CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

6th Hellenic HPV Meeting
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Therapeutic HPV vaccines: therapeutic effect of prophylactic as well as of therapeutic HPV vaccines in patients with diseases

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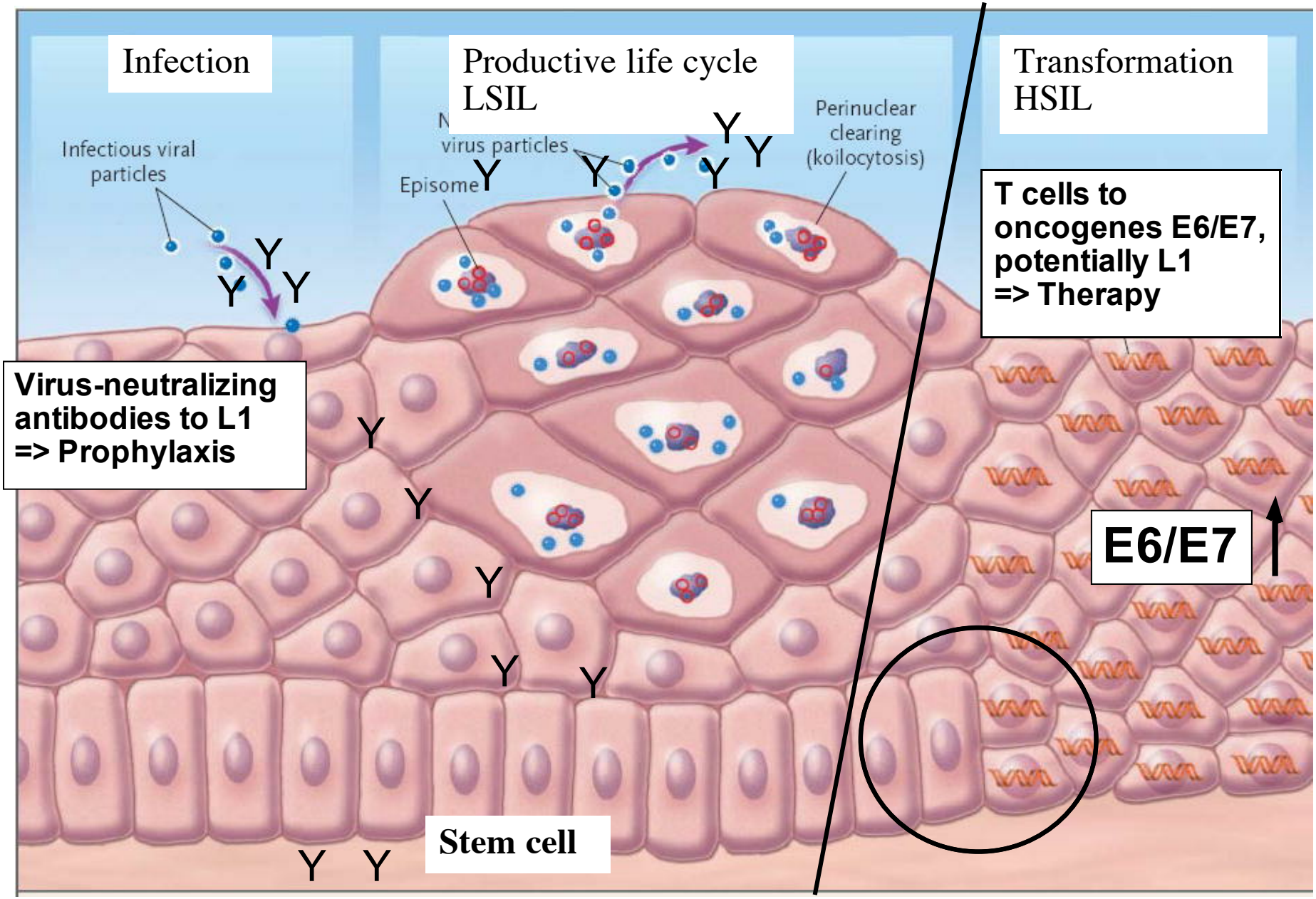
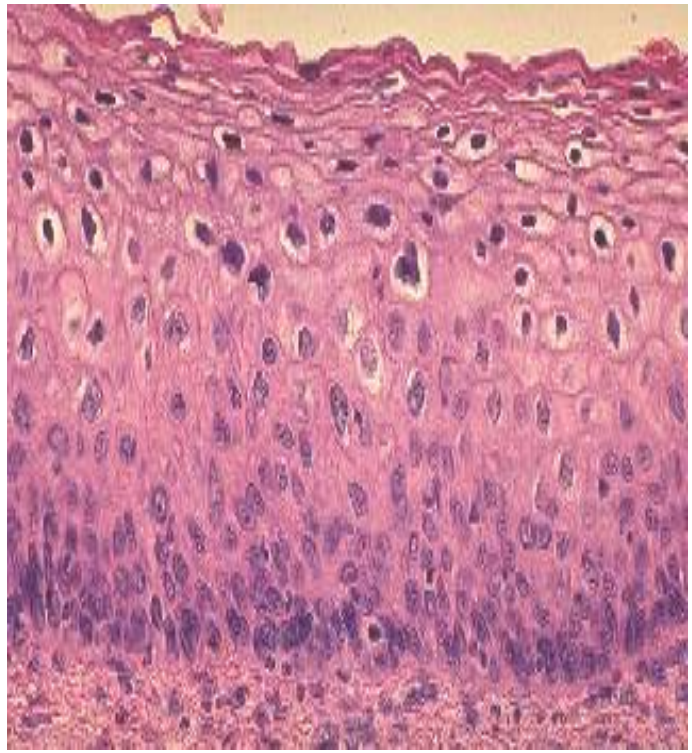
Concept of HPV Vaccines



Adepted from Goodman&Wilbur, NEJM 349:1555 (2003)

Active cellular response against HPV „therapeutic antigens“



expression

L1, L2
E6, E7, (E4)

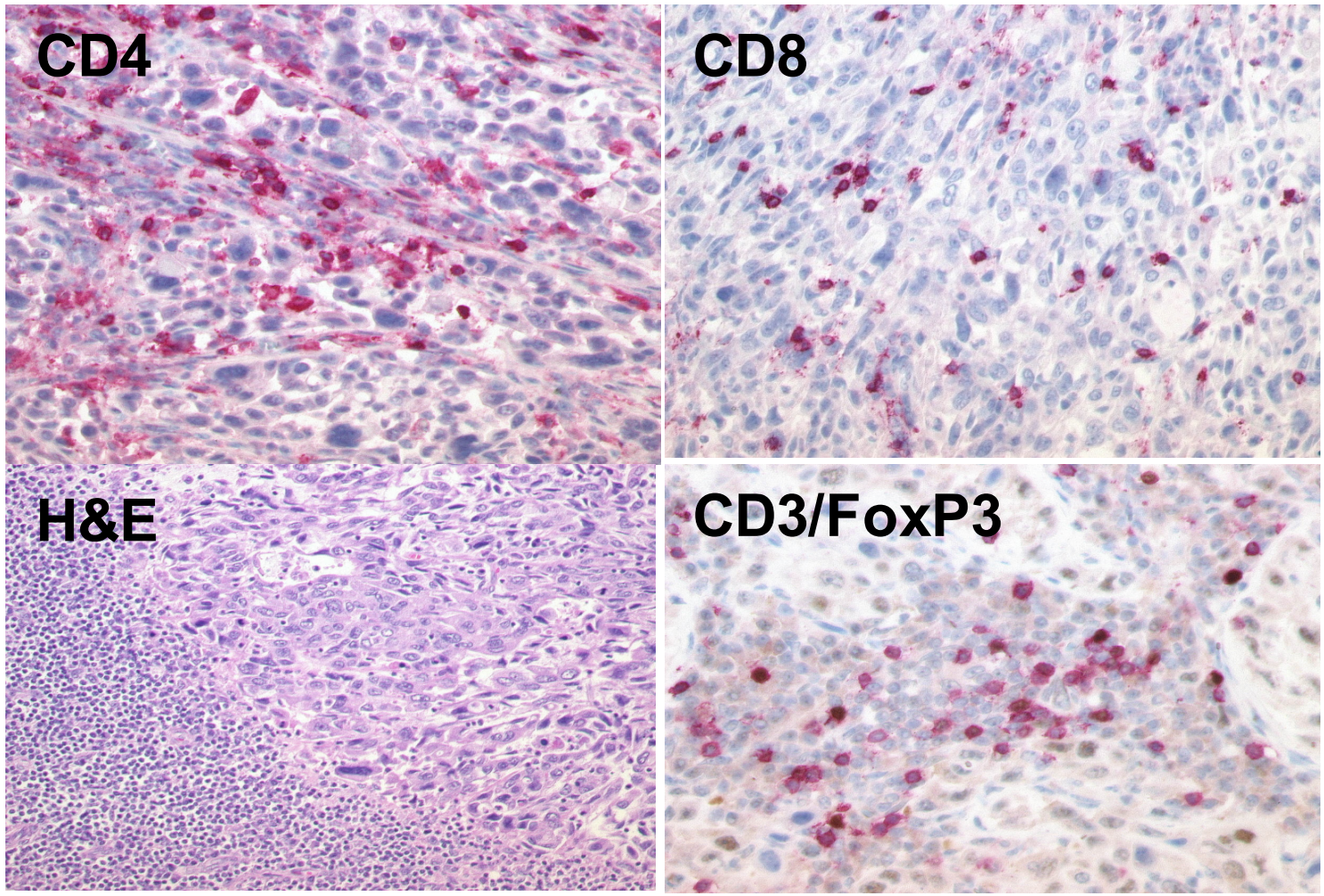
Early genes
E6, E7, E1, E2
No L1 protein detectable!?

E6 & E7: mandatory expression to support immortalised phenotype

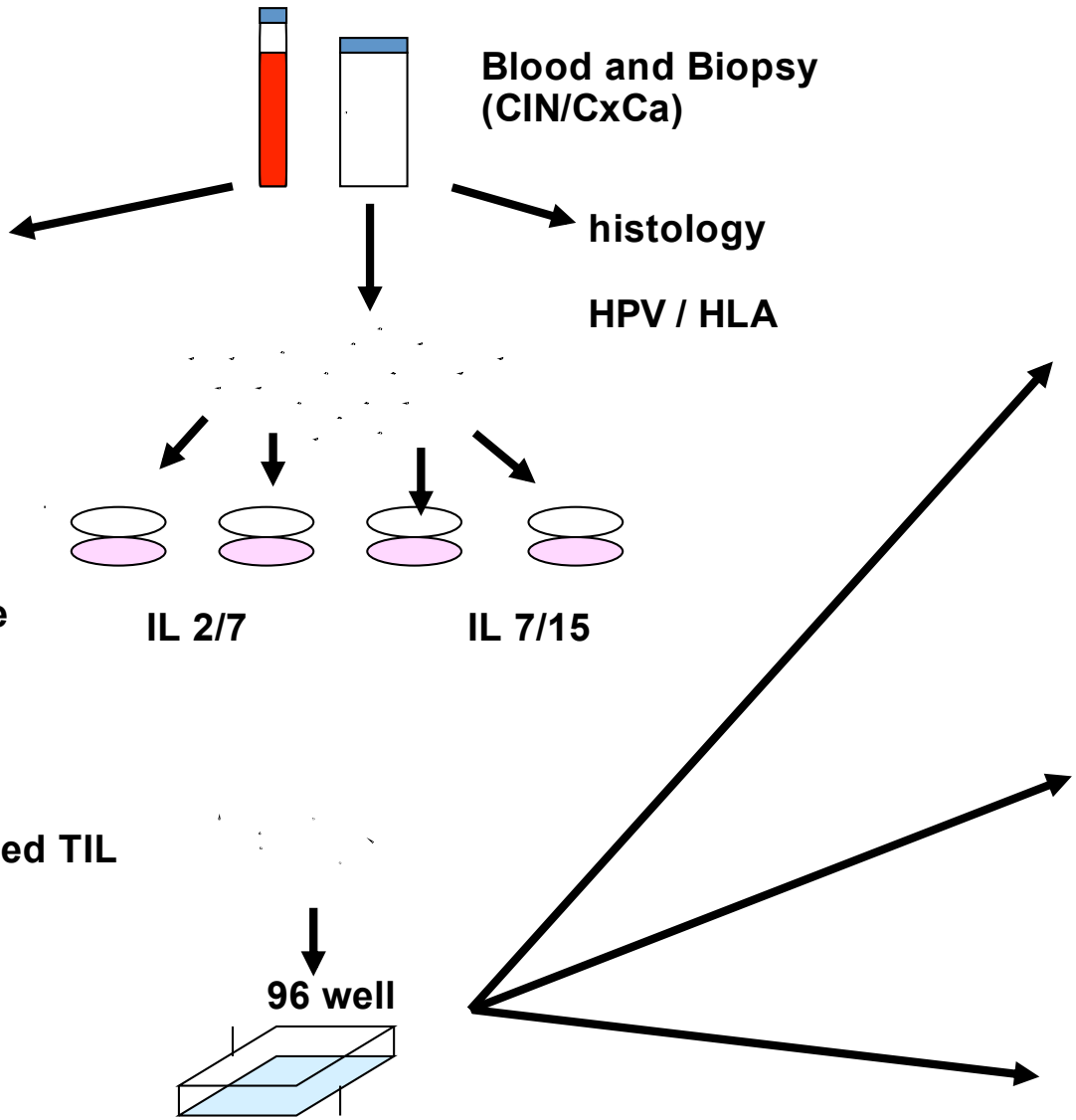
38+ Therapeutic Clinical Vaccine Trials

Vaccine	Stage	Reference	
Peptides	CxCa, CIN, VIN	Steller et al., 1998 van Driel et al., 1999 Ressing et al., 2000	Muderspach et al., 2000 Kenter et al., 2008
rec. Protein	CxCa, CIN, VIN, anal HSIL,	Frazer IH, 1999; Thompson et al., 1999; Lacey et al., 1999 de Jong et al., 2002 Goldstone et al., 2002 Berry and Palefsky, 2003 Kawana et al., 2003	Hallez et al., 2004 Frazer et al., 2004 Davidson et al., 2004 Vandepapeliere et al., 2005 Palefsky et al., 2006 Roman et al., 2007 Einstein et al., 2007
CVLP	CIN	*Kaufmann and Nieland et al., 2007*	
DNA	CIN, cervical / anal HSIL	Klencke et al., 2002 Sheets et al., 2003 Garcia et al., 2004	
rec. Vaccinia	CxCa, CIN, VIN	Borysiewicz et al., 1996 Corona Gutierrez et al., 2000 Adams et al., 2001 *Kaufmann et al., 2002* Davidson et al., 2003 Baldwin et al., 2003	Smyth et al., 2004 Corona Gutierrez et al., 2004 Garcia-Hernandez et al., 2006 Fiander 2006 Albarran et al., 2007
Dendritic cells	CxCa	Santin et al., 2002 Adams et al., 2003	*Ferrara & Nonn et al., 2003* Santin et al., 2008

