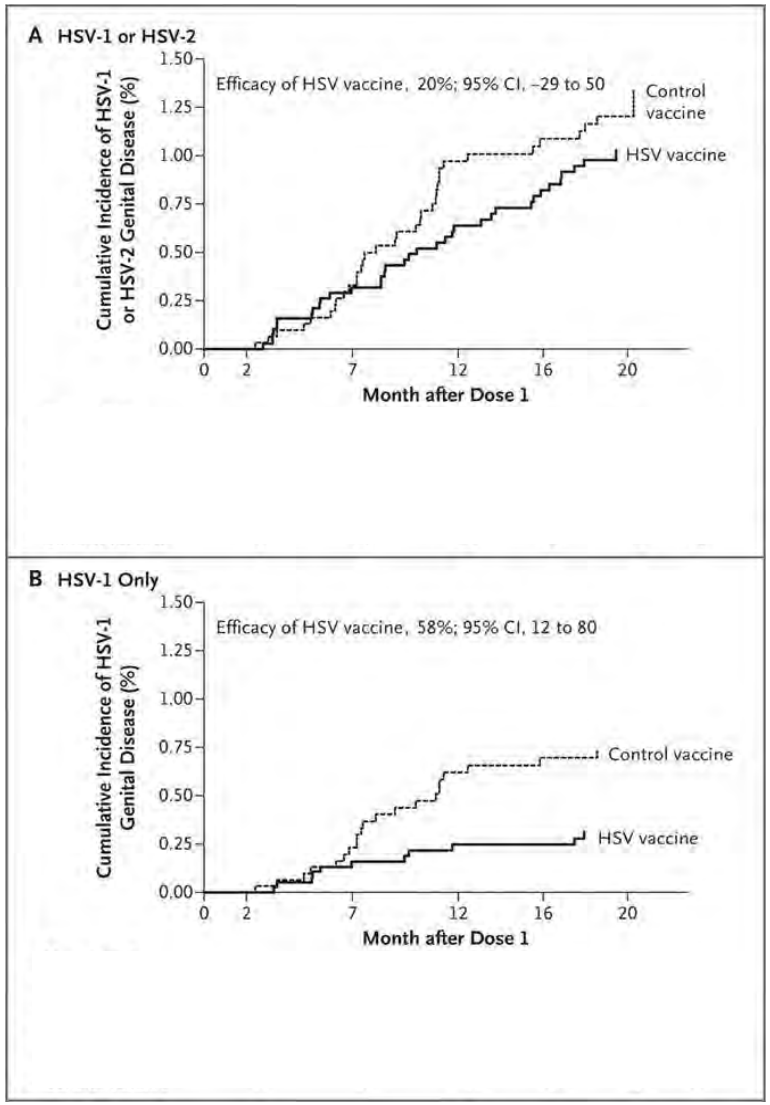
- Antigen: recombinant HSV2 glycoprotein D
- Adjuvant: ASO4 - Alum and monophosphoryl lipid A (DMPL)
  - Induces Th1 response (IFNg) in humans
- Simplirix trial: multicentre, RDBC
  - Consort design: immunize partners of subjects with GHD

Stanberry, Spruance, Cunningham et al NEJM 2002

HSV2 gD vaccine prevents disease in female seronegative subjects (Stanberry, Cunningham et al NEJM 2002)



Herpevac trial 2012



Phase III HSV Vaccine trials: Summary

- **Recombinant glycoprotein D2 with AS04 (dMPL) adjuvant (GlaxoSmithKline)**
  - 73% protection against genital herpes disease in HSV1/2 seronegative women whose partners have genital herpes

    (Stanberry L, Spruance S, Cunningham AL et al NEJM 2002)
  - 58% protection against HSV1 genital herpes disease in randomly selected HSV1/2 seronegative women (Belshe R et al NEJM 2012)
  - Not protective in men
  - Vaccine Induced neutralizing antibody, Th1, and Tfh responses, **no CD8+ T cell responses were detected.**
  - **Chiron vaccine:** gD2 + gB2 +adjuvant MF59: No significant efficacy but high neut antibody titres (Corey L et al JAMA 1999)

Herpes Zoster (shingles)

- Reactivation of latent varicella zoster virus
- Markedly increases after 50 years
- Usually unilateral, vesicular cutaneous eruption with a dermatomal distribution
- Acute pain accompanies the rash in >90% of individuals aged over 50 years
- The most common complication is post herpetic neuralgia (PHN), defined as pain persisting for 90 or more days after rash onset
- >50% of population >85 years will get zoster

