ESMO SYMPOSIUM ON IMMUNO-ONCOLOGY

HPV vaccines

Professor Peter L Stern
Institute of Cancer Sciences
University of Manchester

Disclosure slide

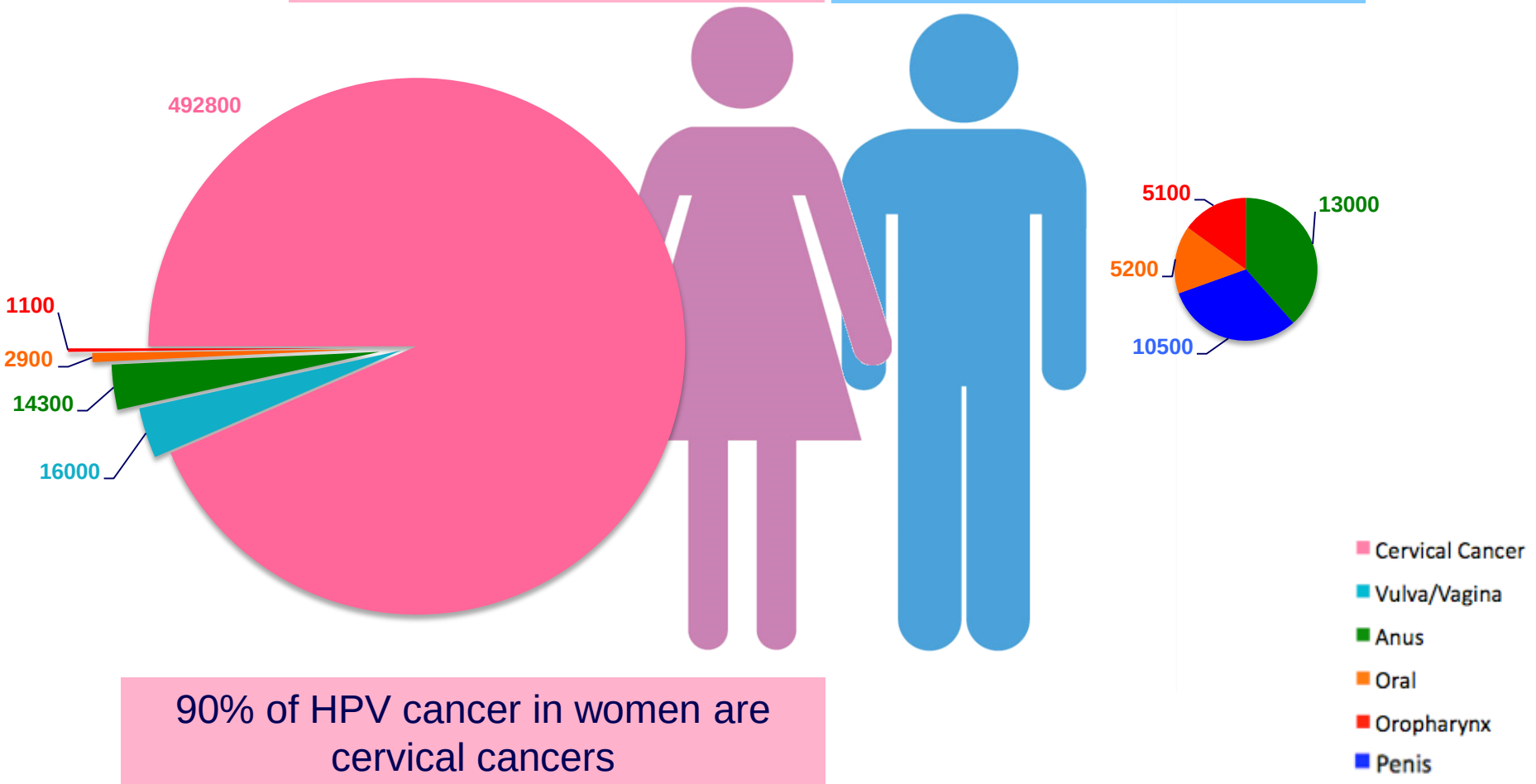
- I have been a member of SABs, receiving honoraria and meeting support from GSK in relation to vaccine development and education.

HPV cancers

Highest burden in cervical cancer

HPV related cancer in women
527,100 cases WW/year

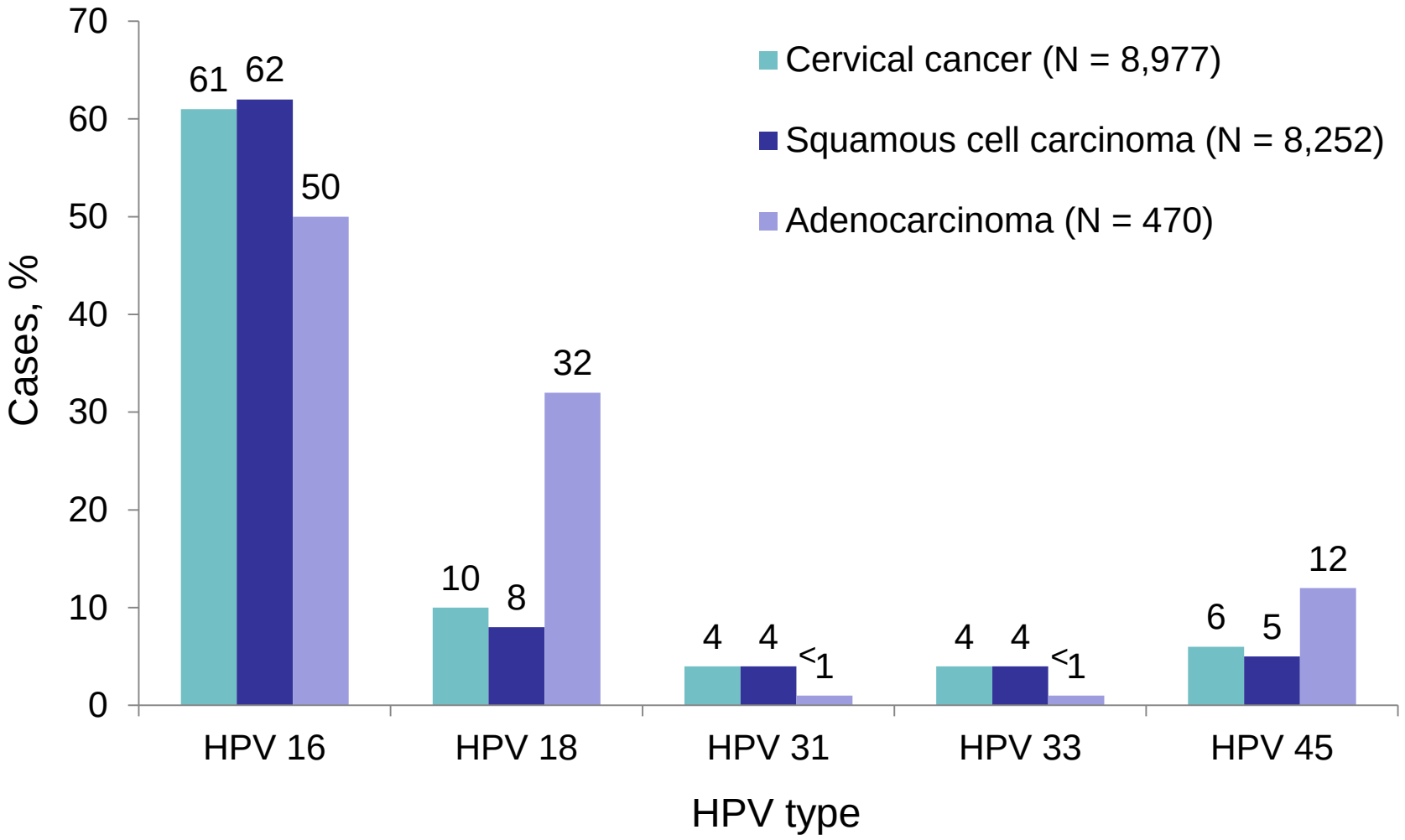
HPV related cancer in men
33,800 cases WW/year