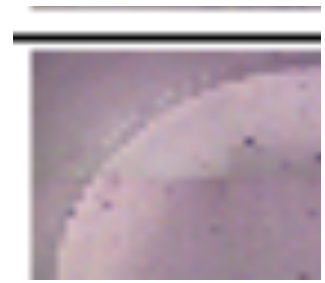
Tumor-infiltrating Lymphocytes *in situ* Immunohistochemistry of CxCa



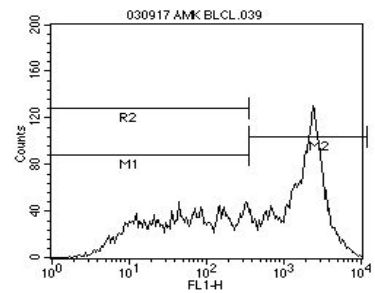
Specificity of Tumor-infiltrating Lymphocytes (TIL)



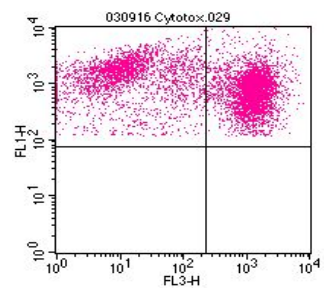
T cell assays:



INF-g ELISpot

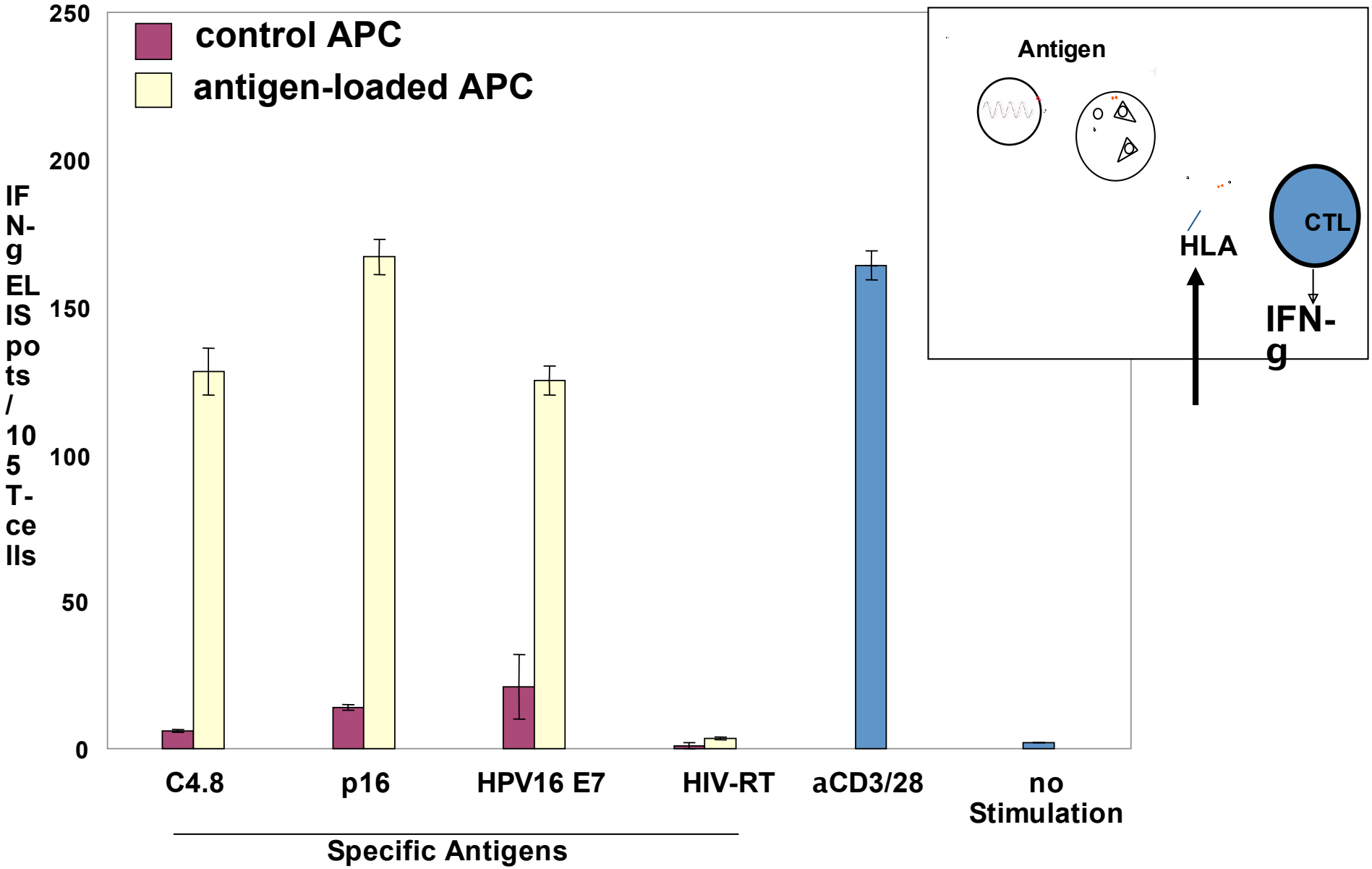


CFSE Proliferation



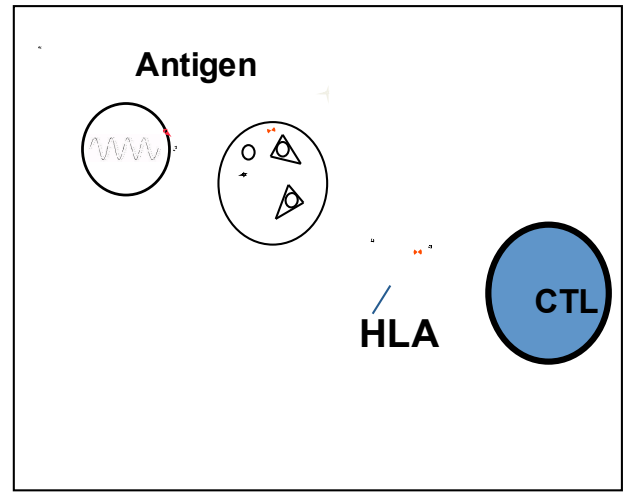
FACS Cytotox

Antigen Specificity of TIL: IFN-g ELISpot



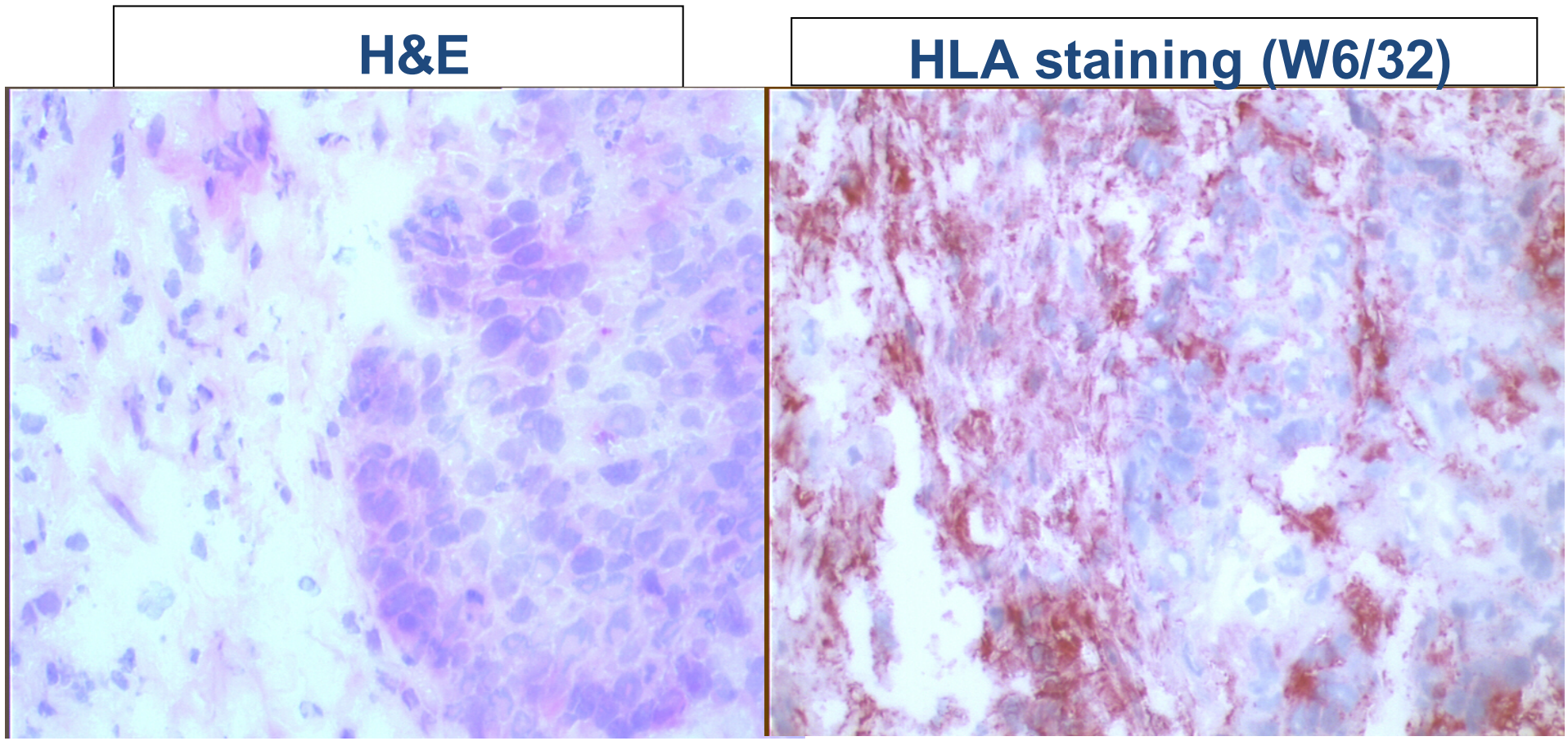
TIL in vitro

- antigen specific
- funktioning
- IFN-g positive
- cytolytic



Still the tumor is there!

Cervical Cancer FIGO IV
Immunohistochemistry for MHC I/HLA-ABC



70% FIGO III/IV CxCa show HLA loss

HLA Loss due to effective T-Cell response

Darwin: „survival of the fittest“

HPV persistency => tumor progression

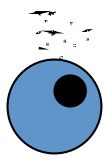
HPV Infection

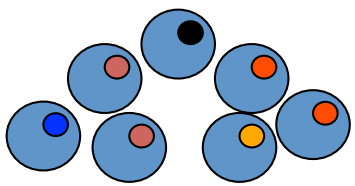
Proliferation, genetic aberration

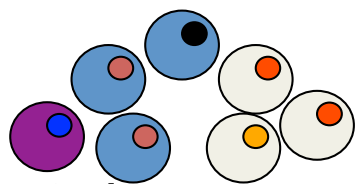
Heterogenisation, Variants

Selection pressure
- Immune response
- Immune evasion

Relaps with HLA loss

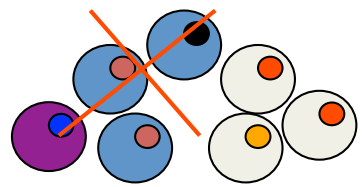




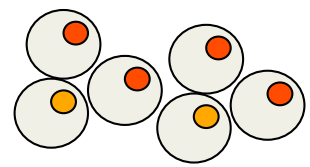


Metastasis

HLA loss

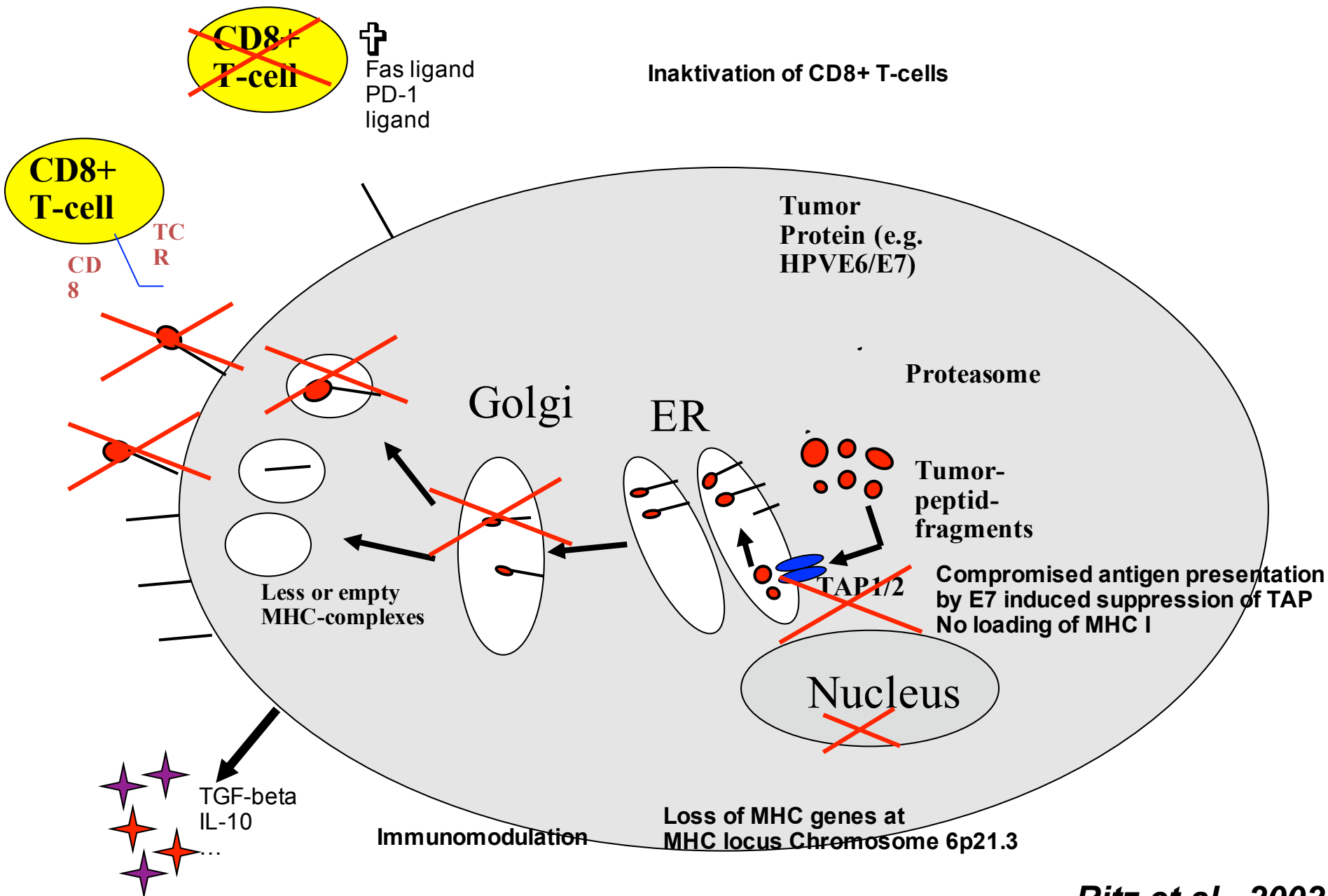


effective T cell lysis !