Gnann, Jr. & Whitley 2002
Dworkin et al. 2007


A
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B
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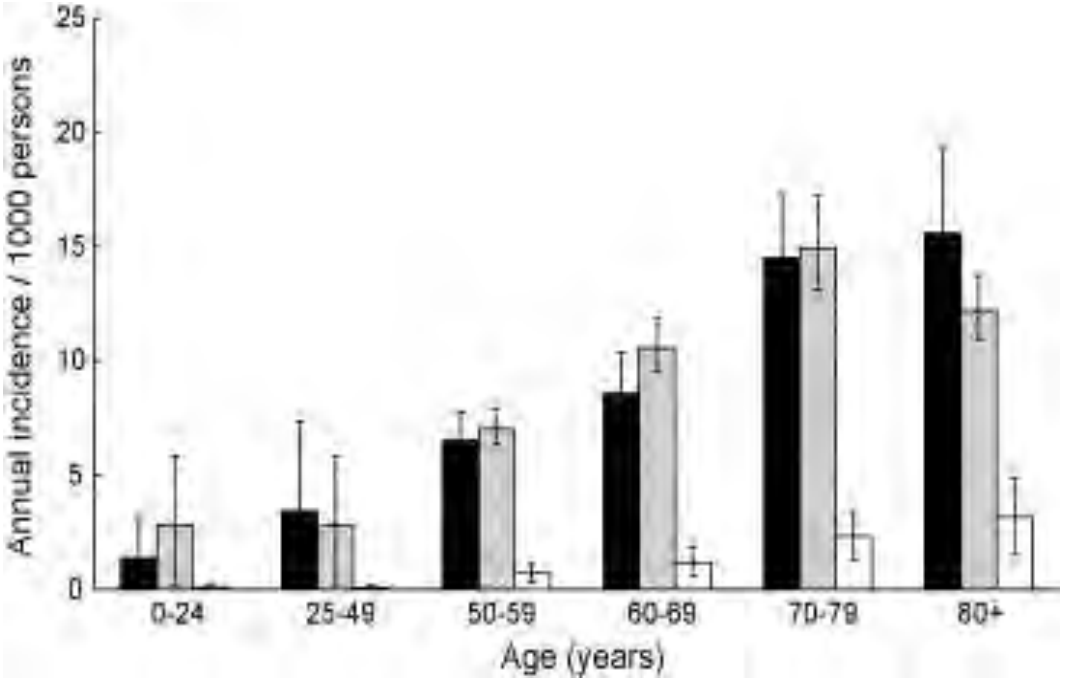
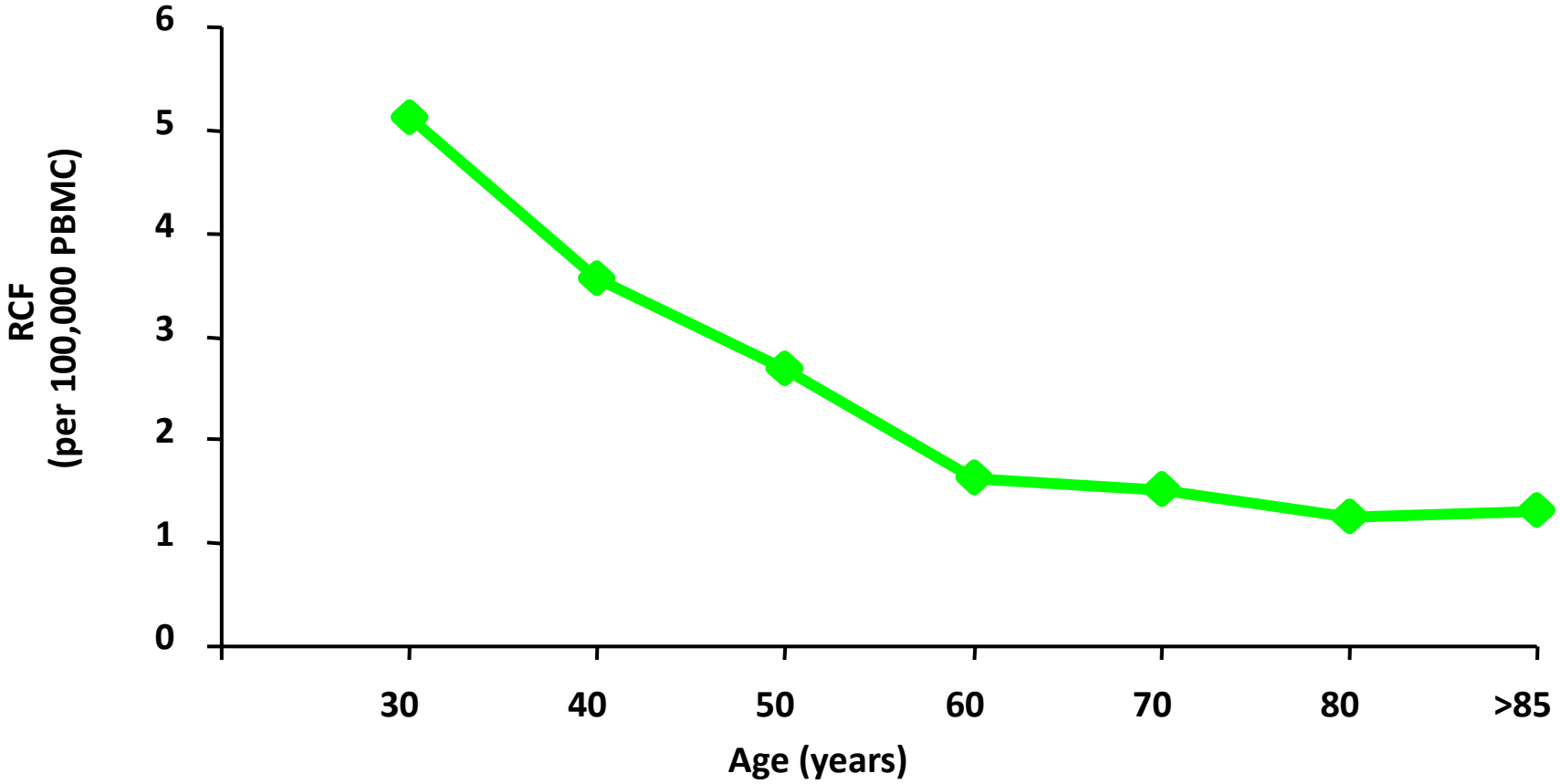
Age dependent incidence of herpes zoster and PHN in Australia



Stein A et al Vaccine 2009

Tcell responses to VZV Decrease With Age



CMI=cell-mediated immunity
PBMC=peripheral blood mononuclear cell
RCF=responder cell frequency

Adapted from Levin M et al. Unpublished results.

Shingles Prevention Study (SPS)

- A double-blind, placebo-controlled trial
  - 22 Sites
- Live, attenuated VZV vaccine
  - Oka/Merck strain (Median = 24,600 pfu)
  - 14-fold greater titer than childhood vaccine
- Subjects = 38,500
  - Median age = 69 years
  - 60-69 years = 20,750
  - ≥ 70 years = 17,800 (46%)
  - ≥ 80 years = ~2500 (>6.5%)

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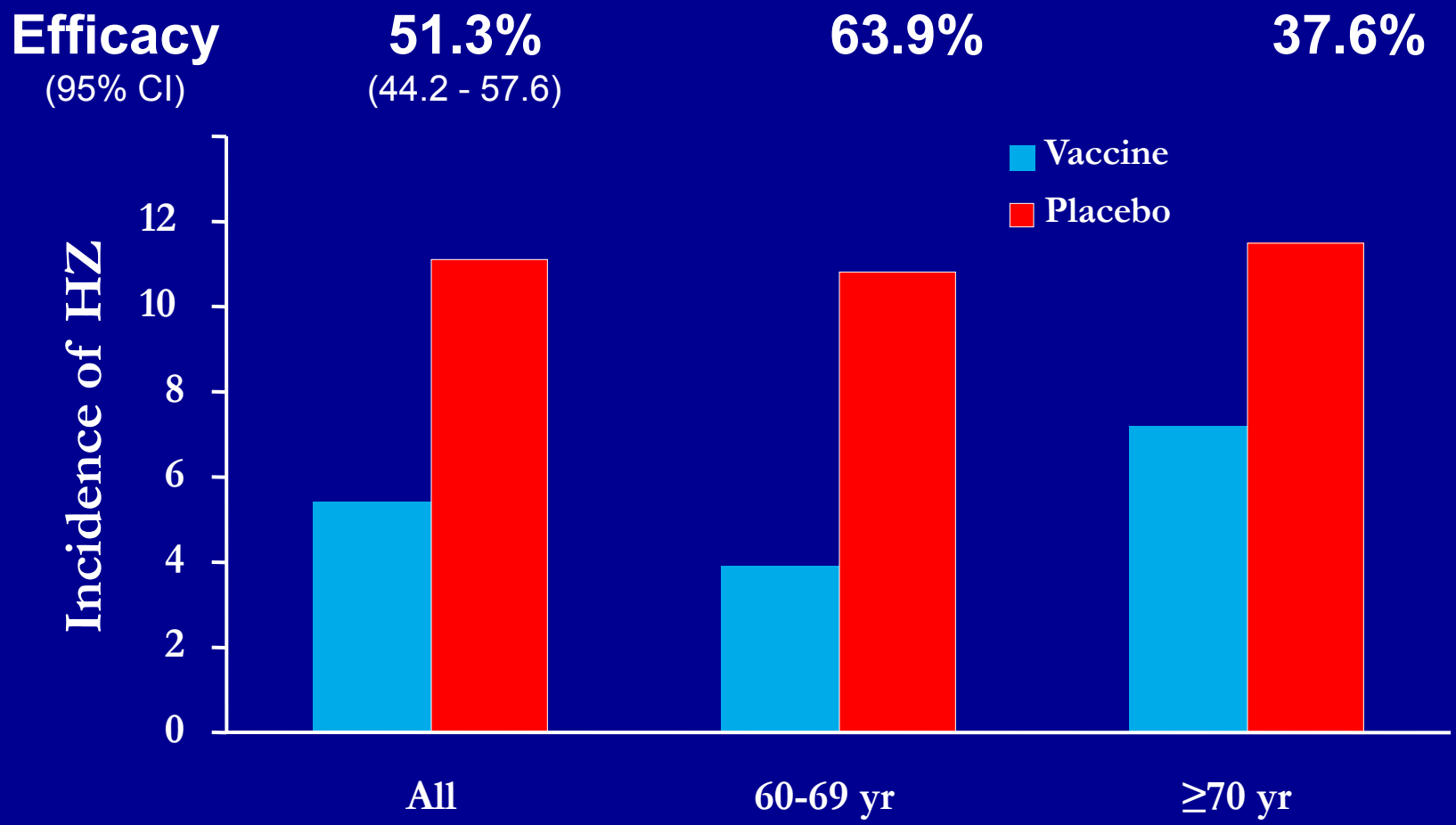
Oxman al. NEJM 352; 2271: 2005