90% of HPV cancer in women are cervical cancers

Adapted from Parkin DM, Bray F. Vaccine. 2006;24 Suppl 3:S11-25

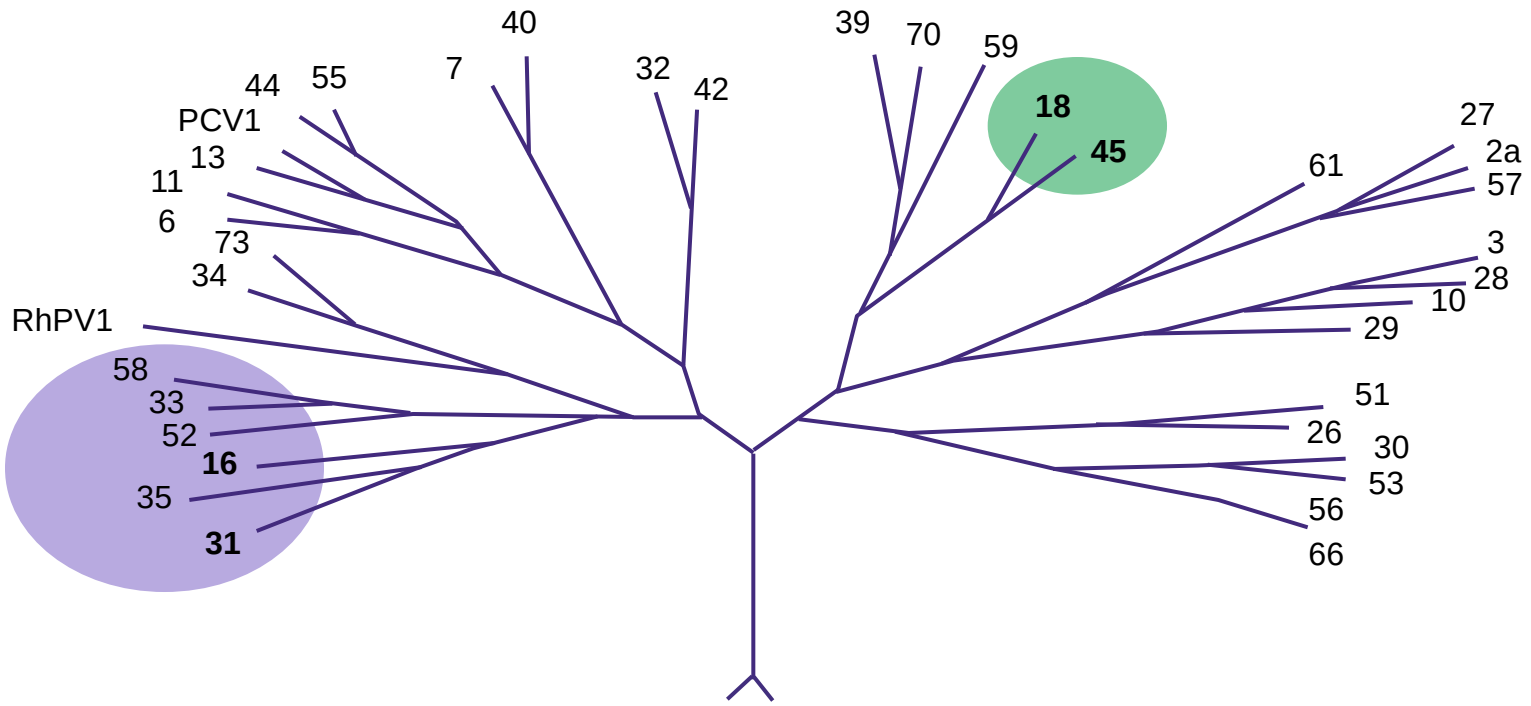
The most relevant single HPV types in cervical cancer by histology



Numbers include lesions infected with > 1 HPV type.

de Sanjosé S, *et al*. *Lancet Oncol* 2010; **11:**1048–1056.