HLA negative: Escape Variants

Mechanisms of Immune Evasion by HPV interference



Ritz et al., 2002

The Immune System has Failed

- **No – otherwise no immune selection**
- **Yes – too late and weak**
- **Can we correct for that?**
  - **Potent adjuvants and immune regulators**

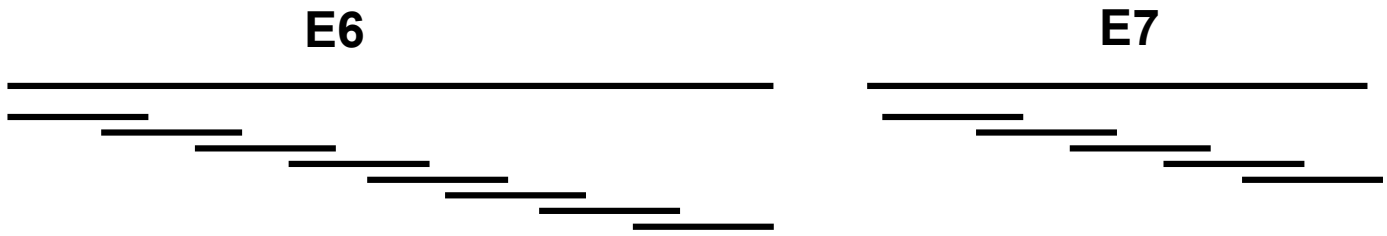
Newer Studies

- **In premalignant lesions (CIN, VIN)**
- **efficacy >50%**
- **Immune correlation to T-cell response (CD4)**

- **problem: also induction of suppressive Treg by vaccination**

Effective therapeutic HPV-Vaccine for CxCa

vaccine: long synthetic E6/E7 Peptides with Adjuvans



300 ug Peptide in DMSO/PBS
+ incomplete Freunds Adjuvans: Montanide ISA-51
2,8 ml

CxCa: Phase I toxicity study, 35 Patients, no options,
3 different application regimens, 4 vaccinations,

- **Toxicity not above grade 2,**
- **Wide and robust T-cell response induced in CxCa patients (normaly none or weak),**
- **1 complete remission, 5 stable disease, (4 with concurrent chemo therapy) 18-25 months post end of study**

Kenter et al., Clin Cancer Res 14: 169-177 (2008)

Therapeutic HPV-Vaccine: VIN III (premalignant Situation)

VIN III: persistent, HPV16 pos., 3-4 vaccinations

ÞSymptoms, Lesion size, Histology, HPV16 DNA

- Month 12: **15/19 (79%) clinical response (>50%),**
  9/19 (47%) complete Response (also Mo 24)
- all patients with complete remission had strong T-cell responses and also smaller lesions
- Patients without remision had no/low T-cell responses, larger lesions

Þ**Immune correlation for efficacy !**

Þ**CD4 TH1 responses**

Kenter et al., N Engl J Med 361:1838-47 (2009)

Long peptide vaccine in VIN Patients: Immune correlation of efficacy

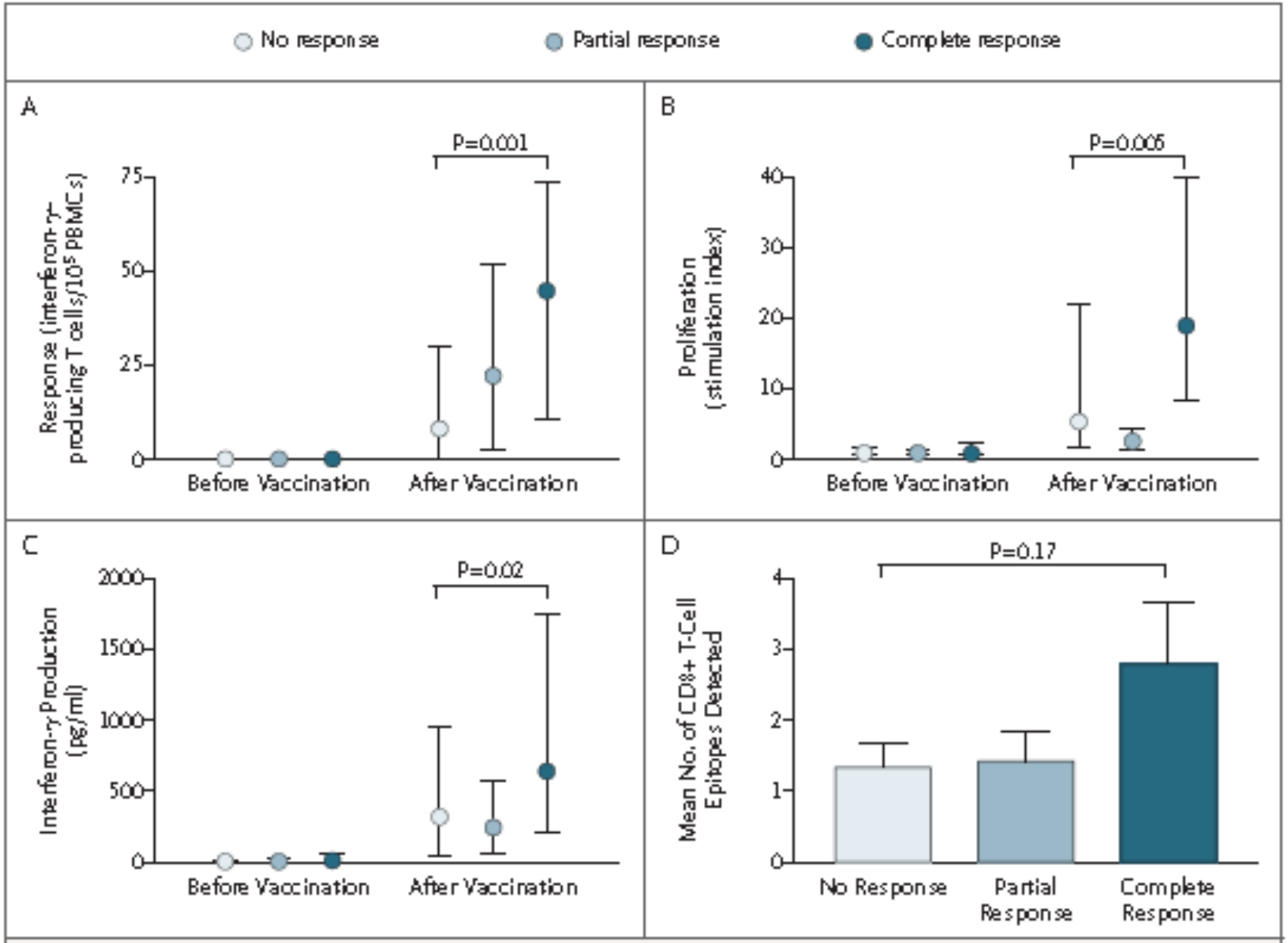


Figure 2. Immune Response before and after Vaccination.

Kenter et al., NEJM 361:1838-47

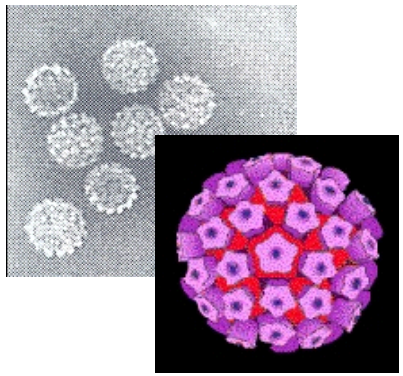
- **New therapeutic vaccines in the pipeline**

- **Better stronger adjuvants**

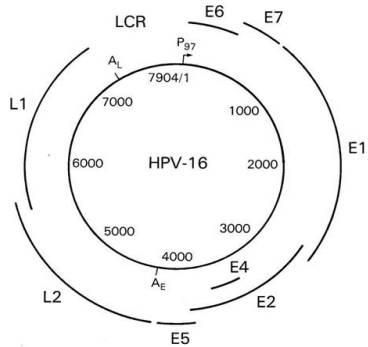
- **Trials in earlier disease stages**
- **LSIL**
- **HPV infection**

Principle of the prophylactic HPV Vaccines

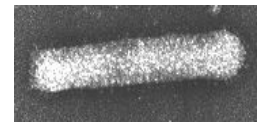
natural
Human Papilloma Virus



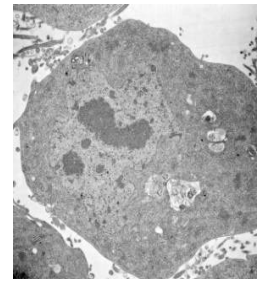
HPV Genome



Gentechnical production of L1

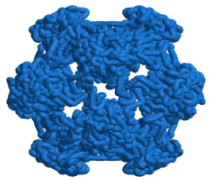


in Bacteria

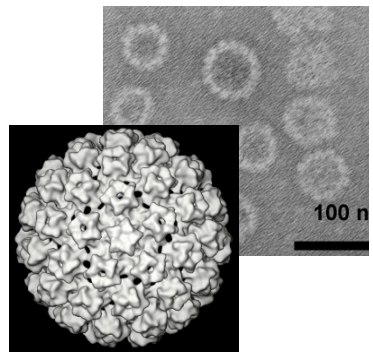


in Yeast o. Insect cells

L1: immunogenoc capsid protein



L1 Protein forms Subunits („Capsomere“)



Virus Like Particle (VLP):
empty virus shell (no viral oncogenes), immunogic, safe

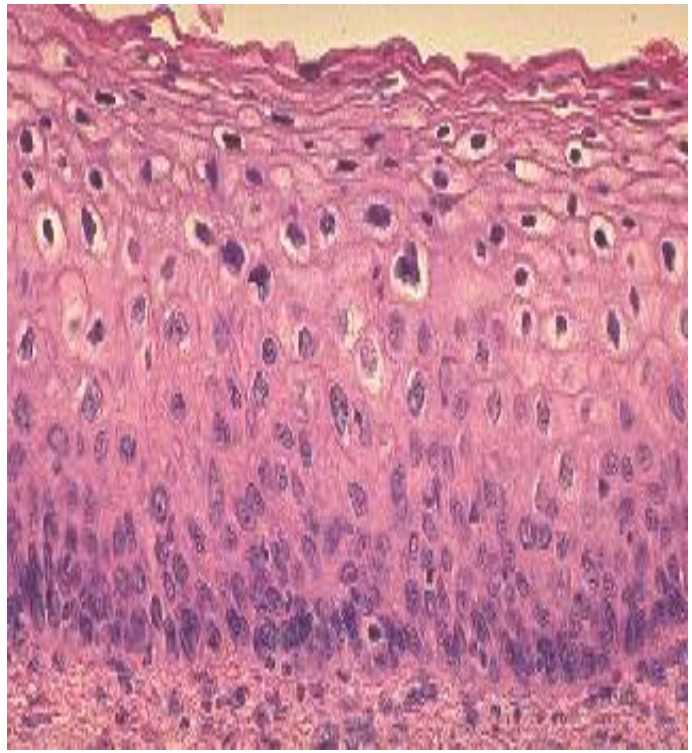
Vaccine:
Mixture VLPs
+ Adjuvant

Active cellular response against HPV „therapeutic antigens“

abundant L1

translated mRNA by switched off repressor

repressed L1 mRNA



expression

L1, L2
E6, E7, (E4)

Early genes
E6, E7, E1, E2
No L1 protein detectable!

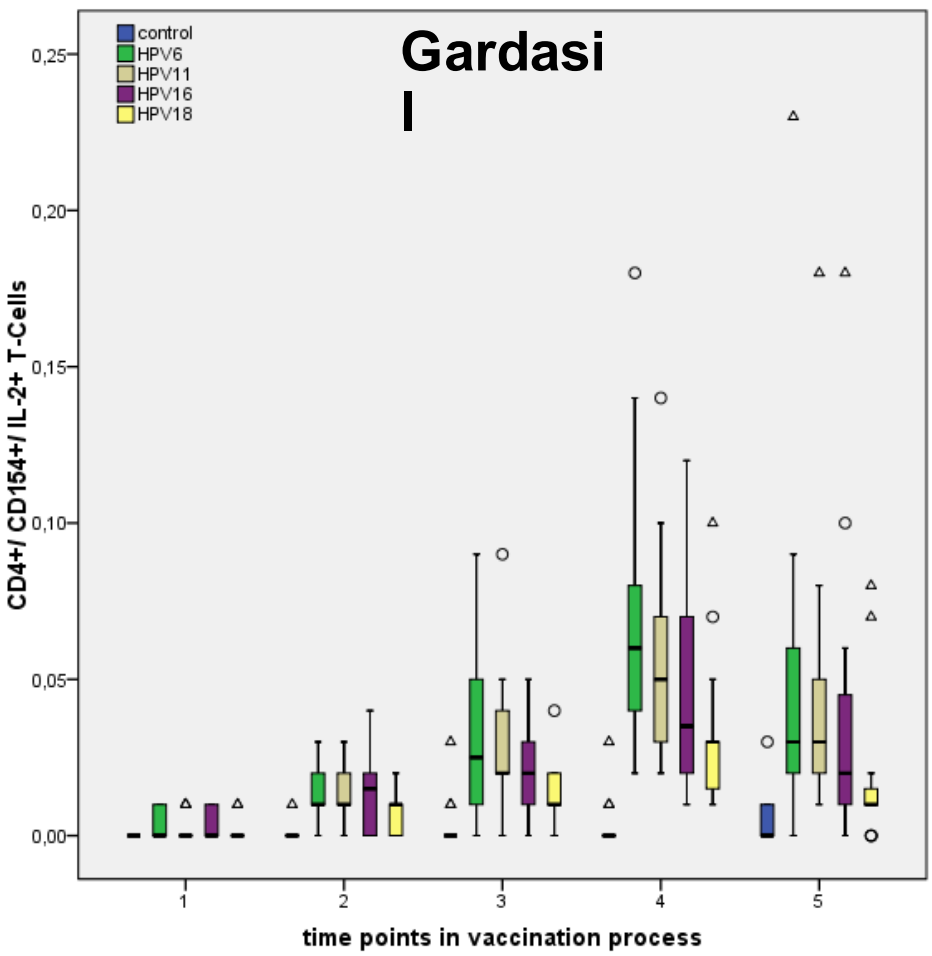
L1 mRNA is translationally controlled (leaky?)
=> low antigen amount present?