Vaccine Efficacy for Incidence of Herpes Zoster



Zostavax: issues

- Moderate efficacy, lower in >80
- Duration of efficacy

  -Need a booster, probably at 10 years
- Cost-effectiveness: ? Commence age 60 + 2 boosters OR at age 70 (cf France, Australia, UK)
- Safety in moderately immunecompromised pts needs better definition

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ORIGINAL ARTICLE

Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

Himal Lal, M.D., Anthony L. Cunningham, M.B., B.S., M.D., Olivier Godeaux, M.D., Roman Chlibek, M.D., Ph.D., Javier Diez-Domingo, M.D., Ph.D., Shinn-Jang Hwang, M.D., Myron J. Levin, M.D., Janet E. McElhaney, M.D., Airi Poder, M.D., Joan Puig-Barberà, M.D., M.P.H., Ph.D., Timo Vesikari, M.D., Ph.D., Daisuke Watanabe, M.D., Ph.D., Lily Weckx, M.D., Ph.D., Toufik Zahaf, Ph.D., and Thomas C. Heineman, M.D., Ph.D., for the ZOE-50 Study Group*

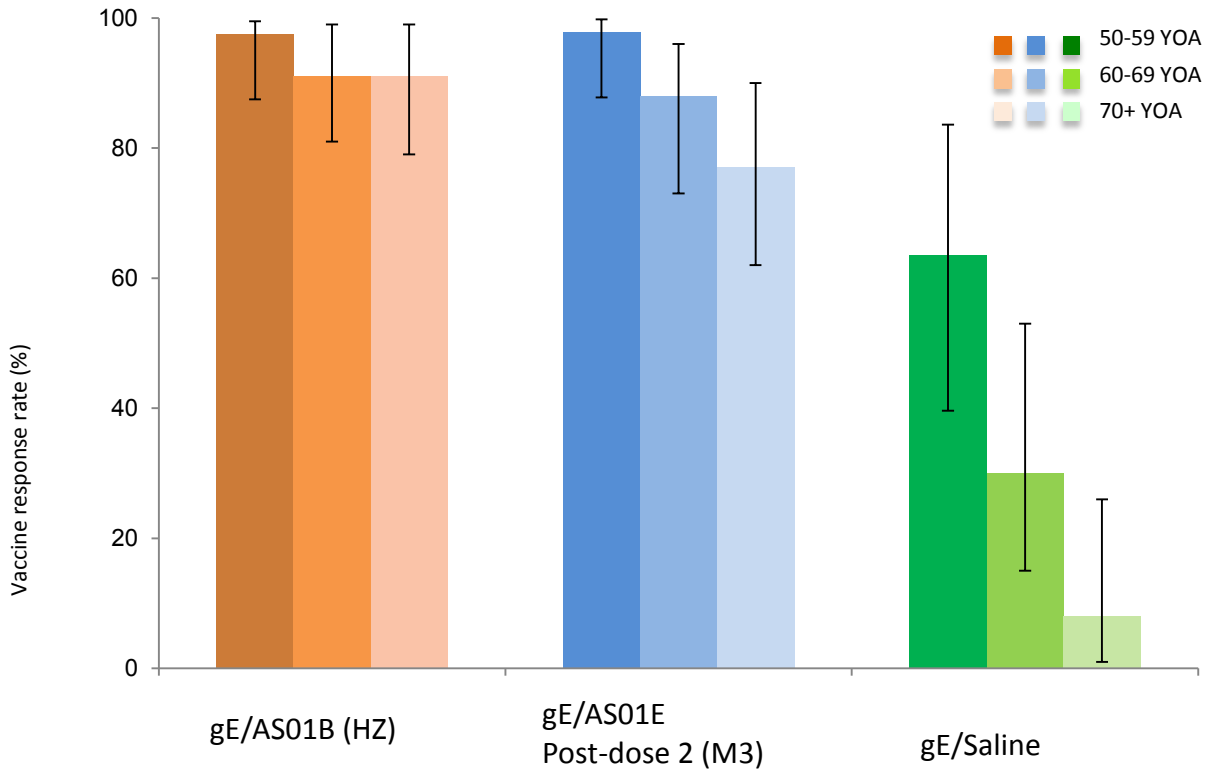
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2016 VOL. 375 NO. 11

Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older

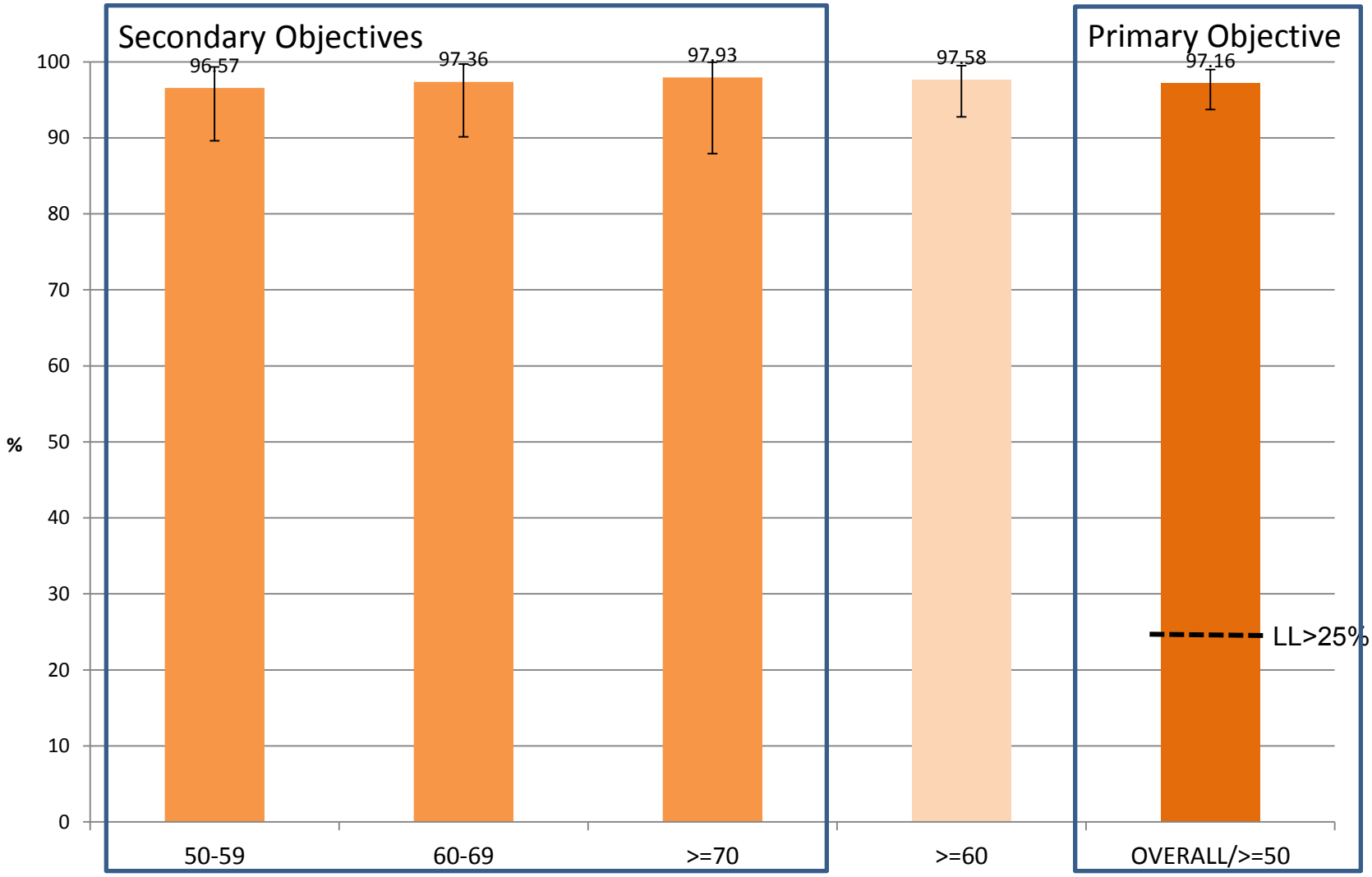
A.L. Cunningham, H. Lal, M. Kovac, R. Chlibek, S.-J. Hwang, J. Díez-Domingo, O. Godeaux, M.J. Levin, J.E. McElhaney, J. Puig-Barberà, C. Vanden Abeele, T. Vesikari, D. Watanabe, T. Zahaf, A. Ahonen, E. Athan, J.F. Barba-Gomez, L. Campora, F. de Looze, H.J. Downey, W. Ghesquiere, I. Gorfinkel, T. Korhonen, E. Leung, S.A. McNeil, L. Oostvogels, L. Rombo, J. Smetana, L. Weckx, W. Yeo, and T.C. Heineman, for the ZOE-70 Study Group*

T cell responses to HZ/su (gE/AS01$_B$) but not gE alone were well-preserved with subject age