Papillomavirus phylogenetic tree

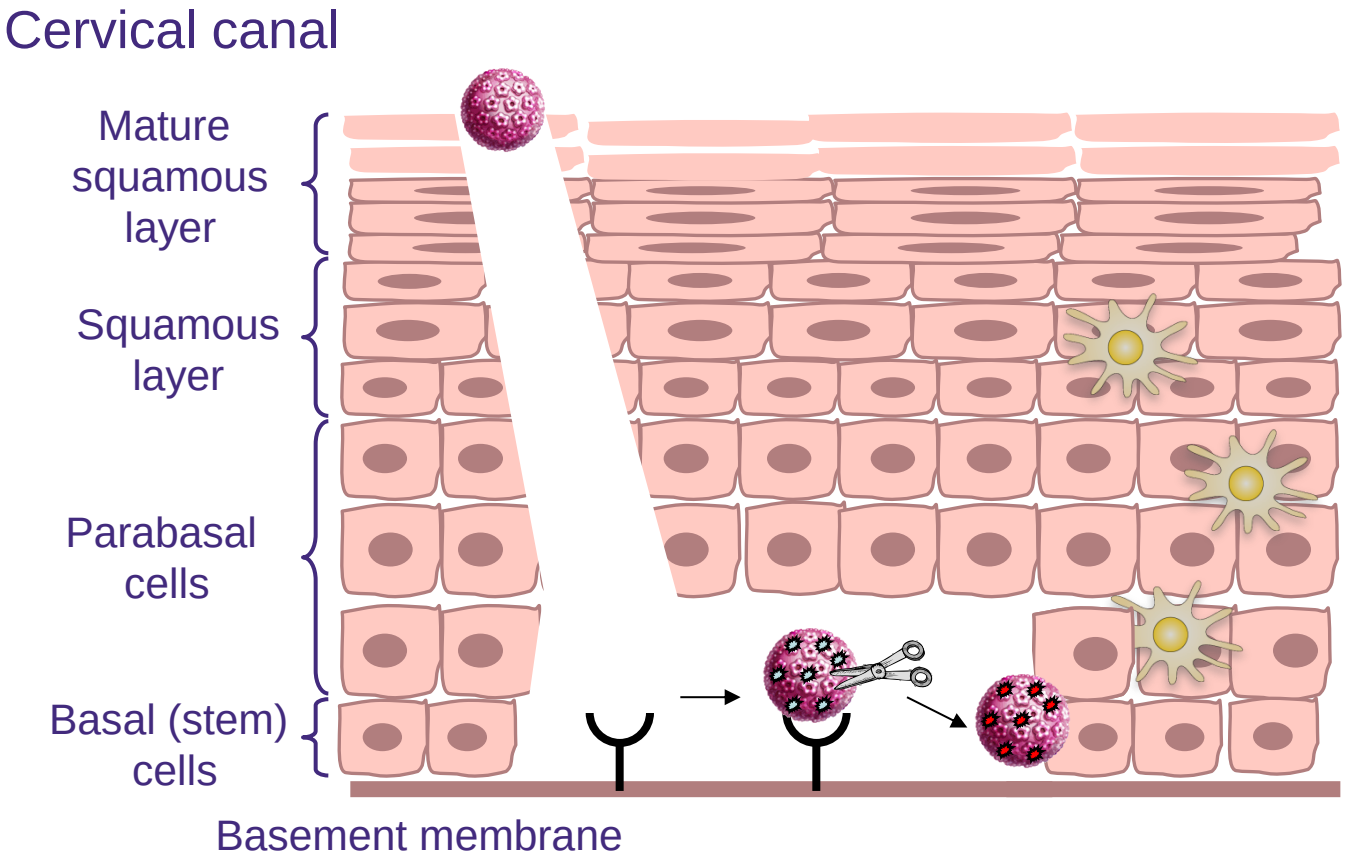


- The alpha-papillomavirus genus of the papillomavirus phylogenetic tree is shown*
- Oncogenic types closely related to HPV 16 and 18 are highlighted
- **HPV 16** is most closely related to **HPV 31**
- **HPV 18** is most closely related to **HPV 45**

* Selected species and types are shown.

Adapted from de Villiers E, *et al. Virology* 2004; **324:**17–27.

Virus infection: uptake and internalization



Microabrasion exposes BM denuded of epithelium

Virion first binds to HSPG on exposed BM

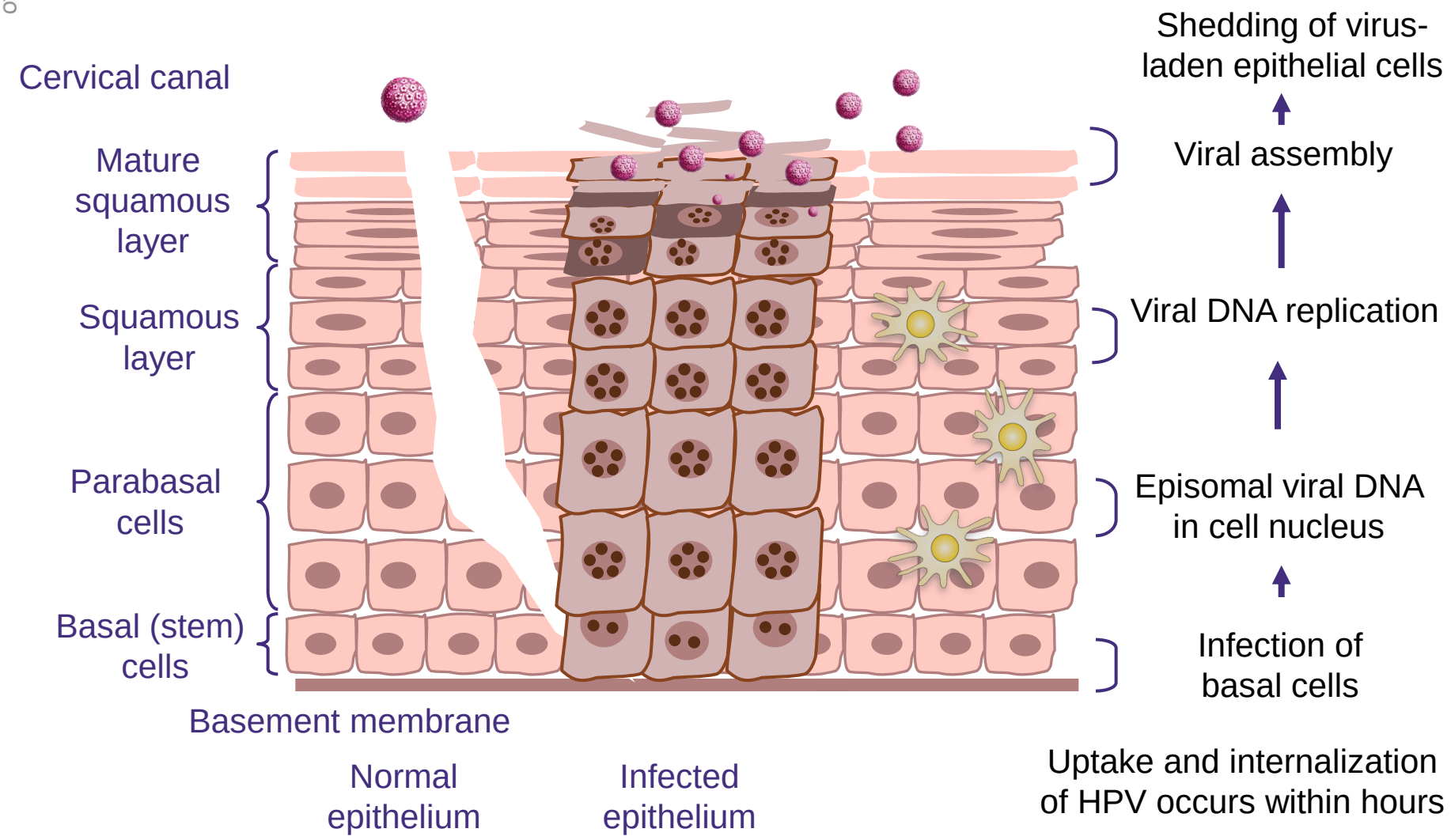
Conformational change exposing a site on L2 susceptible to proprotein convertase (furin or PC 5/6) cleavage

After L2 cleavage, L2 neutralizing epitope exposed and previously unexposed region of L1 binds to unidentified secondary receptor on invading epithelial cells

Uptake and internalization of HPV can occur within hours

Adapted from Stern PL & Einstein MH. The immunobiology of human papillomavirus associated oncogenesis. In *HPV and cervical cancer: achievements in prevention and future prospects* 2012; pp. 45–62. New York: Springer; Kines RC, *et al*. *Proc Natl Acad Sci USA* 2009; **106:**20458–2063.