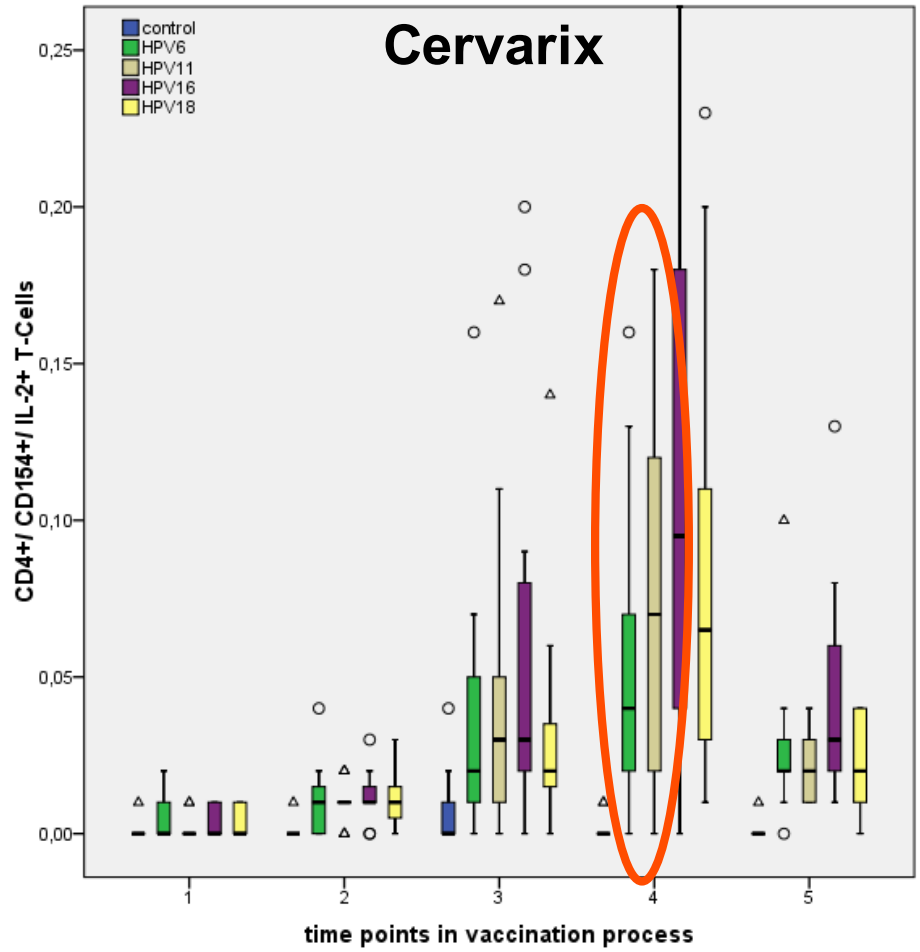
E6 & E7: mandatory expression to support immortalised phenotype

Reasons for T cell resistance of keratinocytes

- **No L1 antigen expressed in stem cells (…?)**
- **Immunosuppressive character of stem cells (at least cancer stem cells)**
- **Immunoprevileged site**
- **Immune escape**

HPV specific CD154/IL-2+ T-helper cell frequency over 1 year





pre vaccination 5 wk post 1st 2 wk post 2nd 1 yr post 1st 5 wk post 3rd

pre vaccination 5 wk post 1st 2 wk post 2nd 1 yr post 1st 5 wk post 3rd

T/B Cell Interaction

Each linear epitope of an antigen, that is presented by MHC II

Activated by APC

T helper type 1/2

CD154 (CD40L)

TCR

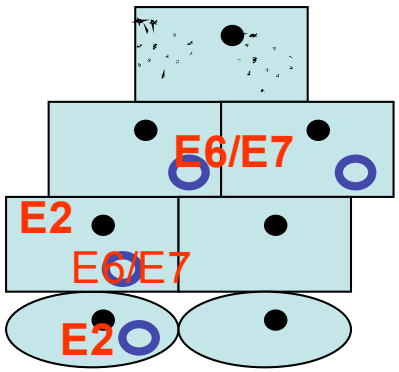
HLA-DR

CD40

B cell

3D conformational neutralising epitopes

Interleukins
IL-2, TNF-a, IFN-g, (IL-4)



L1???

Antibody

activation,
Ig-Isotyp switch,
Memory

May explain some post-infection prophylaxis by CD4 T cells

Post-conisation Vaccination

Both prophylactic HPV vaccines have shown efficacy against relaps (interpreted as reinfection with disease development)

Quadrivalent Vaccine

- Vaccinees have a **65% reduced risk** to relaps within a **1,4 years** observation time

Joura et al., British Medical Journal, 2012

*Kang et al., Gyne Onc 130, 2013 (**prospective study!**)*

Bivalent Vaccine

- Comparable Data from PATRICIA trial **88,2% reduction CIN2+ relaps**

Garland et al., Eurogin, Lisbon, May 2011

(prevention of re-infection = prophylaxis!)

Therapeutic efficacy of prophylactic HPV vaccination

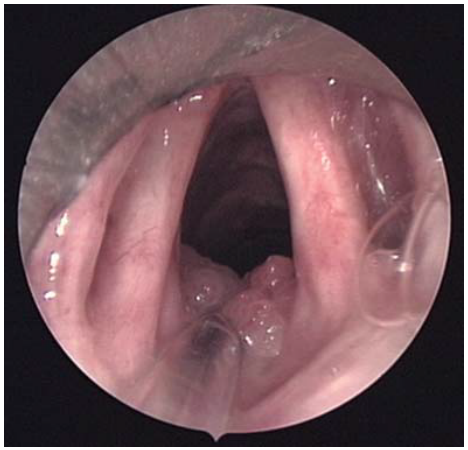
Therapy: improvment of prevalent disease

Circumstantial evidence in individual patients with disease vaccinated with quadrivalent or bivalent HPV vaccine

No other treatment involved than vaccination?

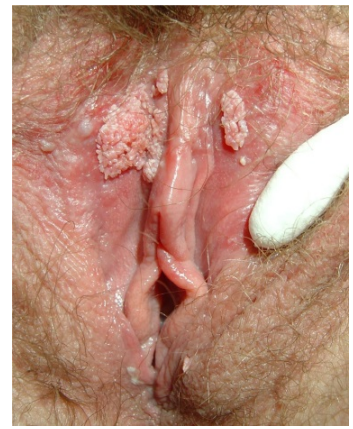
In individual patients with ongoing disease not ethical

Anecdotal „therapeutic“ effects of prophylactic vaccines in certain diseases



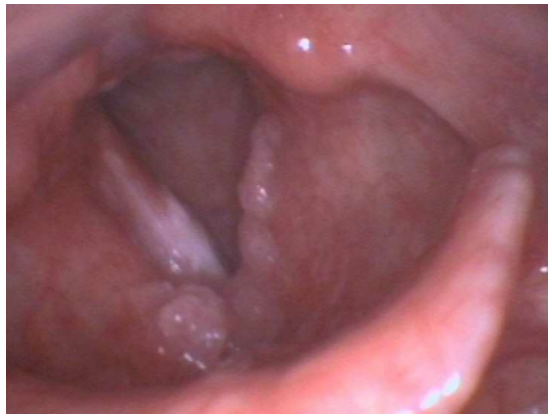
Recurrent Respiratory Papillomatosis (RRP)

- **Anogenital warts**
  - **persistent**
  - **recurrent**



Immune defect patients (WHIM-like, SCID)

RRP series of 22 patients qHPV vaccinated and immune responses analysed



Recurrent Respiratory Papillomatosis (RRP)

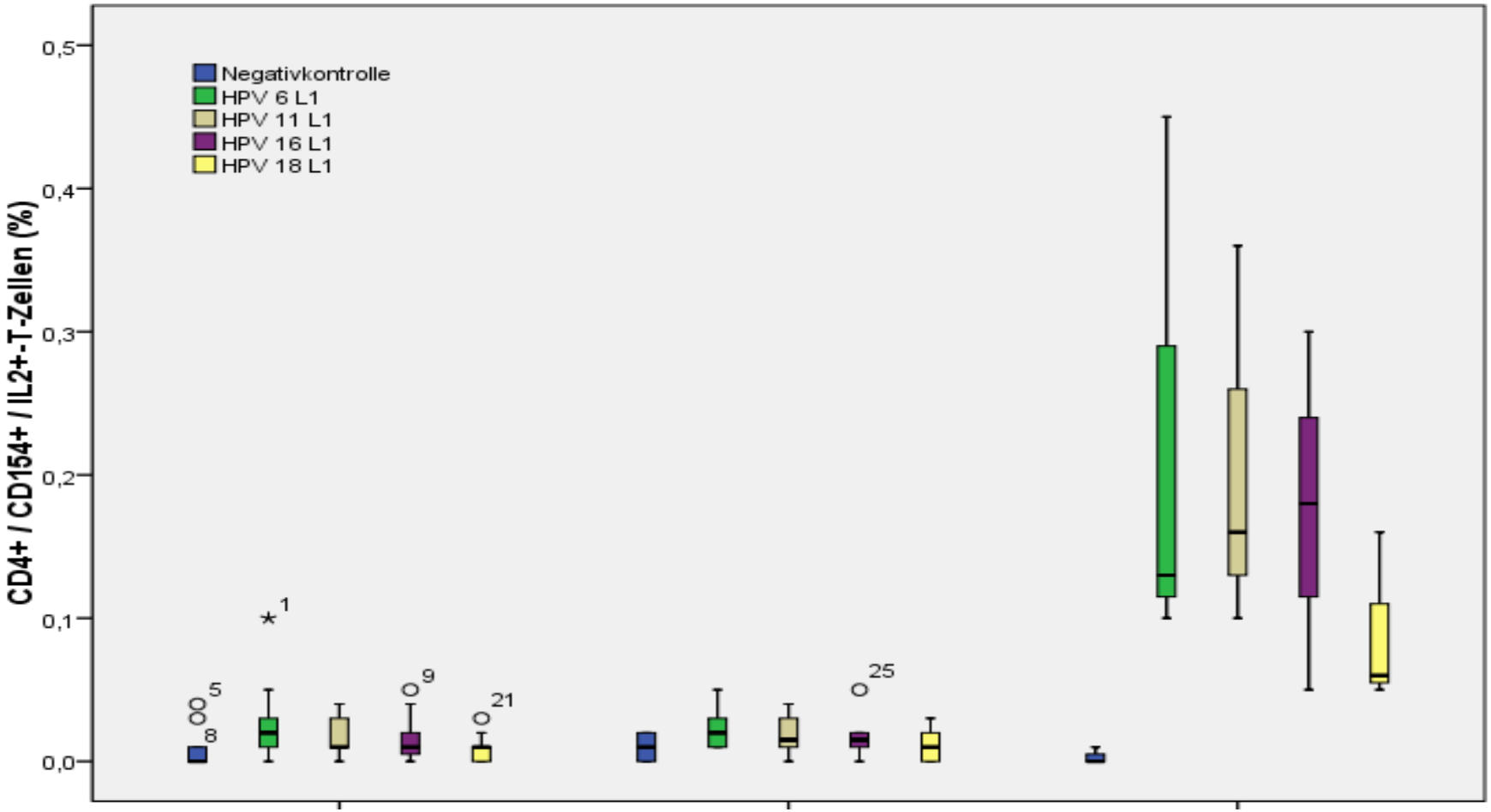
- **>90% associated with HPV 6 and 11**
- **two forms are known: juvenile (3-6 years of age) and adult form**
- **treatment: surgical ablation**
- **treatment rarely cures the disease**

Antibody to L1

M
FI

vaccination **before** **after**

HPV L1-specific IL-2 memory CD4 T cells
Series of RRP patients vaccinated 3x with Gardasil