Chlibek et al 2015

GSK Herpes Zoster (HZ/su) Vaccine Efficacy



Lal H, Cunningham AL et al, N Engl J Med, 2015

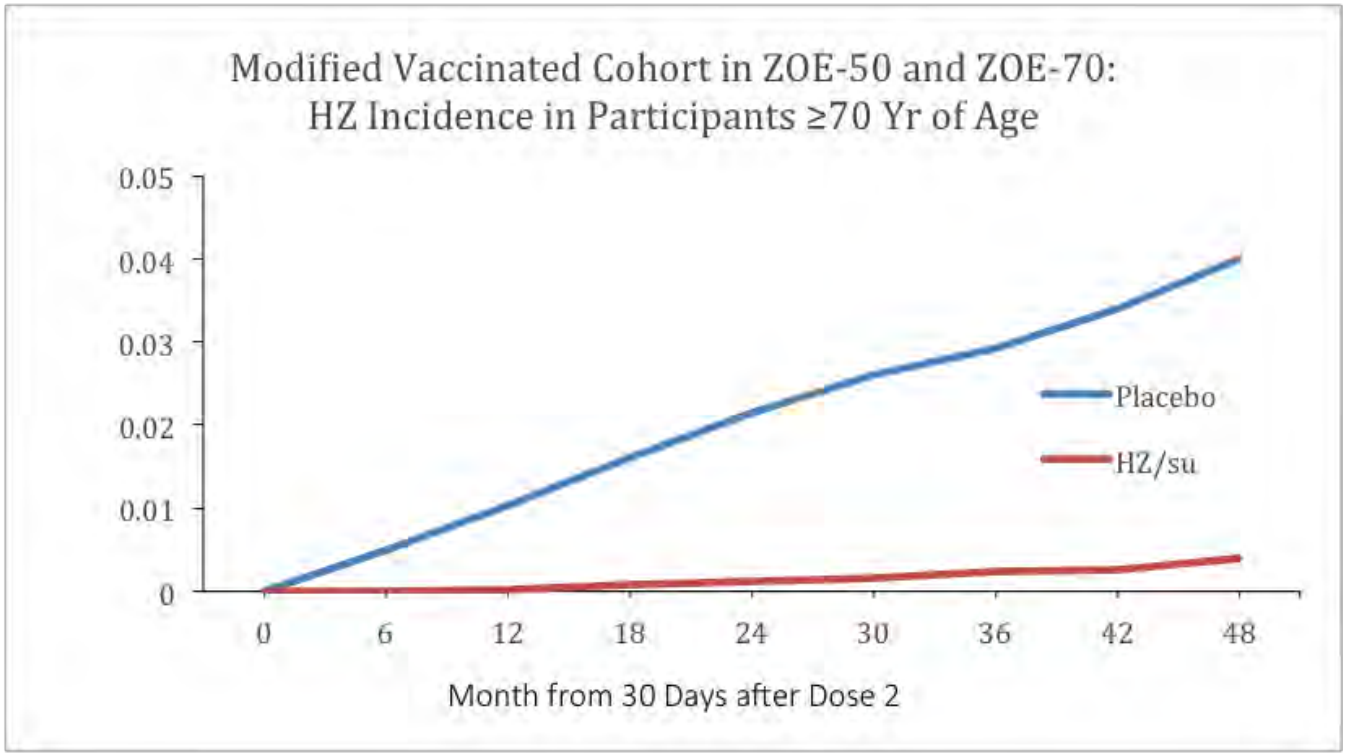
Efficacy of Shingrix

Against PHN

> 50 year old: 91%

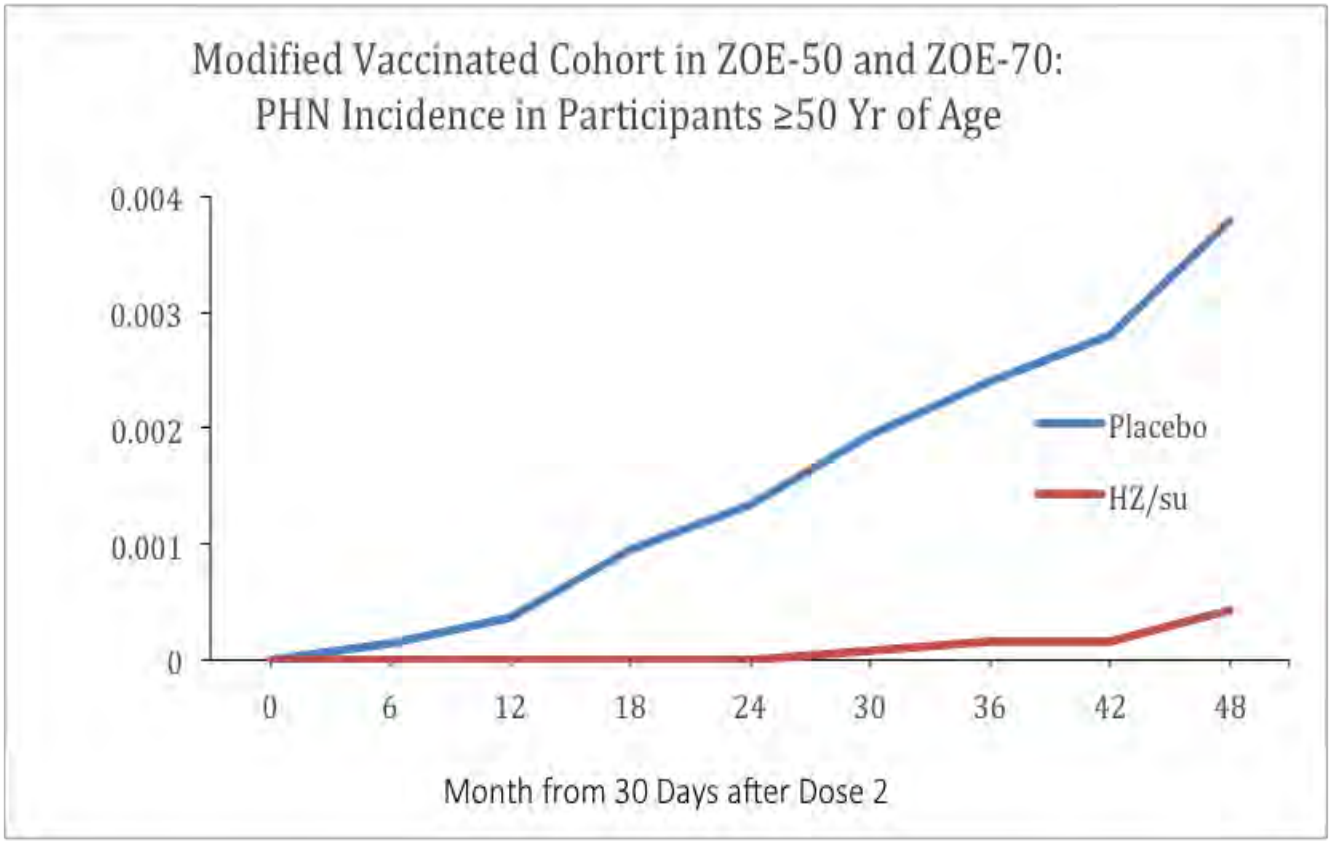
>70 year old: 90%

Risk of development of Herpes zoster after vaccination



Cunningham AL et al N Engl J Med 2016

Risk of development of post-herpetic neuralgia after vaccination



Cunningham AL et al.N Engl J Med 2016

HZ/su:Implications

- HZ/su development and trialling confirms several scientific hypotheses:

- vaccines consisting of a single pathogen protein and adjuvant(s) can be efficacious -and more than a live attenuated vaccine

- such a combination may cut through immunosenescence = hope for other vaccines in older subjects

- Pathogen/vaccine/adjuvant immunology is of increasing relevance for (rational) vaccine development

Shingrix, HZ/su: issues

- Two doses: likely compliance in real world setting (Hepatitis A: 65%), Efficacy after a single dose?
- High reactogenicity (severe local: 9%); can efficacious adjuvants without reactogenicity eventually be developed
- Duration of efficacy to be determined (T cell immunogenicity plateaus for 3-9 years- promising)
- - long term followup trials commenced
- Risk of auto-immunity with new adjuvants: needs long term post marketing surveillance
- Efficacy in severely immunecompromised: phase III trial results available soon

HZ/su: Remaining Immunologic questions

- Duration of humoral and CD4 T cell responses?
- Mechanisms:

  -Relative importance of antibodies and T cells, correlation?

  - Are polyfunctional T cells induced –importance?

  - Role of memory CD8 T cell responses?

  - Role of innate immune responses (NK, mono, DCs)
- Correlates of protection? Can thresholds be defined as surrogates? But difficult with few breakthrough HZ cases (2)
- Why the difference in protection against HZ and PHN in Zostavax and HZ/su

Initial interactions of HSV with dendritic cells in anogenital mucosa

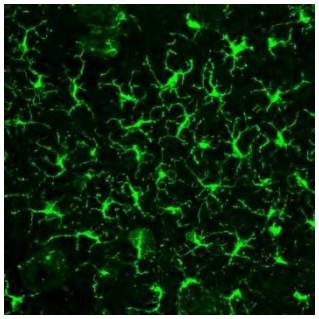
- Understanding HSV1 and 2 penetrate anogenital epithelium and their initial interactions with first line constitutive innate immune cells is critical for understanding how to boost such defences with vaccines