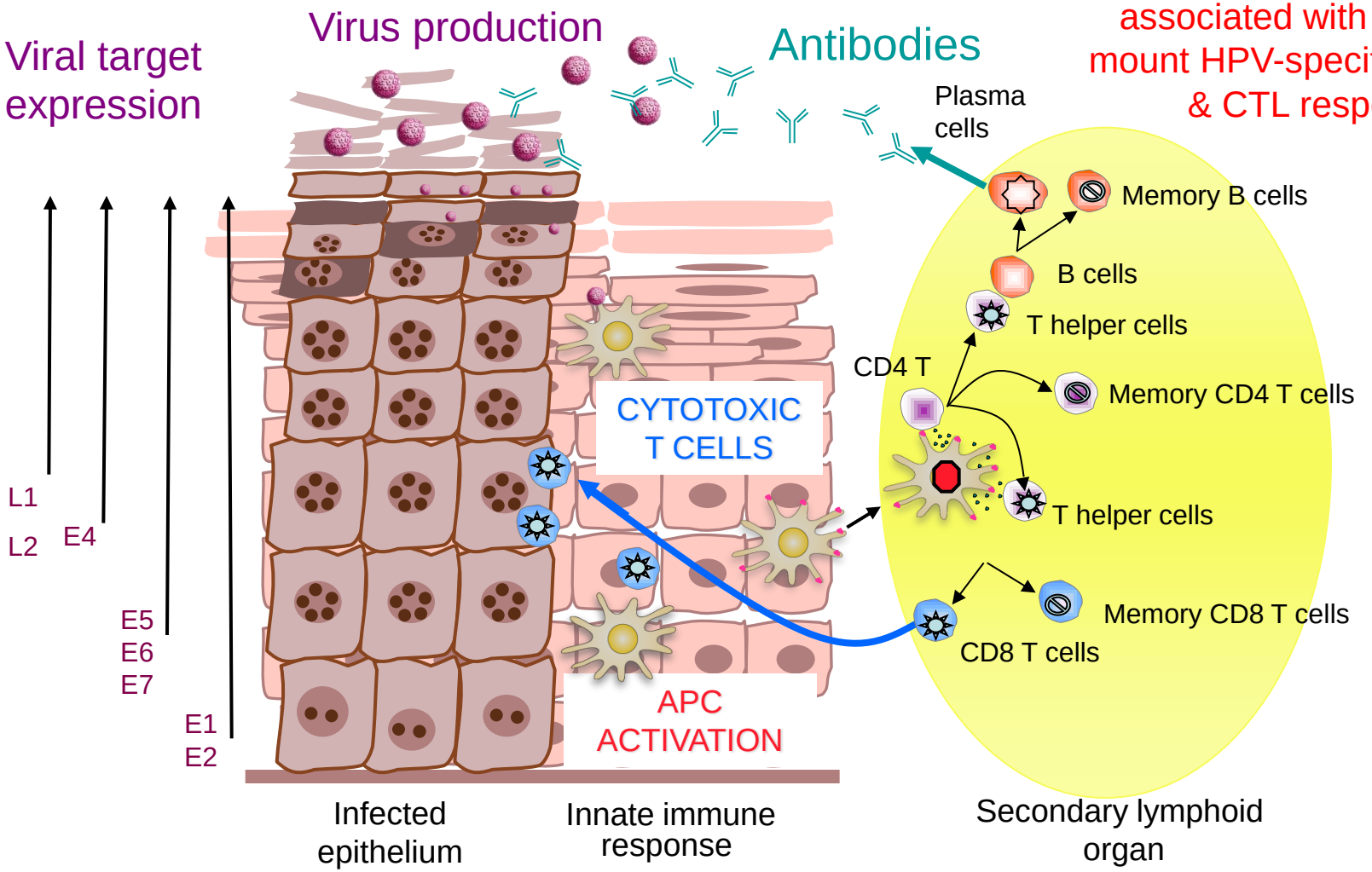
Natural infection: HPV lifecycle in the cervix



Adapted from Stern PL & Einstein MH. The immunobiology of human papillomavirus associated oncogenesis. In *HPV and cervical cancer: achievements in prevention and future prospects* 2012; pp. 45–62. New York: Springer; Frazer IH. *Nat Rev Immunol* 2004; **4:**46–54.

Natural immune control of HPV infection depends on local cellular immunity

HPV-induced cancer is associated with failure to mount HPV-specific T helper & CTL response