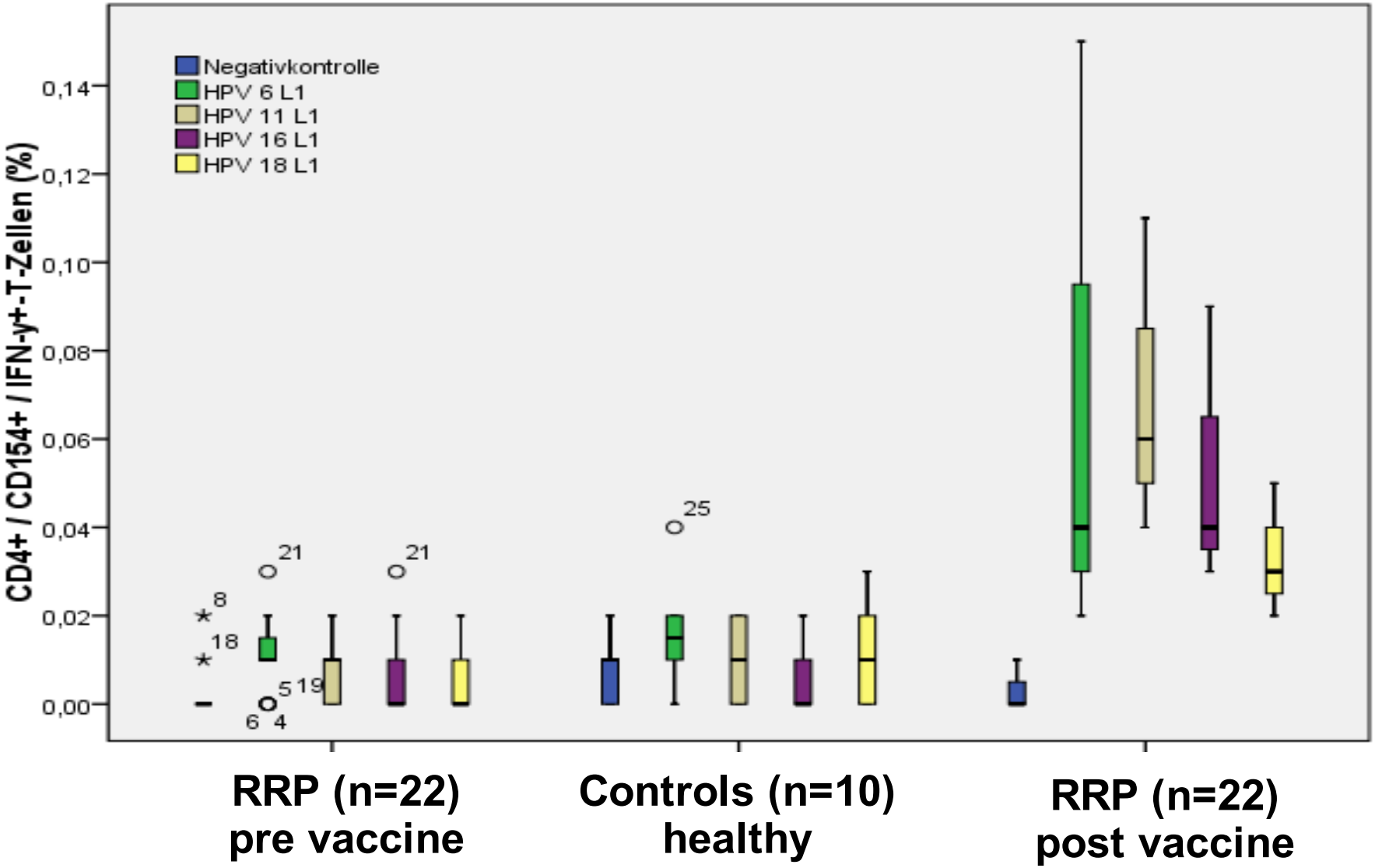


RRP (n=22) pre vaccine

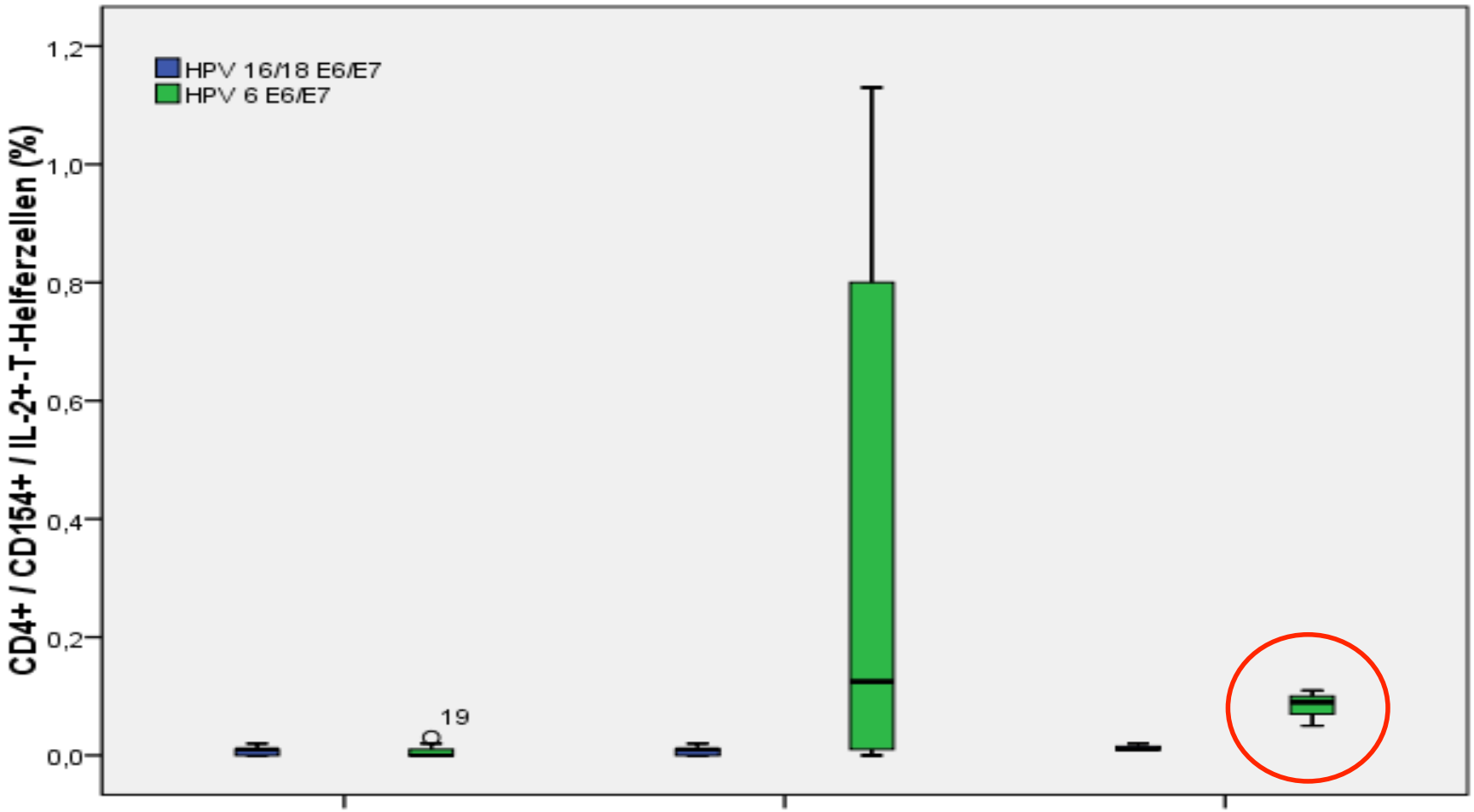
Controls (n=10) healthy

RRP (n=22) post vaccine

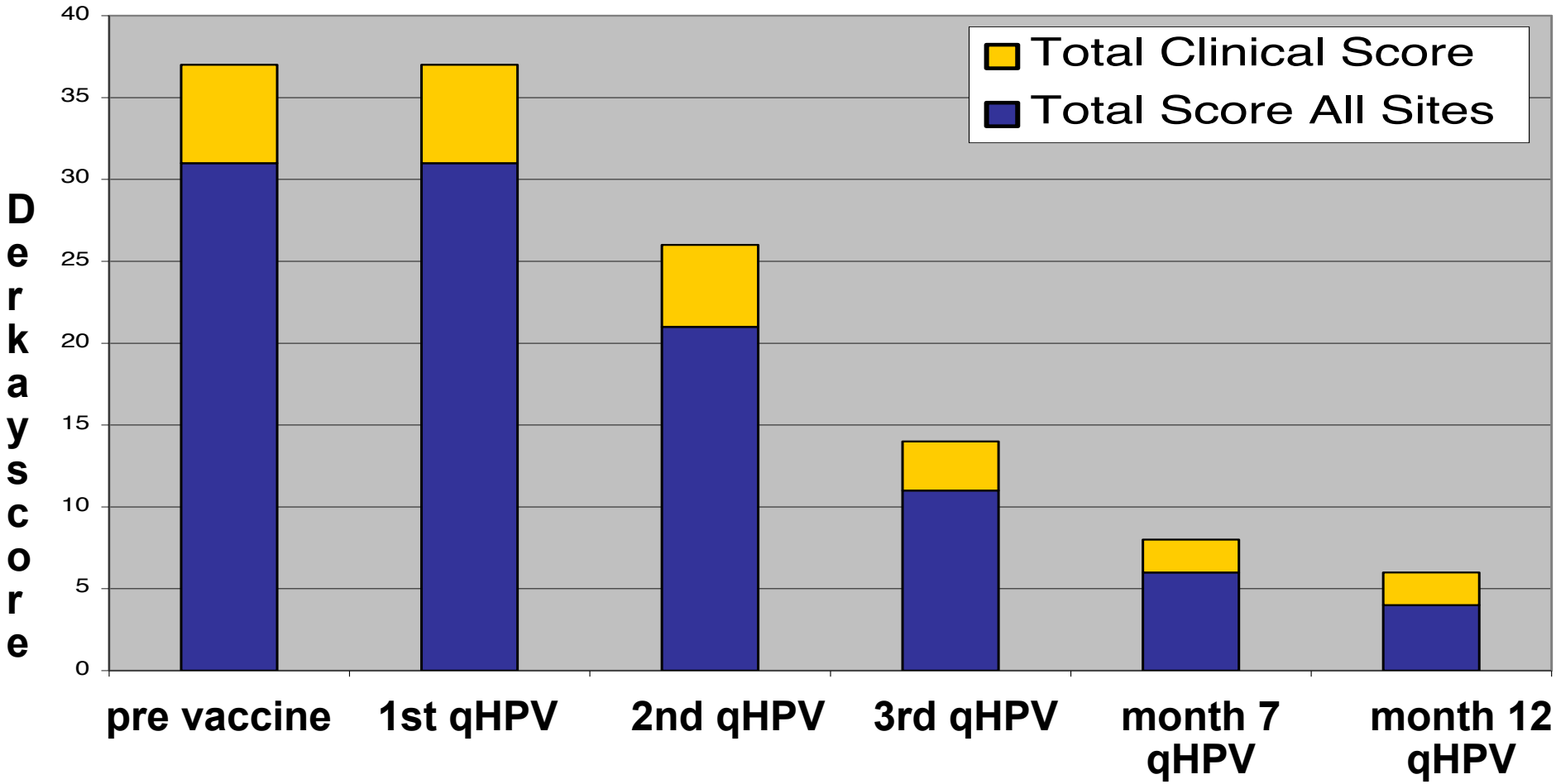
HPV L1-specific INF-g memory CD4 T cells
Series of RRP patients vaccinated 3x with Gardasil



HPV E6/E7-specific IL-2 memory CD4 T cells
Series of RRP patients vaccinated 3x with Gardasil



Clinical Derkay-score
example of one responding patient

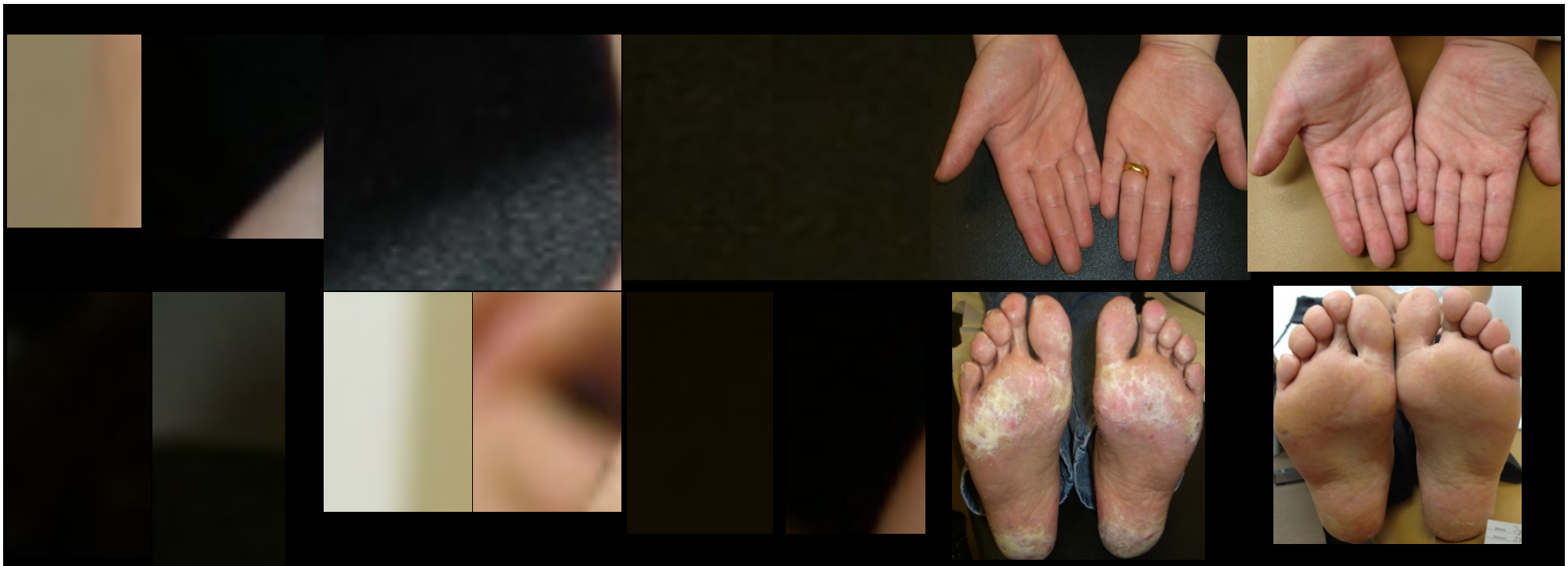


Clinical benefit

- 50% patients showed improvment of symptoms
- 2 had complete resolution (>1 year)
- 1 progressed to lung cancer (HPV11+)
- younger patients were more likely to benefit
- No adverse effects

Warts, Hypogammaglobulinemia, Infections, Myelokathexis syndrome (WHIM)

Immune defect (CXCR4), 2nd grade consanguine parents, warts (HPV27) since 10 years, plantar, condylomata accuminata frustrating therapy outcomes, Vaccination w/ Gardasil



07.2010 | 04.2011 | 07.2011 | 02.2012 | 08.2012

biweekly cryotherapy, Guttaplast and Verumal since 07/2010
Vaccination 03/2012, Vaccination 10/2012

Ex vivo antigen-specific CD4 T cell frequencies

Antigen	ex-vivo April 2011		ex-vivo April 2012		ex-vivo January 2013	
	IFNy/CD40L	IL-2/CD40L	IFNy/CD40L	IL-2/CD40L	IFNy/CD40L	IL-2/CD40L
T cell control	0,01	0,04	0,01	0,02	0,01	0,04
SEB	5,73	16,92	7,54	18,56	6,76	17,86
6L1	0,00	0,02	0,00	0,02	0,03	0,07
11L1	0,05	0,07	0,00	0,01	0,01	0,05
16L1	0,03	0,07	0,00	0,01	0,17	0,19
18L1	0,01	0,07	0,00	0,01	0,20	0,22
31L1	0,00	0,02	0,00	0,01	0,07	0,07
45L1	0,00	0,02	0,00	0,00	0,08	0,09
HPV16/18						
E6/7	0,00	0,02	0,00	0,01	0,05	0,07