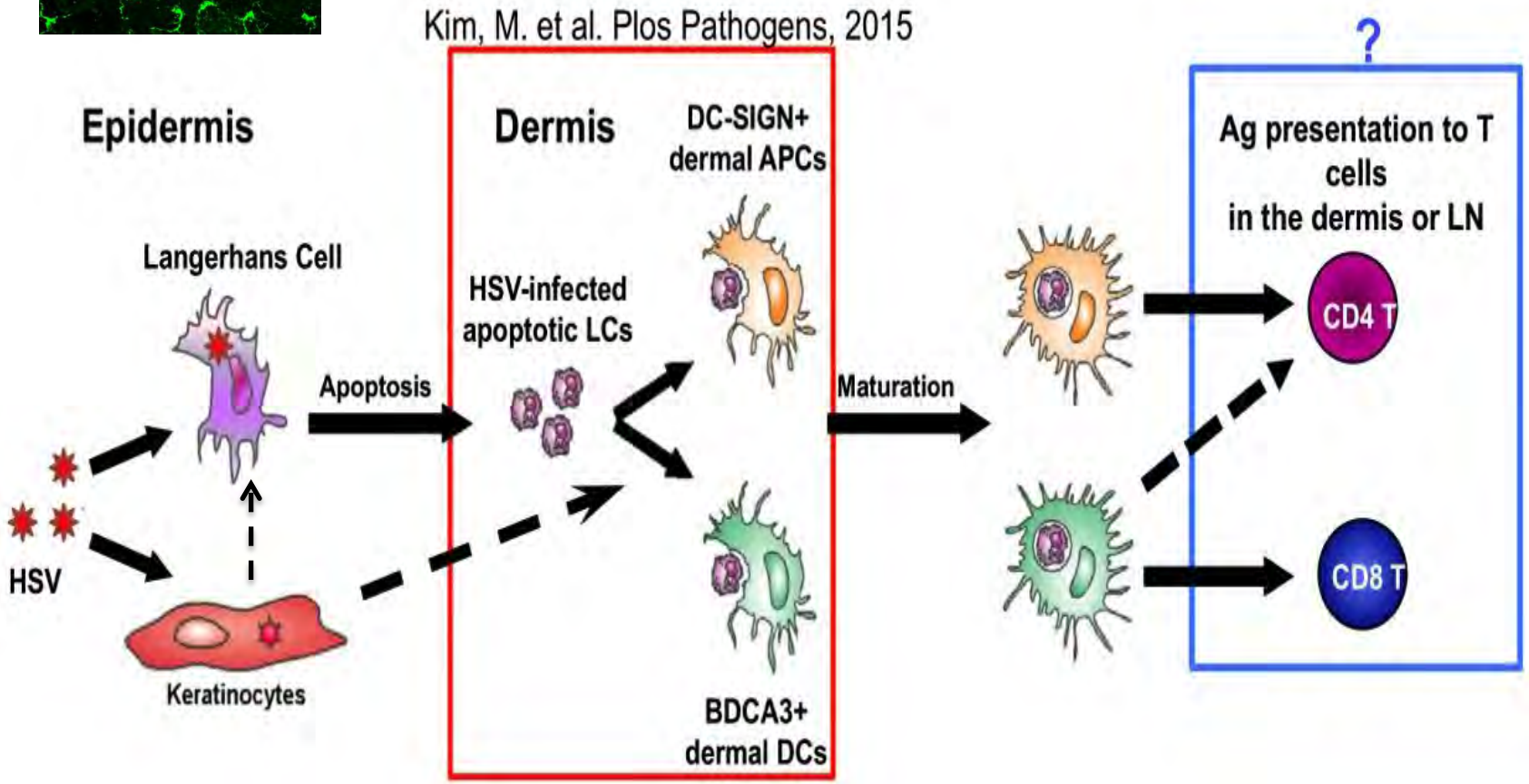
- There is increasing interest in targetting mucosal immunity through topical or intradermal approaches

- 'Immune correlates' of vaccine efficacy in defining which immune modalities correlate with protected vs unprotected subjects have not been sufficiently studied

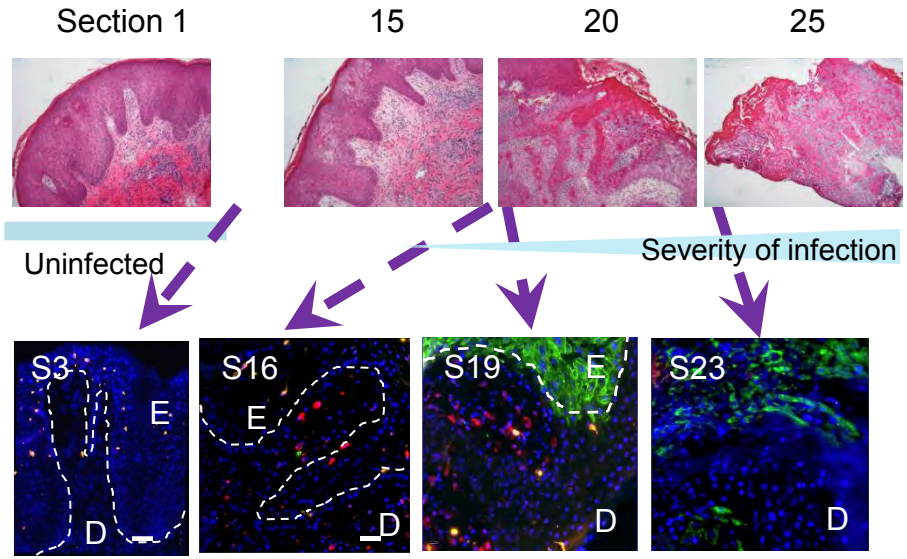
- In mice LCs take up HSV in epithelium but different (dermal) DCs exit skin with hSV and stimulate CD8 T cells in lymph nodes (Sprecher et al 1986, Carbone/Heath/Bedoui/Gebhardt labs 2003, 2009, 2011, Zhao et al 2003, Puttur et al 2010)

HSV-epidermal-dermal DC relay

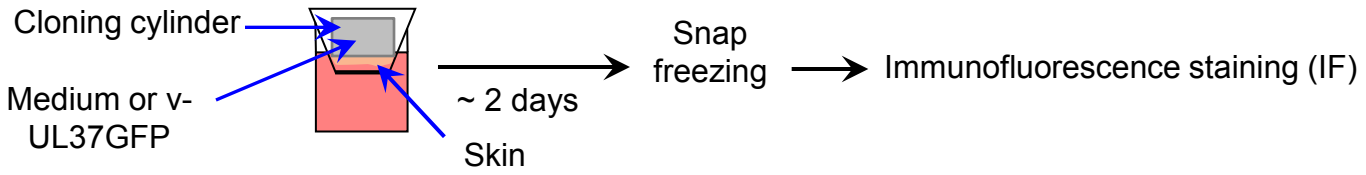




A Primary genital herpes biopsy (**biopsy**)

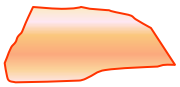


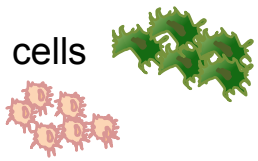
B Inner foreskin explant system (**foreskin tissue**)