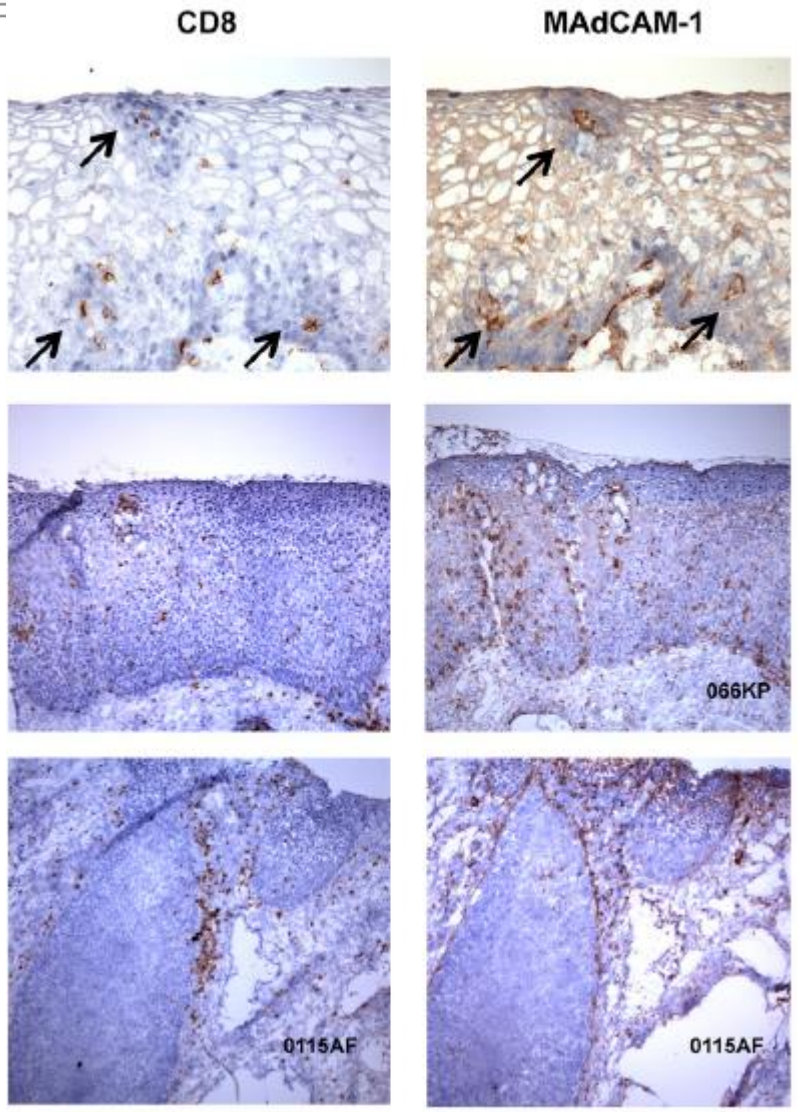


Toll-like receptors recognize danger signals

Adapted from Stern PL & Einstein MH. The immunobiology of human papillomavirus associated oncogenesis. 2012; de Jong A, *et al*. *Cancer Res* 2004; 64:5449–55;.

For lesion regression: Endothelial MAdCAM-1 supports entry of α4β7 CD8 T cells to the target epithelium

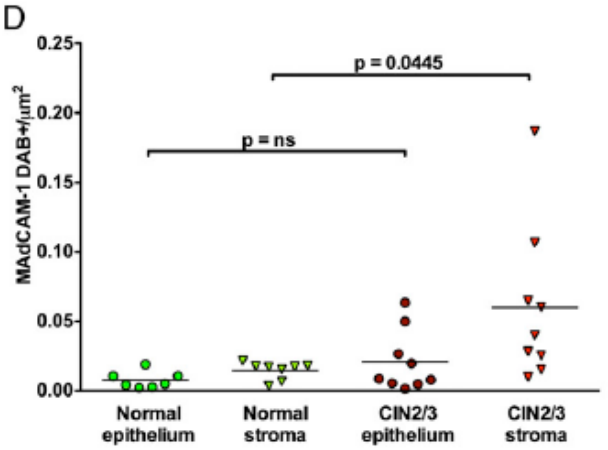
Trimble CL, *et al*. *J Immunol* 2010; 185:7107–7114

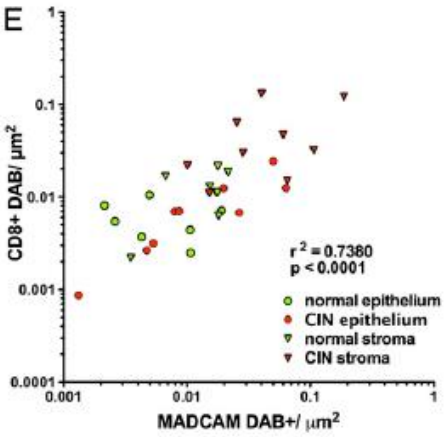


Normal epithelium
CD8+ cells clustered around vasculature
MAdCAM expressed on vascular endothelium

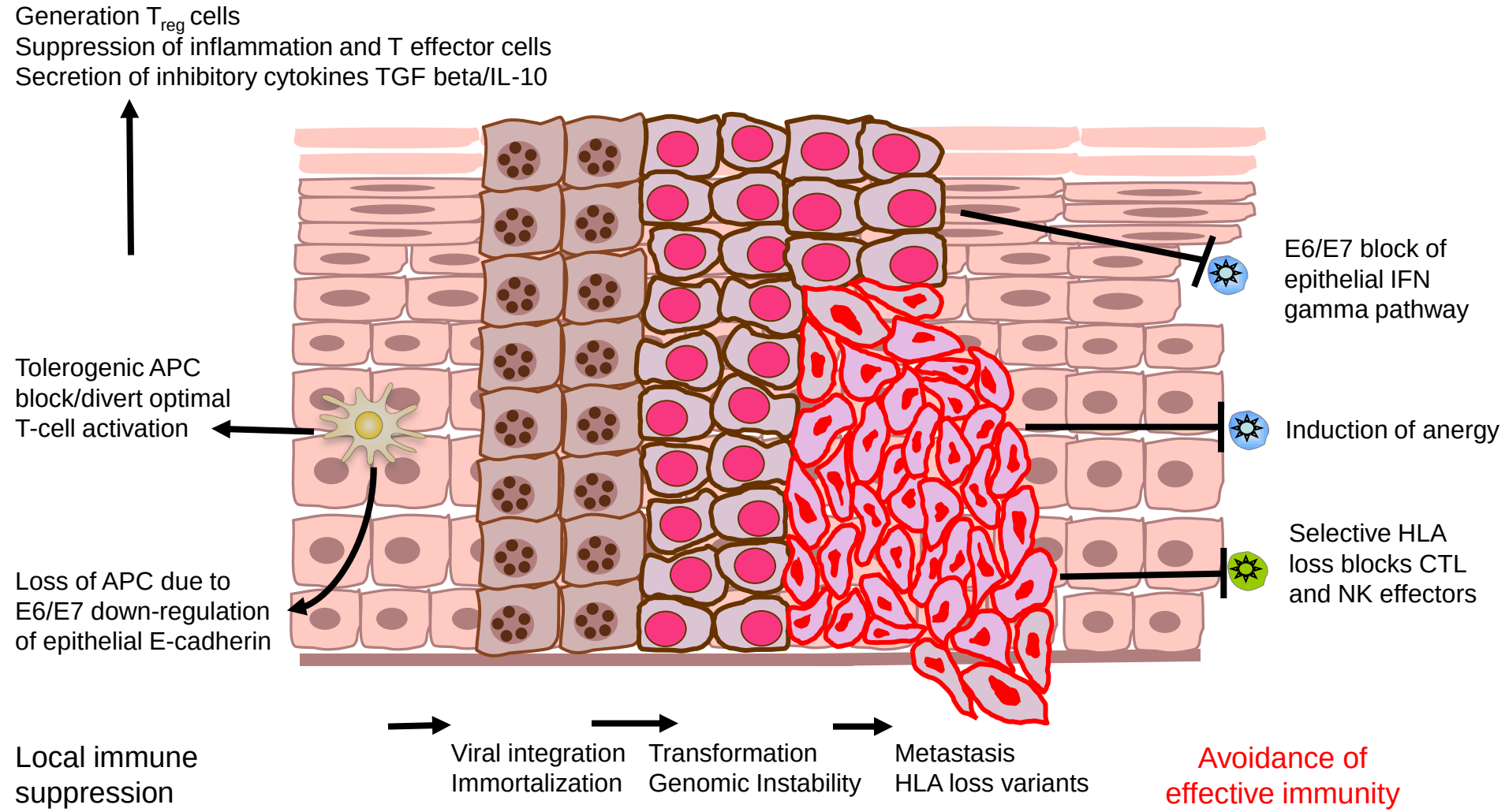
CIN2/3 epithelium
intraepithelial CD8+ cells and
MAdCAM expression