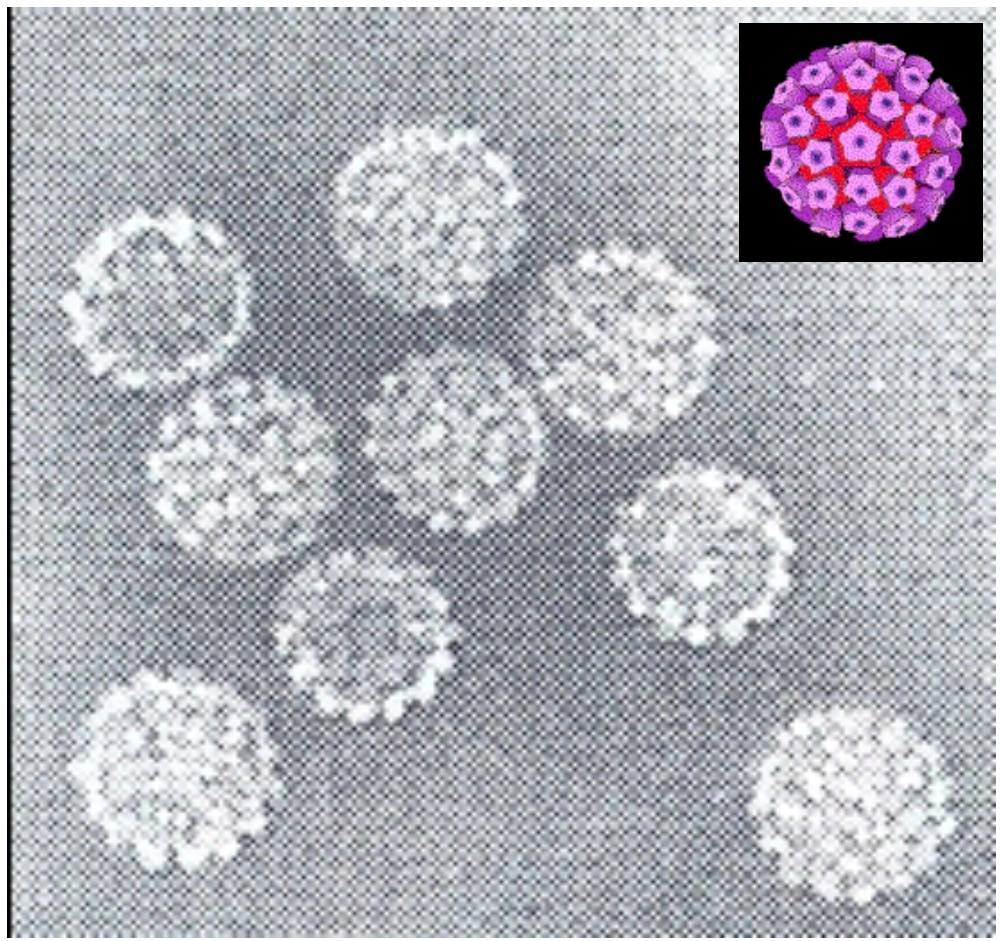
Summary

HPV infection and dysplasia is strongly immuno suppressive

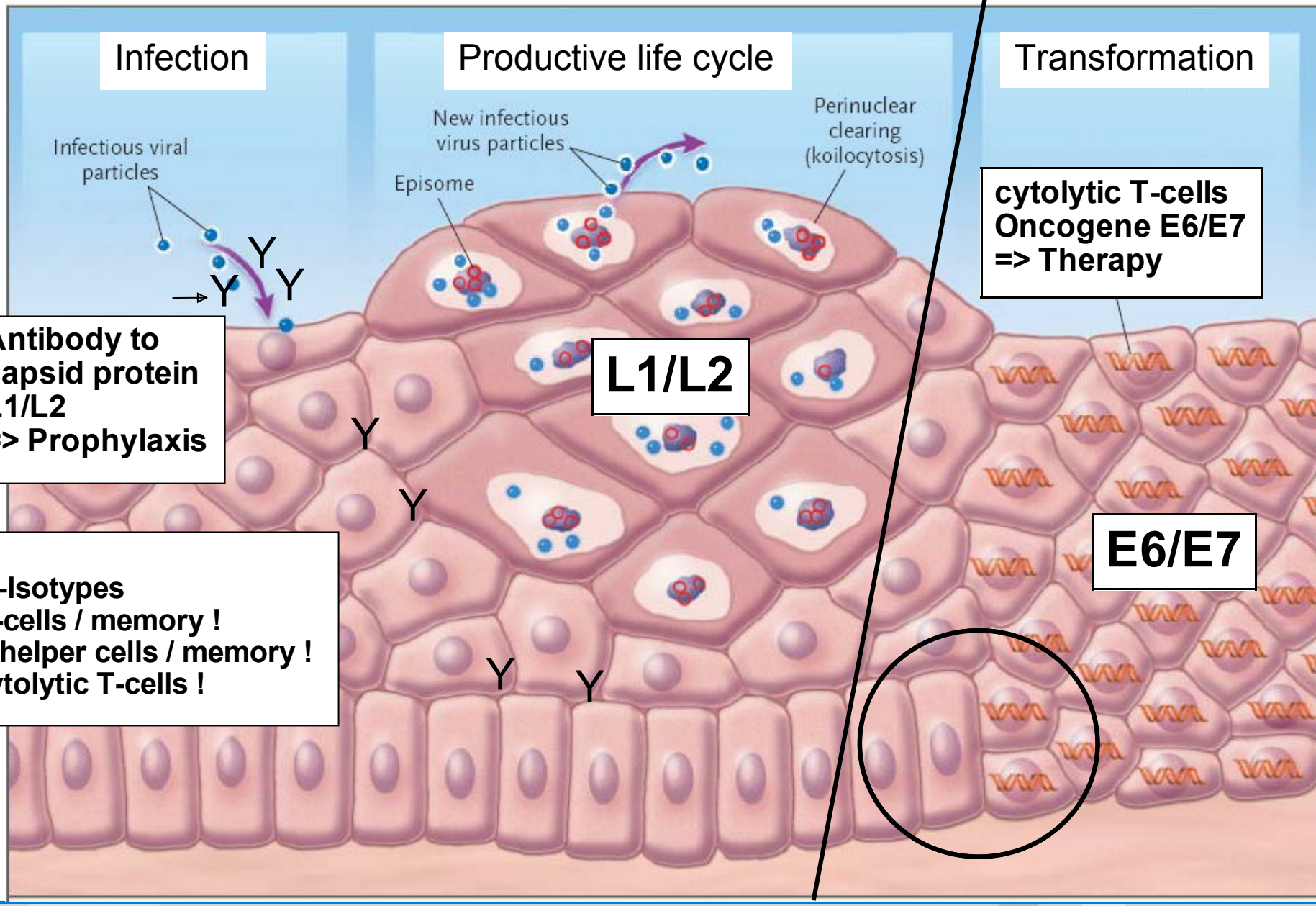
Prophylactic vaccination is based on antibodies – but also T cells may play an important role.
Some efficacy in patients with disease.

Therapeutic vaccination has to act on an immune system that has already failed. This is challenging. Better adjuvants and antigen formats show promising results in initial trials.
Again more approaches are being tested.

Thank You!

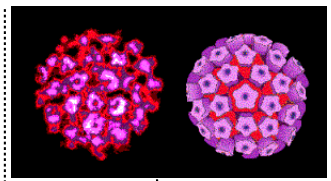


Natural life Cycle and Immunity



modified from Goodman&Wilbur, NEJM 349:1555 (2003)

HPV Infection and Immunity



8-18 months
Infection!

spont. regression:
natural immunity

HPV Infection (n = 100)

n = 80

n = 20

n = 1-2 (5?)

CIN → CA

(premalignant Lesion
Persistence, Progression)

Age years

15 20 22 40 55

Immunoselection/Evasion

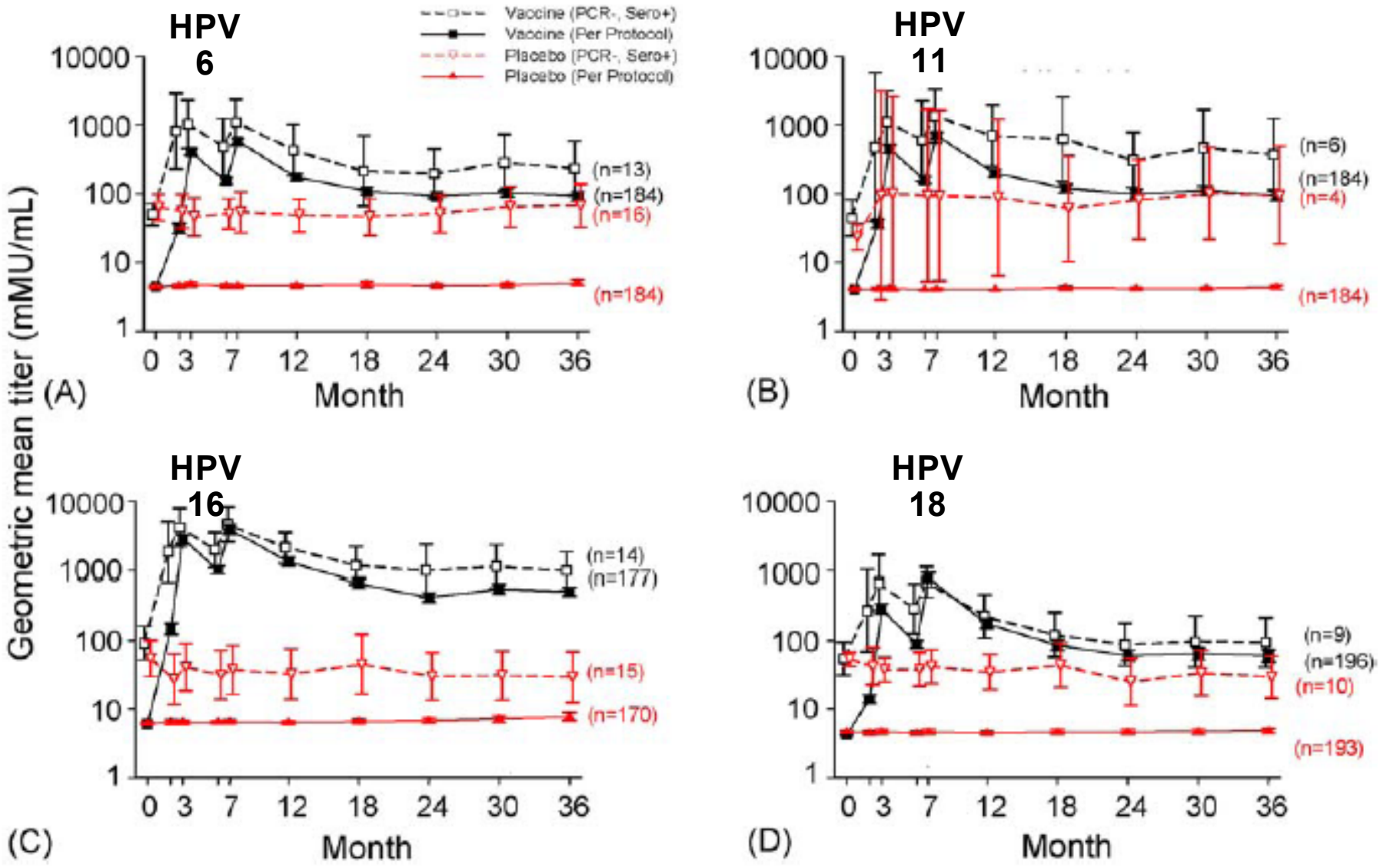
HPV Prophylaxis

CxCa Prophylaxis/Therapy
Screening

Differences of two vacciens

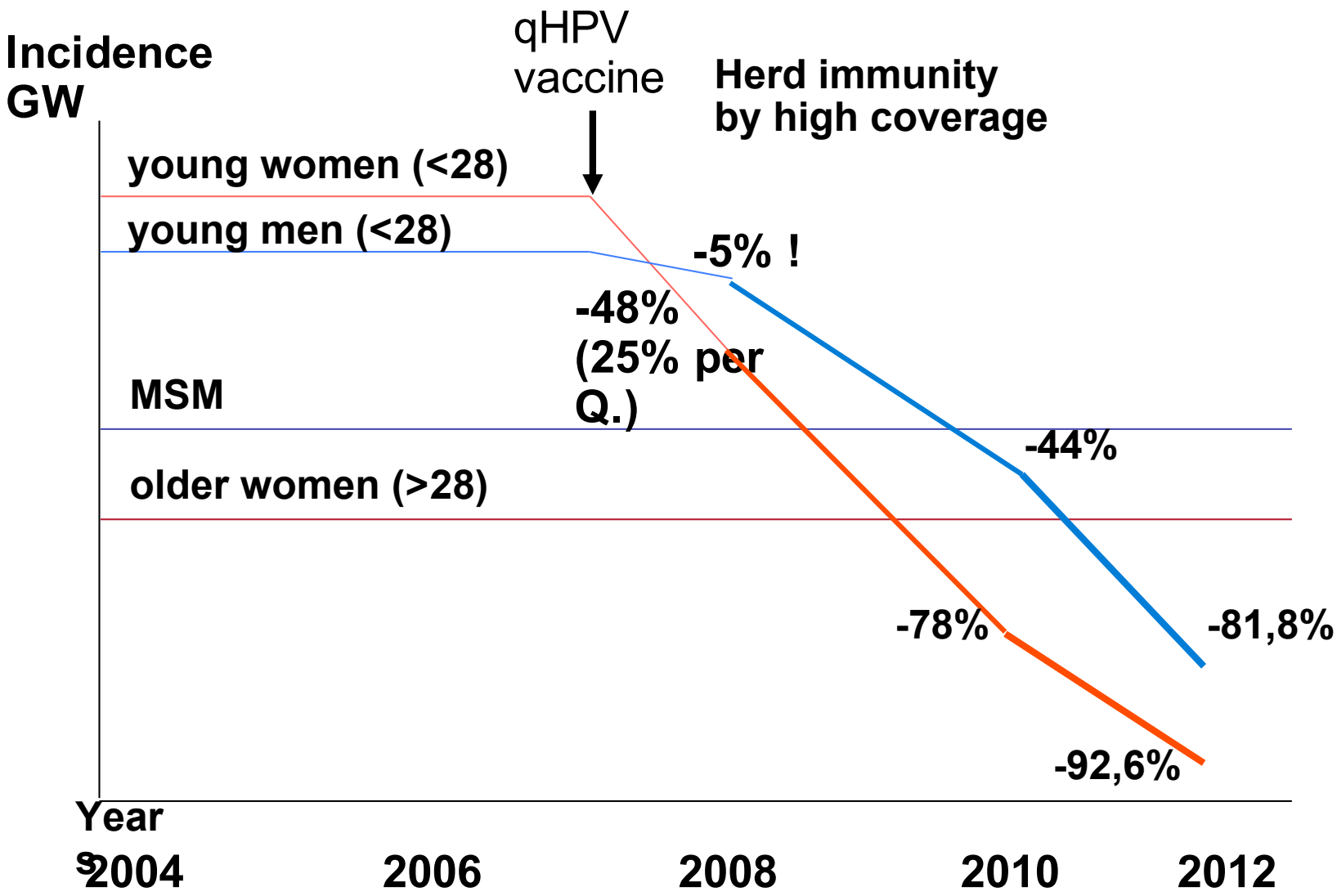
Comparison	Gardasil®	Cervarix®
Company	Sanofi Pasteur & MSD	GlaxoSmithKline
Production by recombinant technology	*Saccharomyces cerevisiae* CANADE 3C-5 (Stamm 1895) Hefe	*Spodoptera frugiperda Sf-9, Trichoplusia ni* Hi-5 Insektenzellen Zellsubstrat
Composition	*20 µg HPV 6 L1 VLP* *40 µg HPV 11 L1 VLP* 40 µg HPV 16 L1 VLP 20 µg HPV 18 L1 VLP	20 µg HPV 16 L1 VLP 20 µg HPV 18 L1 VLP
Adjuvans	AAHS: 225 µg amorphes Aluminiumhydroxy-phosphatsulfat	*AS04*: 500 µg Aluminiumhydroxid 50 µg 3-deacylated mono-phosphoryl lipid A
Vaccination Scheme	Monat 0, 2, 6	Monat 0, 1, 6
EMA Approval	Oktober 2006	Oktober 2007