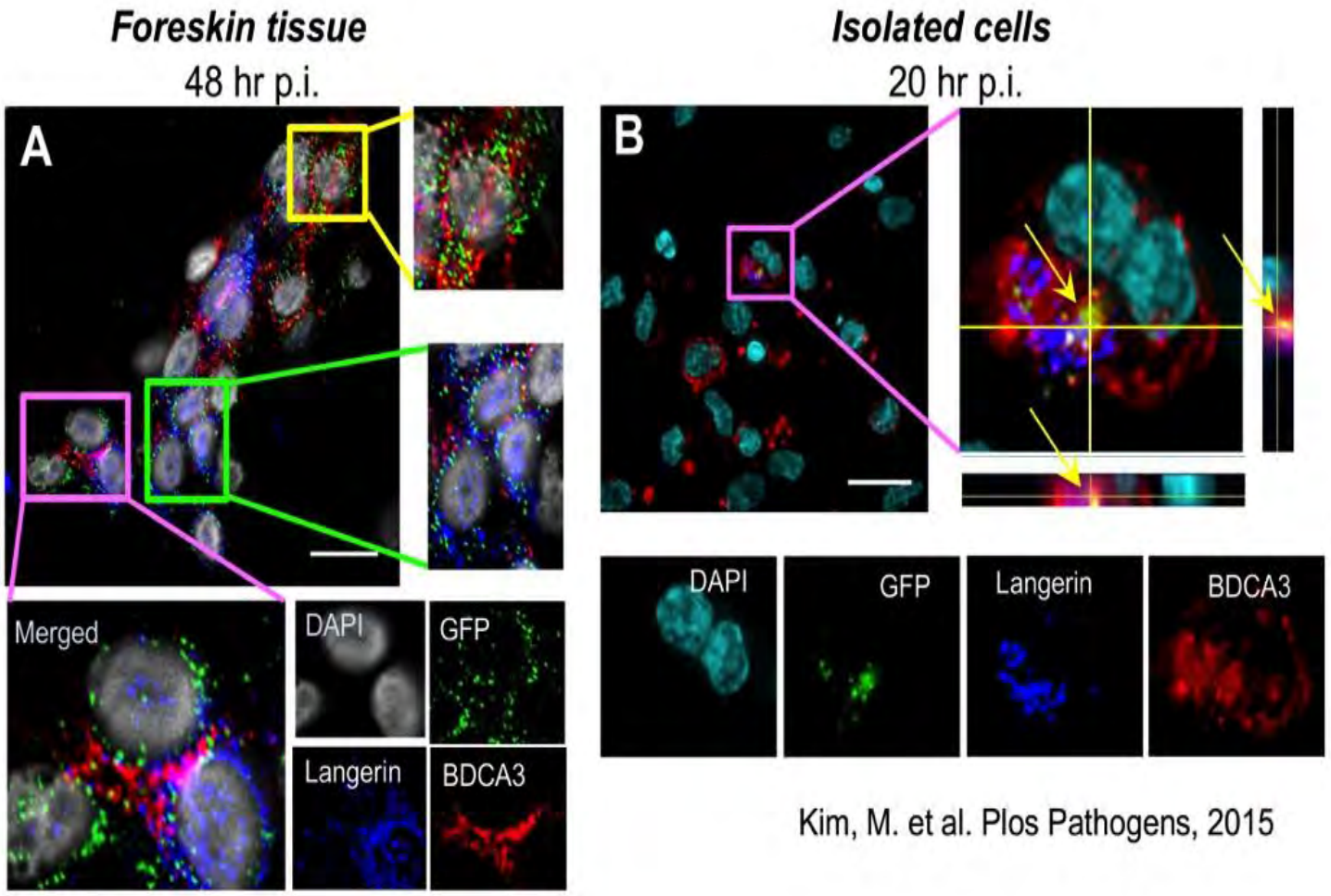
C Isolated Langerhans cells and dermal dendritic cells (**isolated cells**)