CIN2/3 epithelium
No intraepithelial CD8+ cells or
MAdCAM expression





HPV infection is necessary for cancer development but is not sufficient: loss of immune control and escape

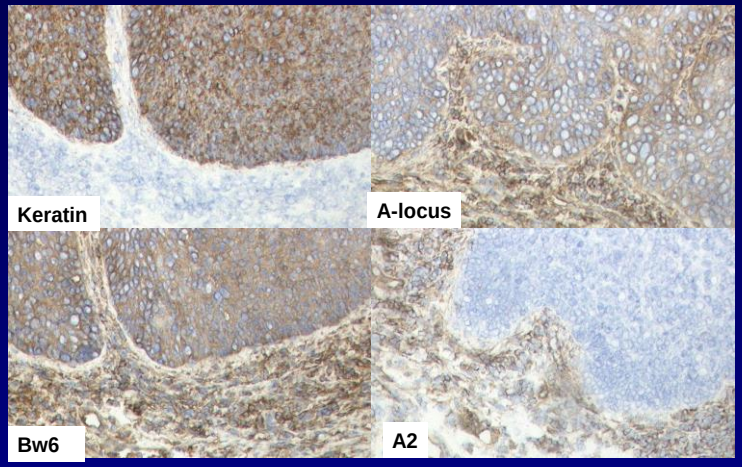


Adapted from Stern PL & Einstein MH. The immunobiology of human papillomavirus associated oncogenesis. In *HPV and cervical cancer: achievements in prevention and future prospects* 2012; pp. 45–62. New York: Springer; Stern PL & Einstein MH. *Curr Cancer Ther Rev* 2010; **6:**110–116.

HLA loss phenotypes and cancer

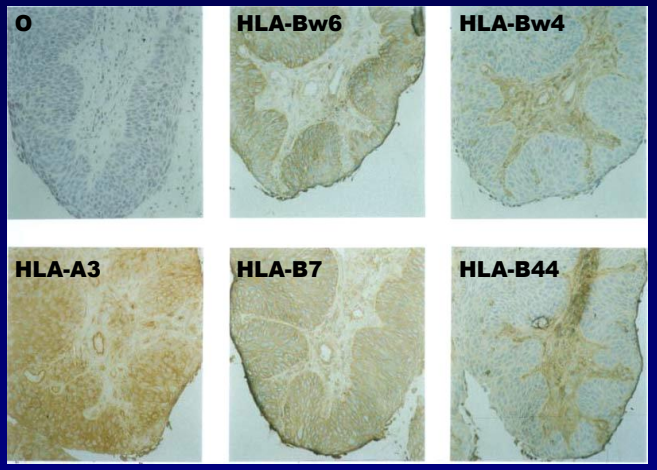
VIN III: Abdelhady et al 2001

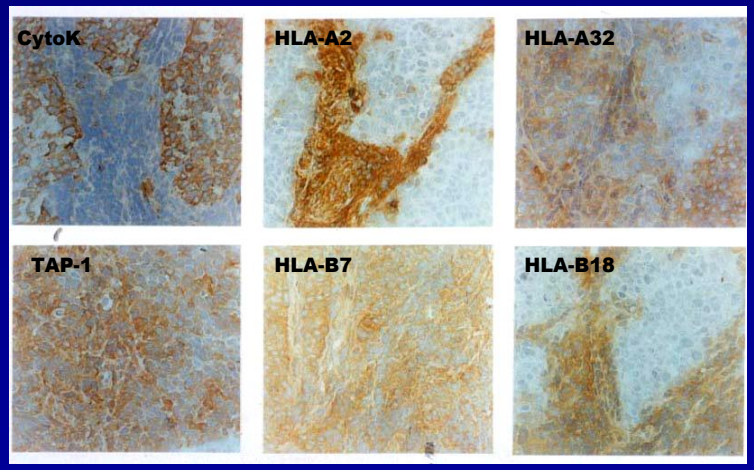
Cancer Research 61: 192



CIN III : Bontkes et al 1998

Lancet 351: 187





CaCX: Koopman et al 2000 JEM 191: 961

CIN III	CaCX	VIN III	CaVU
30%	90%	28%	82%

Immune response after natural infection: Protection correlates with antibody titre

- High antibody levels against HPV 16 and 18 following a natural infection are associated with a reduced risk of subsequent HPV 16 and 18 infections

Costa Rica Vaccine trial (placebo arm)

Antibody level category*	HPV 16			HPV 18		
	Infections	Incidence 100/PY	Multivariable RR (95% CI)†	Infections	Incidence 100/PY	Multivariable RR (95% CI)†
Negative	231	3.92	1.00 (-)	136	2.14	1.00 (-)
0–33rd percentile	20	3.19	0.79 (0.48–1.22)	19	3.06	1.36 (0.81–2.15)
33–66th percentile	28	3.74	0.83 (0.53–1.25)	17	2.24	1.01 (0.59–1.65)
≥ 66th percentile	12	2.06	0.50 (0.26–0.86)	6	0.89	0.36 (0.14–0.76)

* Antibody levels were assessed using a VLP-based direct ELISA.
† Models adjusted for age, education, marital status, lifetime number of partners and smoking status.
PY = person years; RR = rate ratio.

Safaeian M, *et al*. *J Natl Cancer Inst* 2010; **102:**1–10.

MANCHESTER 1824

The University of Manchester

Requirements for a vaccine to meet the challenges of preventing HPV infection and cervical cancer

- **Virus-like particles closely mimic the virus structure[1]**
  - Induction of neutralizing antibodies – major basis of vaccine-induced protection[2,3]
- **Greatest possible protection against cervical cancer-causing HPV types**
  - Include VLPs for HPV 16 and 18[2]
- **An immune response that improves on natural immunity[2]**
  - As natural serological immunity does not guarantee protection[4]
- **As boostability of B-cell memory by natural infection is unknown, maximal longevity of antibody levels is needed[5]**
  - To maintain protective immune responses throughout sexually active life
- **Imprinted Lifespan Model suggests that plasma cells are imprinted with a predetermined lifespan based on the magnitude of B-cell signalling that occurs during induction of an antigen-specific humoral immune response[5]**
  - Magnitude and longevity likely significantly influenced by adjuvants[6]

1. Deschuyteneer M, *et al. Hum Vaccin* 2010; **6:**407–419; 2. Stanley M, *et al. Vaccine* 2012; **30(suppl 5):**F83–F87; 3. Stanley M, *et al. Vaccine* 2006; **24(suppl 3):**S106–S113; 4. Schwarz TF. *Expert Rev Vaccines* 2008; **7:**1465–1473; 5. Amanna IJ & Slifka MK. *Immunological Reviews* 2010; **236:**125–138; 6. Giannini SL, *et al. Vaccine*, 2006; **24:**5937–5949.