Gardasil induced Antibody Titer



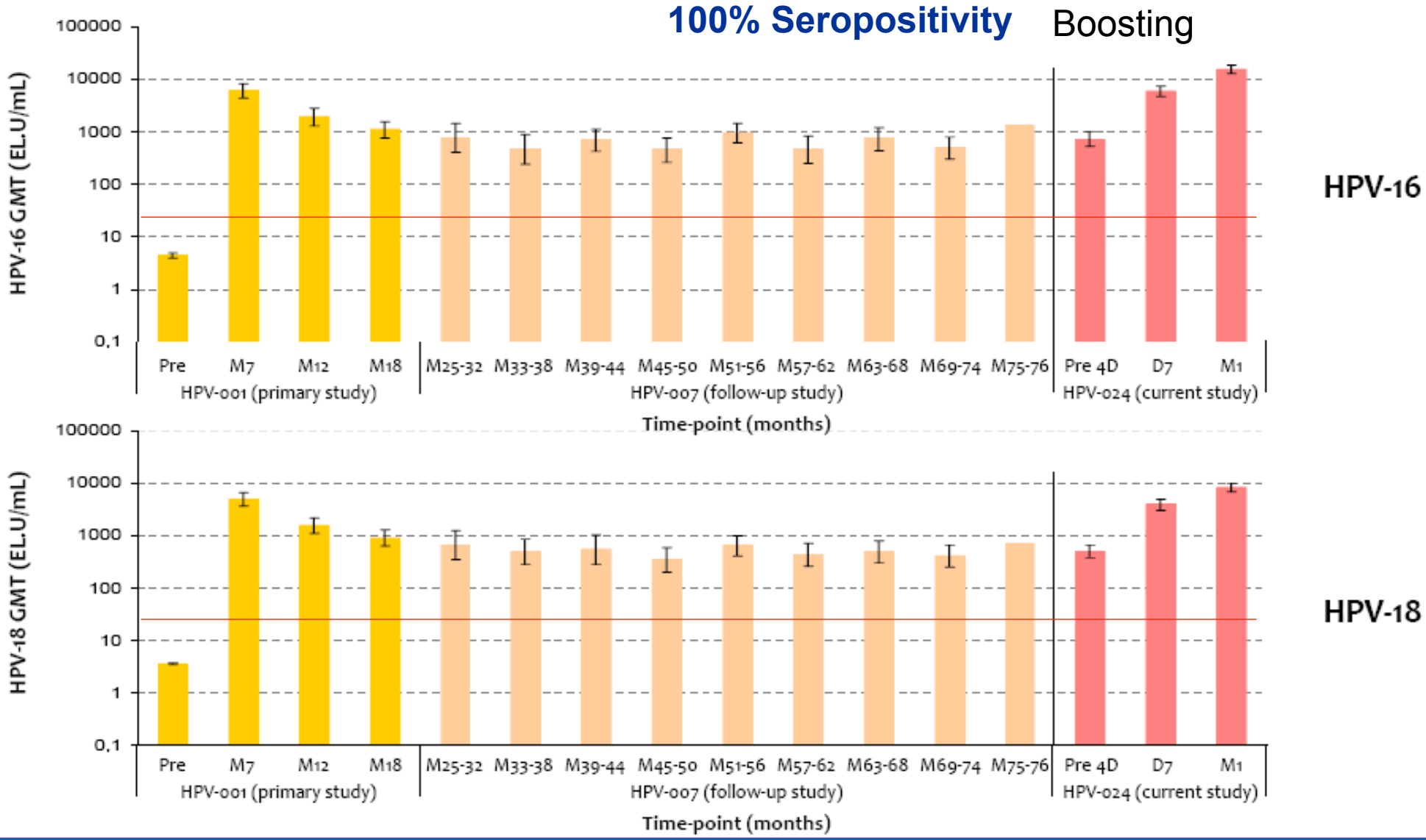
L.L. Villa et al. Vaccine 24 (2006) 5571–5583

Rapid Disappearance of Genital Warts in Australia qHPV and high coverage (>80%)



(schematic graph acc. Fairley 2009, Brotherton 2011, Ali 2013)

Cervarix®
Sustained High Antibody Titers >9.4 years



Moscicki AB; Eurogin 2010

Prospective mathematic modelling of antibody resposnses by *bivalent vaccine*

Protection from re-Infection by natural antibodies:

Women with upper 30% titre hight have 50% protection
Womenwith middle 30% titre hight have 10% proection
Women with lower 30% titre hight have 0% protection

Safaeian M. et al., J

?

Plausibility!

- time will tell -

CI, confidence interval; EU, enzyme-linked immunosorbent assay units; GMT, geometric mean titre

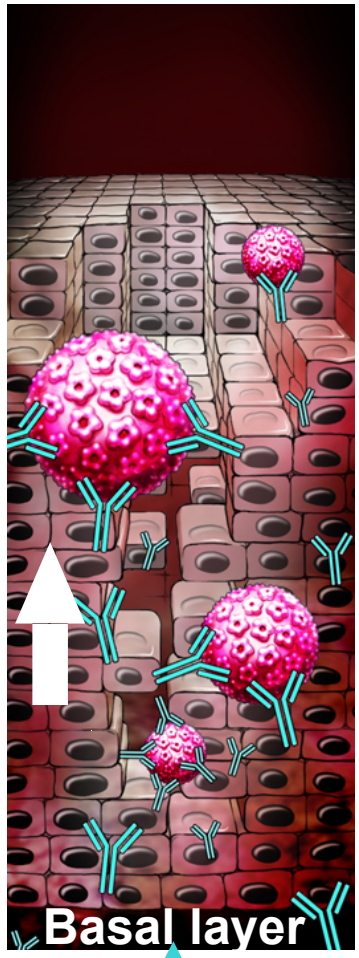
1. Paavonen J et al. Lancet 2007;369:2161-70

David MP et al. Gyncecol Oncol (2009)

High sustained antibody titers necessary for protection

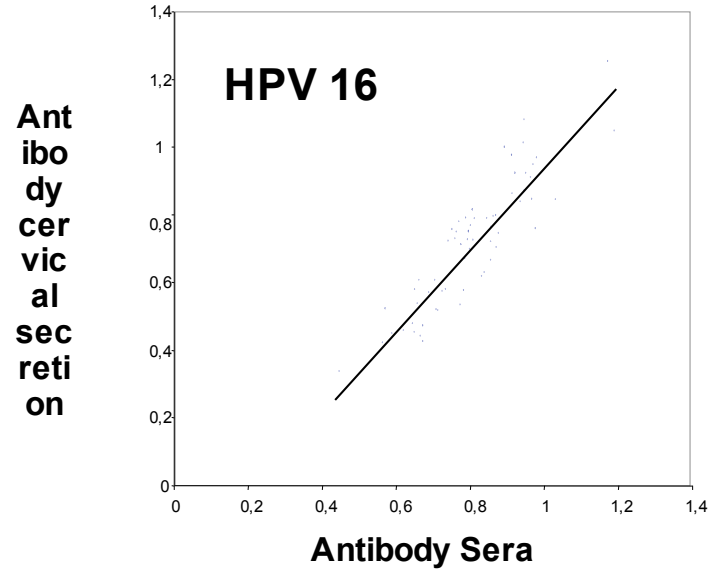
- Neutralising Antibodies protect from primary infection 1
- Antibodies in serum transudate to lesion2,3, IgG!
- High concentrations in serum correlate with higher antibody concentration in cervical mucus 3,4

Epithelium



Dermis

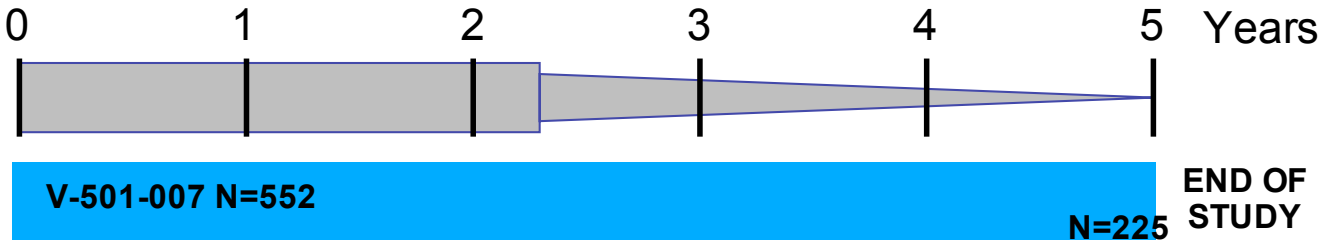
Antibodies inm Serum



1. Stanley M. HPV Today 2007; 11: 1-16
2. Stanley M. Vaccine 2006; 24: S106-13
3. Nardelli-Haefliger D et al. J Natl Cancer Inst 2003; 95: 1128
4. Presentation Poncelet S. ESPID 2007

HPV Vaccines
pivotal trials for efficacy against CIN 1–3, Phase II Studies

Gardasil



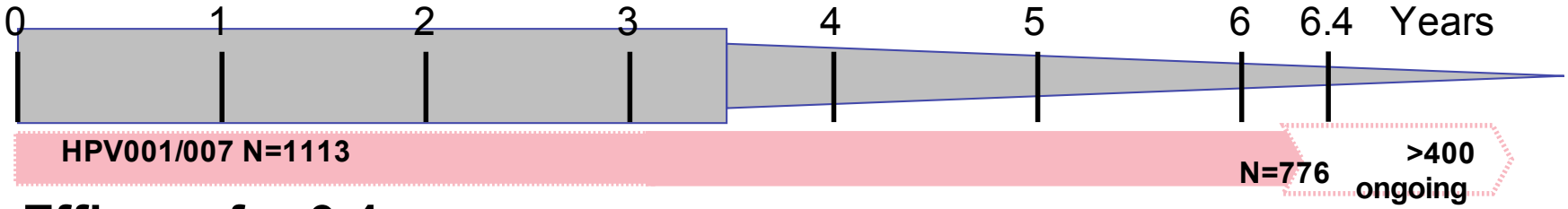
Adapted from Villa LL et al. Br J Cancer 2006;95:1459–66, Villa LL et al. Lancet Oncol 2005;6:271–8

Efficacy for 5 years

CIN 1-3 100% (<0.0-100)
HPV 16 pers. infection or disease 96.6% (79-99)
HPV 18 pers. infection or disease 90.6% (35-99)

Cervarix

9.4 years



Efficacy for 9.4 years

HPV 16/18 CIN2+ 100% * (51-100)
HPV 16/18 pers. infection 100% (86-100)

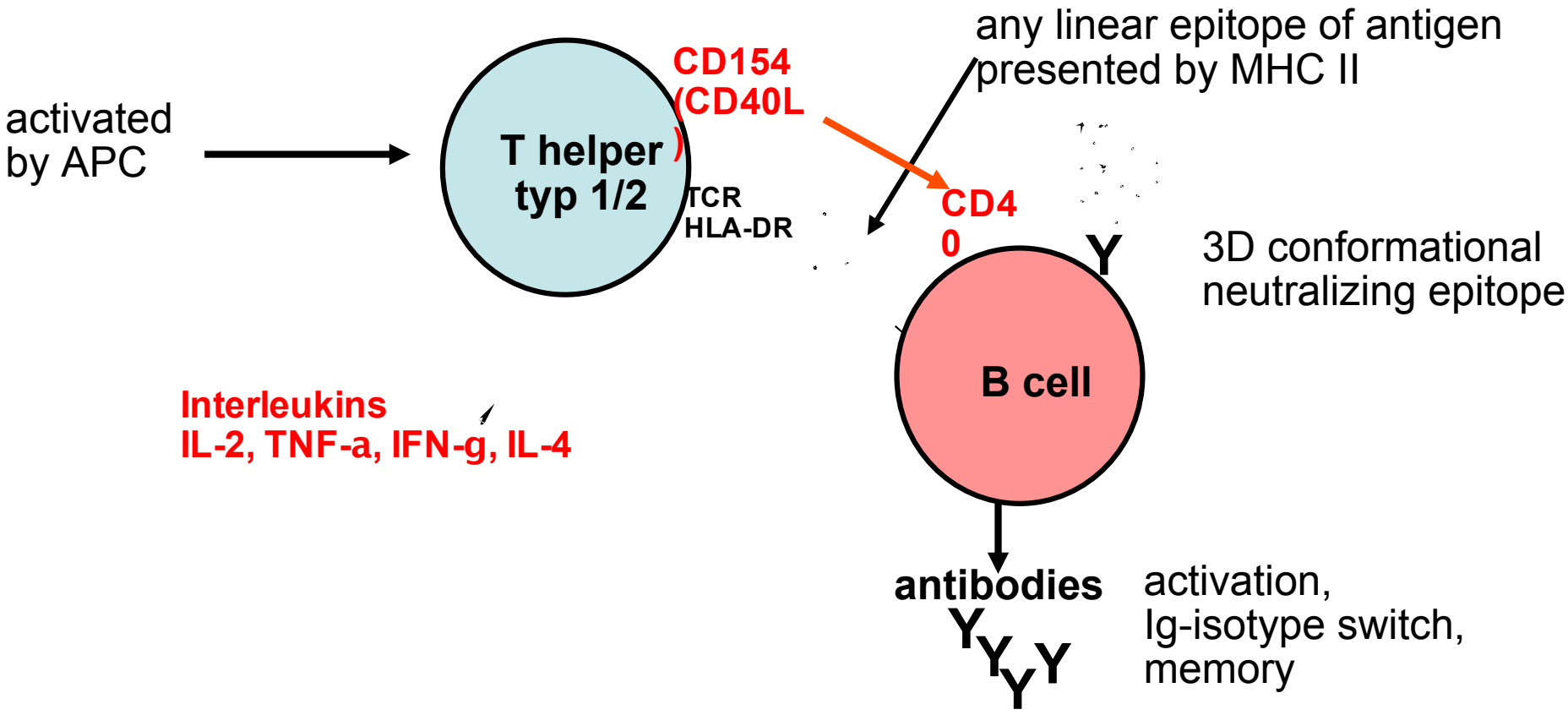
* Aufgrund der geringen Anzahl aufgetretener CIN 2*-Fälle konnte für HPV 18 bisher noch keine statistische Signifikanz erzielt werden.

Adapted from Harper DM et al. Lancet 2004;364:1757–65, Harper DM et al. Lancet 2006;367:1247–55, Gall S et al. AACR, Los Angeles, CA, 2007 Abstract 4900, Harper DM et al. Gynecol Oncol 2008;109:158–159

Nota bene

Both vaccines have comparable efficacy for vaccine-type HPV until now

T/B Cell Interaction



The peptide derives from the antigen, not necessarily from the neutralizing epitope - ……or even the identical HPV type?

T/B Cell Interaction

Each linear epitope of an antigen, that is presented by MHC II

Activated by APC

T helper type 1/2

CD154 (CD40L)

TCR

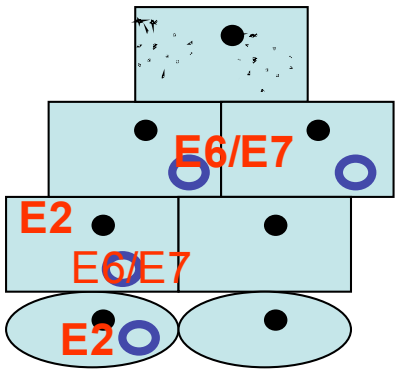
HLA-DR

CD40

B cell

3D conformational neutralising epitopes

Interleukins
IL-2, TNF-a, IFN-g, (IL-4)



L1???