Discarded human abdominal skin→ dispase → collagenase→ sorting→ cells



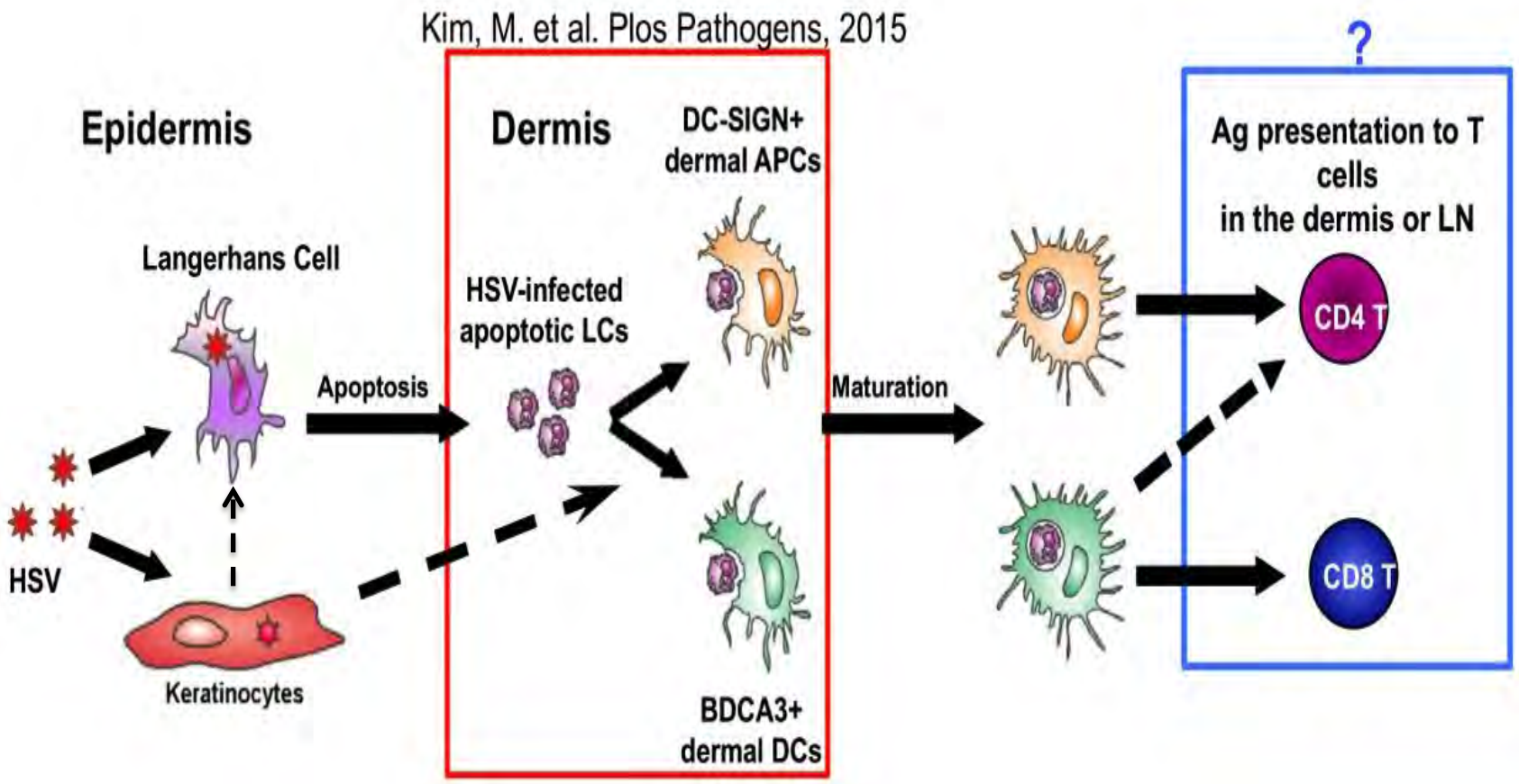


HSV infected apoptotic LCs are taken up by dermal DCs

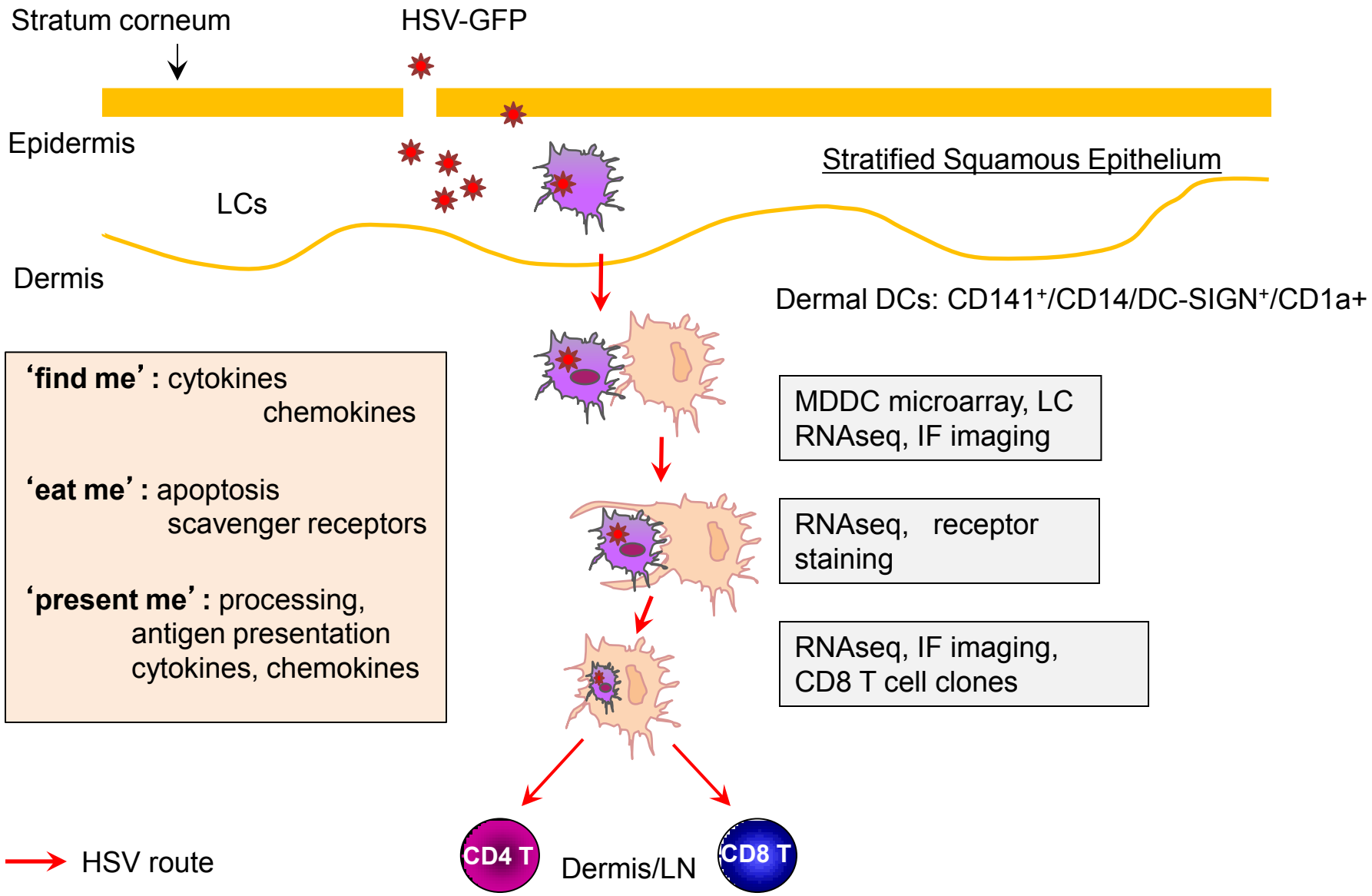


Kim, M. et al. Plos Pathogens, 2015

HSV-epidermal-dermal DC relay



Mechanism of the HSV-epidermal-dermal DC relay



Conclusions and Questions

- There is transfer/relay of HSV in apoptotic LCs to two (?three) dermal DC subsets within large cell clusters in the upper dermis
  - Probably facilitated by chemokines released by HSV infected LCs and phagococytic uptake via dDC apoptotic receptors

- There is selective intimate interaction of CD8 T cells with CD141+ DC subsets in the dermis of initial genital herpes lesions 3 days after onset. Are these HSV specific? Are they attracted by chemokines? Can the CD141+ DCs stimulate CD8 T cells? Which dC subset stimulates CD4T cells

Implication:

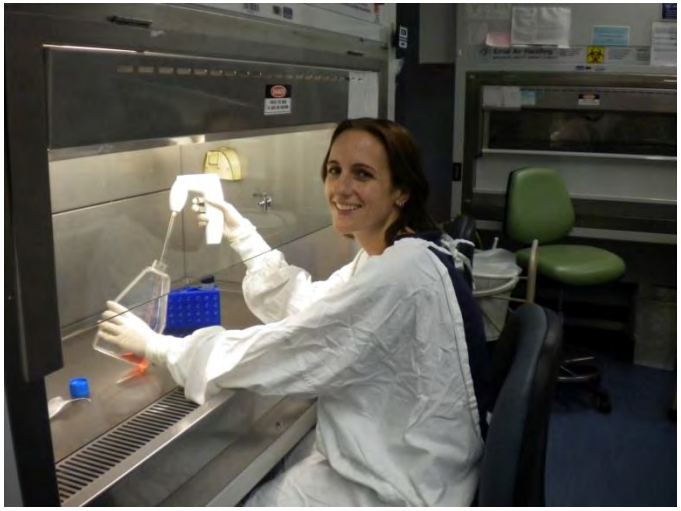
Should HSV vaccines/adjuvants be targeted at LCs or dermal DC subsets?

Andrew Harman

Min Kim & Kirstie Bertram

Kerrie Sandgren

Najla Nasr



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