Vaccine design

Bivalent HPV vaccine

- Contains HPV 16 &18 VLPs (made in baculovirus), adjuvanted with AS04 Adjuvant System (Aluminium salt + Monophosphoryl lipid, MPL)
- Recognition of MPL by TLR4 leads to enhanced and more Th1-biased, humoral and cellular responses

Giannini SL et al. *Vaccine* 2006;24:5937–5949

Quadrivalent HPV vaccine

- Contains HPV 16, 18, 6 & 11 VLPs (made in yeast), adjuvanted with an aluminium salt: amorphous aluminium hydroxyphosphate sulphate (AAHS**)**
- Classical aluminium salt adjuvant potentiated immune response

Villa LL, *et al. Vaccine* 2006; **24:**5571–5583

Vaccination immunogenicity/efficacy clinical trials

- ~100% seroconversion rates
- Superiority over natural antibody levels
- Approaching 100% protection against HPV 16/18 infection/lesions in naïve individuals for at least 5 years

Vaccine efficacy against CIN2+/CIN3+ irrespective of HPV type

No head to head efficacy studies were carried out – those comparisons are only informative

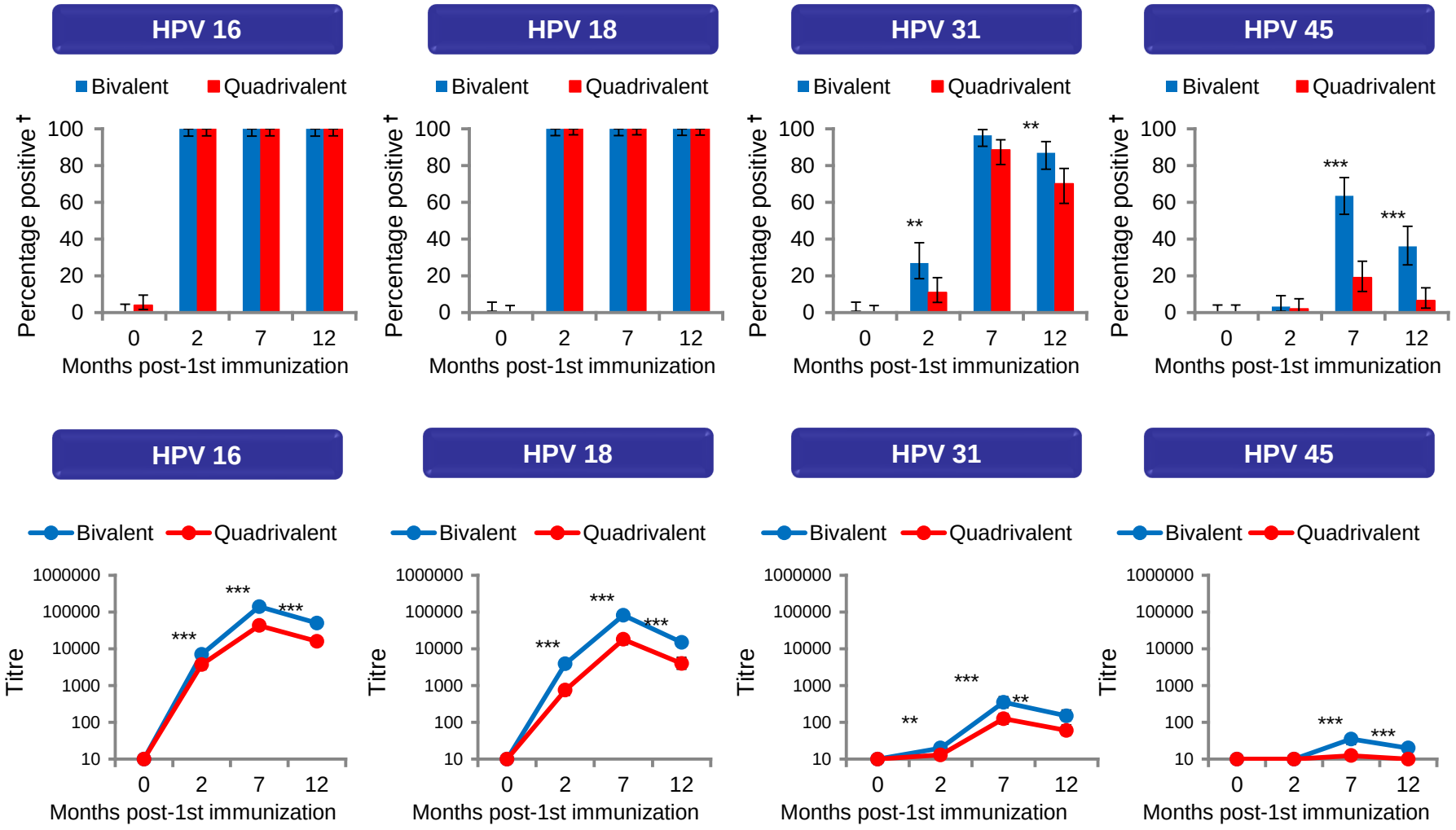
	Quadrivalent Combined protocols Future I, Future II R-MITT-2 cohort (EOS data)*[1]					*Bivalent Protocol 008 TVC-naïve cohort (48 months of FU**)*[2,3]				
Lesion	***Gardasil®***		**Control**		**%Efficacy (95% CI)**	***Cervarix®***		**Control**		**%Efficacy (95% CI)**
	N	**n**	**N**	**n**		**N**	**n**	**N**	**n**	
CIN2+, irrespective of causal HPV type	4616	77	4680	136	**42.7** (23.7; 57.3)	-	61	-	172	**64.9** (52.7; 74.2)
CIN3+, irrespective of causal HPV type	4616	36	4680	64	**43.0** (13.0; 63.2)#	-	3	-	44	**93.2** (78.9; 98.7)

*Naive cohort = ≥1 dose of vaccine and at enrollment, seronegative and DNA negative for HPV types 6, 11, 16 and 18; DNA negative for 10 non-vaccine HR types (31, 33, 35, 39, 45, 51, 52, 56, 58 and 59); and had a normal Pap test result; average duration of follow-up for the combined protocols 013 and 015 was 3.6 years after receipt of dose 1 and maximum of 4.9 years. # for *Quadrivalent* the endpoint was CIN3

**TVC-naïve cohort=Population naïve to 14 oncogenic HPV types at baseline; N = number of evaluable women in each group; n = number of evaluable women reporting at least one event in each group; BOLD = statistically significant.

1. *1. Munoz et al. J Natl Cancer Inst 2010; 102:1–15; 2. Lehtinin Lancet Oncology 2012; 13 89-99; 3. Wheeler et al Lancet Oncology 2012; 13 100-110*

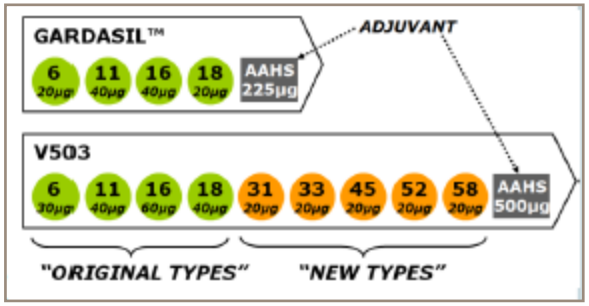
Bivalent vs Quadrivalent responses in girls aged 12–15 years



† Percentage of vaccinees with titres of ≥ 20; Error bars, ±95% CI; $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
Bivalent M0 (n = 94), M2 (n = 91), M7 (n = 91), M12 (n = 92);
Quadrivalent M0 (n = 93), M2 (n = 98), M7 (n = 97), M12 (n = 96).

Adapted from Draper E, *et al*. *PlosOne* 2013; **8:**e61825.

V503: 9-valent HPV vaccine (HPV6, 11, 16,18, 31, 33 ,45, 52, 58)



- If V503 achieves the same level results in efficacy compared to the efficacy shown for HPV16/18 and vaccination programs are effectively implemented, almost the 90% of invasive cervical cancers (ICC) cases worldwide could be prevented.
- Only 4,5% of cervical adenocarcinomas are related with HPV types not included in V503.

Efficacy & immunogenicity in 16-26 year old women. Joura et al 2014

- 14,204 healthy 16-26 year-old women, double-blind study of 9vHPV vaccine (controlled with qHPV). Subjects received 9vHPV vaccine or qHPV at day 1, month 2 & month 6. Analyses included subjects seronegative at day 1 & PCR negative from day 1 through month 7 for HPV type being analyzed
- Anti-HPV 6/11/16/18 responses generated by 9vHPV vaccine non-inferior to qHPV vaccine.
- Efficacy of 9vHPV vaccine against a composite endpoint of HPV 31/33/45/52/58-related high-grade cervical/vulvar/vaginal disease was 96.7% ([95%CI: 80.9-99.8]
- Efficacy against HPV 31/33/45/52/58-related 6-month persistent infection in the PPE was 96.0% (95% CI: 94.4-97.2).

Therapeutic vaccine to treat HPV infection and/or cancer

- HPV oncogenes necessary for oncogenesis. Generation of HPV E6 & E7 specific T cells to eliminate infected or transformed cells; maybe other early gene targets.
  - Need to target at least HPV-16/18

- Need an immune response that overcomes HPV evasion strategies or any immune suppression mechanisms. Animal models are of limited value
  - Different vectors (DNA, viral, bacterial)
  - Protein/peptides with different adjuvants
  - Immune response modifiers

- Until recently therapeutic HPV vaccines had shown very limited clinical benefits & lack of correlation with immunogenicity
  - Need a clinical endpoint for proof of principle CaCx, CIN, VIN, infection

Effective therapeutic vaccines would also be protective & long-lived

Immune therapies for HPV 16 associated VIN

- Most patients had pre-existing T cell proliferative response to HPV 16
- Clinical responders showed significant increased T cell proliferative responses to vaccine, non-responders did not but were immune competent
- The density and subtype of T cells associated with the lesions was different after treatment in clinical responders and non-responders (increased Tregs)

Therapeutic effect of treatment depends on differential immune response of individuals locally & systemically

Daayana S et al. *Br J Cancer* 2010;102:1129–1136

Bagarazzi et al Sci Transl Med 4, 155ra138 (2012)

- Inovio's VGX-3100 is an immunotherapy containing two DNA plasmids targeting the E6 and E7 oncogenes of HPV types 16 and 18. The treatment is administered to patients by injection into muscle (typically in the arm), followed by electroporation using Inovio's CELLECTRA® device.

- VGX-3100 has been shown to induce a robust immune response against the E6 and E7 oncogenes associated with HPV types 16 and 18.

- Randomized, double-blind, placebo-controlled phase II trial of VGX-3100 in women with biopsy-proven cervical intraepithelial neoplasia 2/3 (CIN2/3) associated with human papillomavirus (HPV) types 16 or 18

- Women in the active group received three 6 mg doses of VGX-3100 in a 1 mL intramuscular injection followed by electroporation at weeks 0, 4, and 12. Cervical tissue was examined before starting blinded treatment and 9 months later.

HPV Immunotherapy Achieves Primary Efficacy Endpoint in Randomized Phase II Cervical Dysplasia Trial

- Treatment was randomized 3:1 between the VGX-3100 and placebo groups, and was stratified by age and severity of CIN. The primary endpoint, histologic regression, was evaluated 36 weeks after the first treatment

- In the per protocol analysis, CIN2/3 resolved to CIN1 or no disease in 53 of 107 (49.5%) women treated with VGX-3100 compared to 11 of 36 (30.6%) who received placebo. This difference was statistically significant ($p<0.025$).

- Virological clearance of HPV 16 or 18 from the cervix in conjunction with histopathological regression of cervical dysplasia to CIN1 or no disease, a secondary endpoint of the trial, was observed in 43 of 107 (40.2%) VGX-3100 recipients compared to 5 of 35 (14.3%) placebo recipients ($p<0.025$).

- As in the phase I study, VGX-3100 elicited robust HPV-specific T cell responses in the majority of treated subjects.

Challenges for therapeutic vaccines

- Most vaccines are HPV 16 or 16 & 18 E6/E7
- Many being tested in small clinical trials
  - Design may not provide sufficient momentum for further development
    - CaCx: late disease too much immune escape; early disease too long follow up required.
    - CIN3: need to better be than cure rates with LEEP etc
    - VIN3 ~ encouraging results but need higher level of cure e.g cf imiquimod.
- Proof of principle might come from looking for treatment of HPV infections with follow up to look at protection against subsequent infection

Cervical cancer in rural Africa

Thanks to Xavier Bosch