Antibody

activation,
Ig-Isotyp switch,
Memory

May explain some post-infection prophylaxis by CD4 T cells

Study Design: direct access to vaccine-specific T-helper cell responses

recruited participants >18 years, non-pregnant, planning to get vaccinated, no condylomata acuminata, signed informed consent

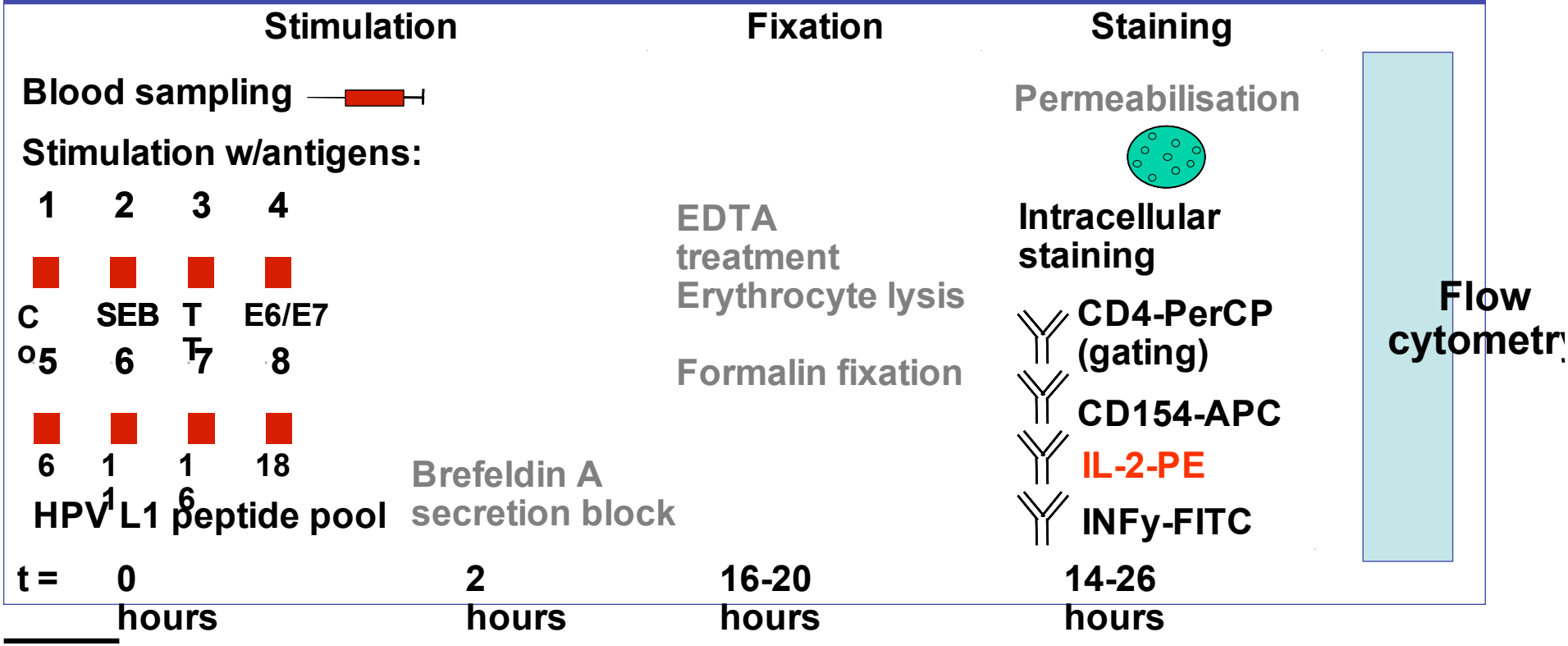
5 x blood sampling / ex vivo assay

18 subjects vaccinated w/ Gardasil 24 years (SD 2,3)	before vaccination + questionnaire	5 weeks post 1st vacc. (SD2)	5 weeks post 2nd vacc. (SD2)	6 weeks post 3rd vacc. (SD4)	20 weeks post 3rd vacc. (SD4)
1 lost to follow-up					
16 subjects vaccinated w/ Cervarix 25 years (SD 5,5)	before vaccination + questionnaire	5 weeks post 1st vacc. (SD1)	5 weeks post 2nd vacc. (SD1)	6 weeks post 3rd vacc. (SD2)	25 weeks post 3rd vacc. (SD4)
3 lost to follow-up					

Method – CD154 based *ex vivo* analysis

Basis	Frentsch et al., Nat Med 2005;11:1118-24 Direct access to CD4+ T cells specific for defined antigens according to CD154 expression

HPV vaccine adapted assay:



synthetic 30mer overlapping peptides

Homologous cross-r
and their posi

Conserved due to cross-linking function in pentamer

0033

HPV11 L1 95 ... CKGTQCSN 174
HPV18 L1 159 LVWACAGVEIGRGQPLGVGLSGHPFYNKLDDTESS ... WAKGTACKS 238
HPV31 L1 99 LVWACVGLEVGRGQPLGVGISGHPLLNKFDDTENS ... WGKGSPCSN 178
HPV45 L1 125 LVWACVGMEIGRGQPLGIGLSGHPFYNKLDDTESA ... WAKGTLCKP 204
BPV1 L1 94 LVWAVIGVQVSRGQPLGGTVTGHPTFNALLDAENV ... WTTARPCVT 173

HPV16 L1 178 VAVNPGDCPPLELINTVIQDGDMVDTGFGAMDFTT ... YLRREQMFV 257
HPV6 L1 174 TPVQAGDCPPLELITSVIQDGDMVDTGFGAMNFAD ... FLRKEQMFA 253
HPV11 L1 175 ... SVIQDGDMVDTGFGAMNFAD ... YLRKEQMFA 254
HPV18 L1 239 RPLSQGDCPPLELKNTVLEDGDMVDTGYGAMDFST ... CLRREQLFA 318
HPV31 L1 179 NAITPGDCPPLELKNSVIQDGDMVDTGFGAMDFTA ... YLRREQMFV 258
HPV45 L1 205 AQLQPGDCPPLELKNTIIEDGDMVDTGYGAMDFST ... CLRREQLFA 284
BPV1 L1 174 DRLENGACPPLELKNKHIEDGDMMEIGFGAANFKE ... FARKEQVYV 253

Peptide 80025

HPV16 L1 336 TTRSTNMSLCAAISTS-ETTYKNTNFKEYLRHGE ... GLQPPPGGTL 414
HPV6 L1 332 TTRSTNMTLCASVTTS--STYTNSDYKEYMRHVE ... GLSPPPNGTL 409
HPV11 L1 333 TTRSTNMTLCASVSKS--ATYTNSDYKEYMRHVE ... GLSPPPNGTL 410

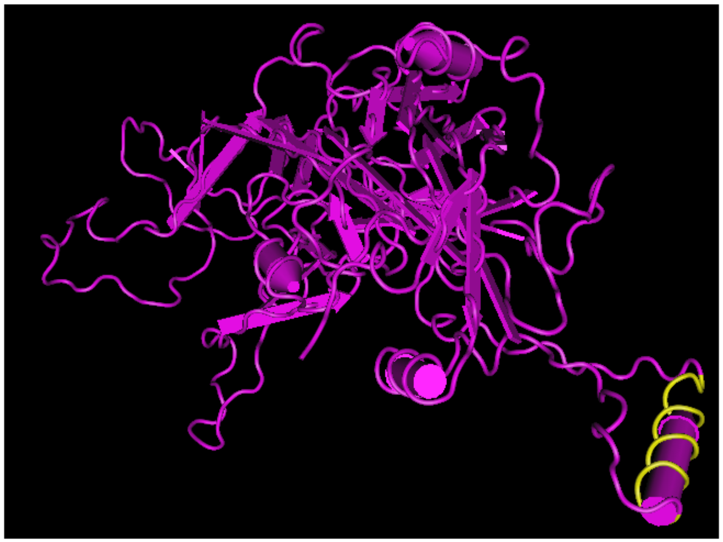
... KQYSRHVE ... SL
... KEYLRHGE ... SL
... KHYSRHVE ... SL
... NVYHRHME ... IL

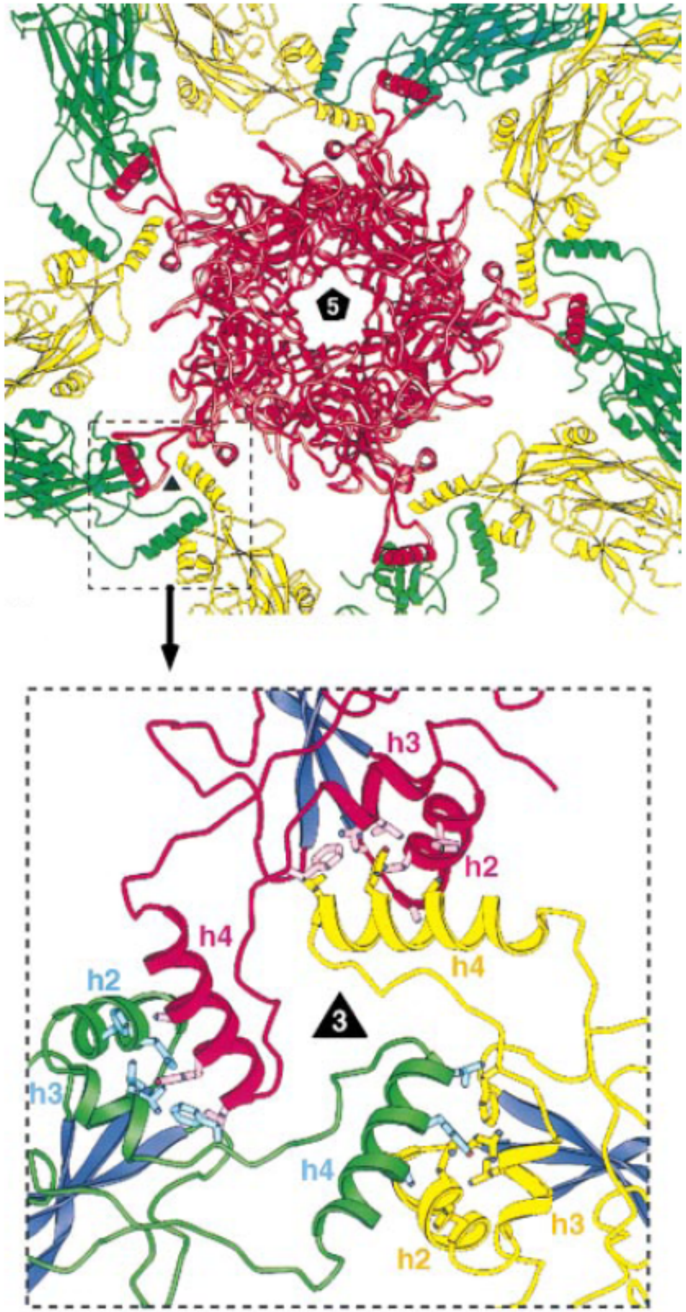
... PLKKYTFWE ... SS
... PYKNLSFWE ... KA
... PYKDMSFWEVNLKE ... VSKP

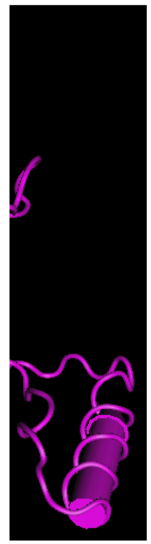
In cross-linking a-helix

-sheet

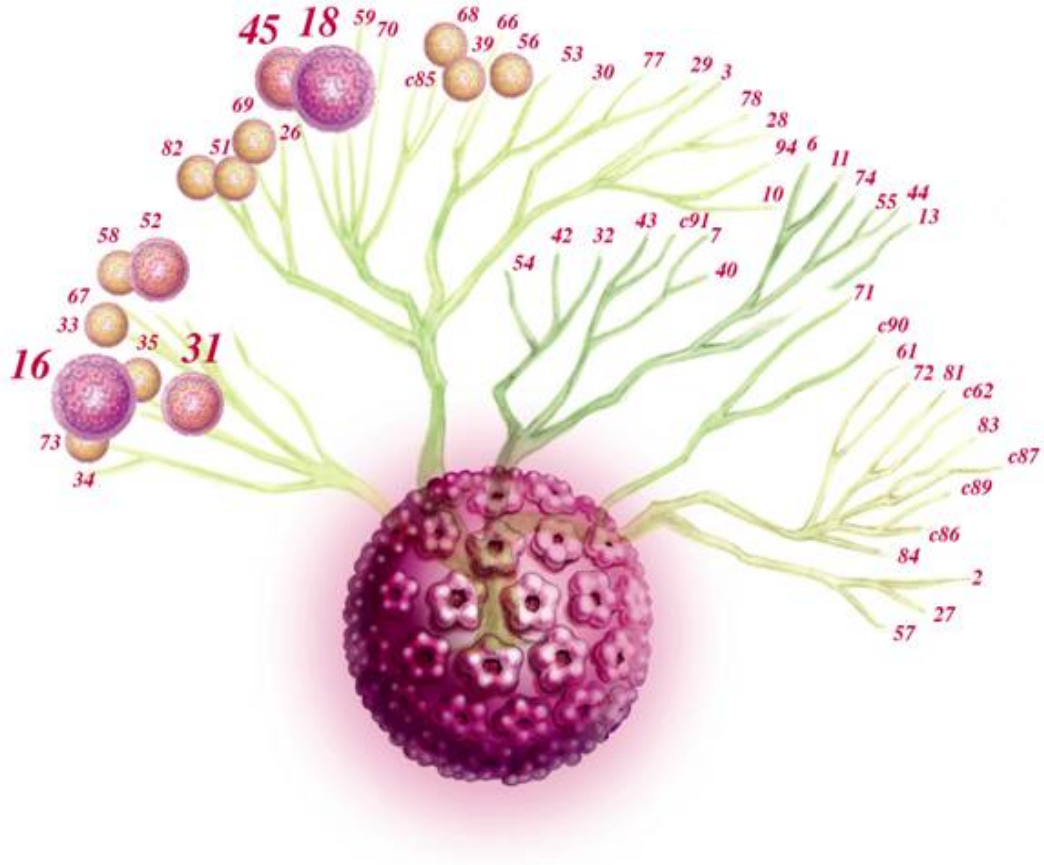
HPV16_L1 Monomer
gelb: Peptid 80025







Relatedness of HPV Genotypes

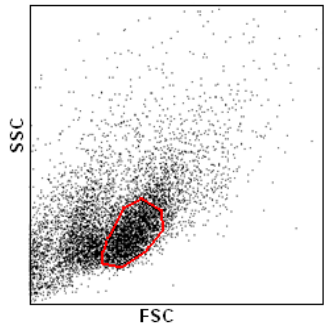


e.g. HPV 16 and 31

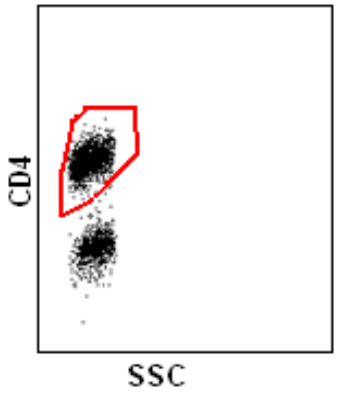
Cross-Reaction of CD4+ T Cell Clones: flow cytometric analysis

amino acid sequences: HPV1601
TNIYYHAGTSRLLAV
HPV3101 TNIYYHAGSARLLTV

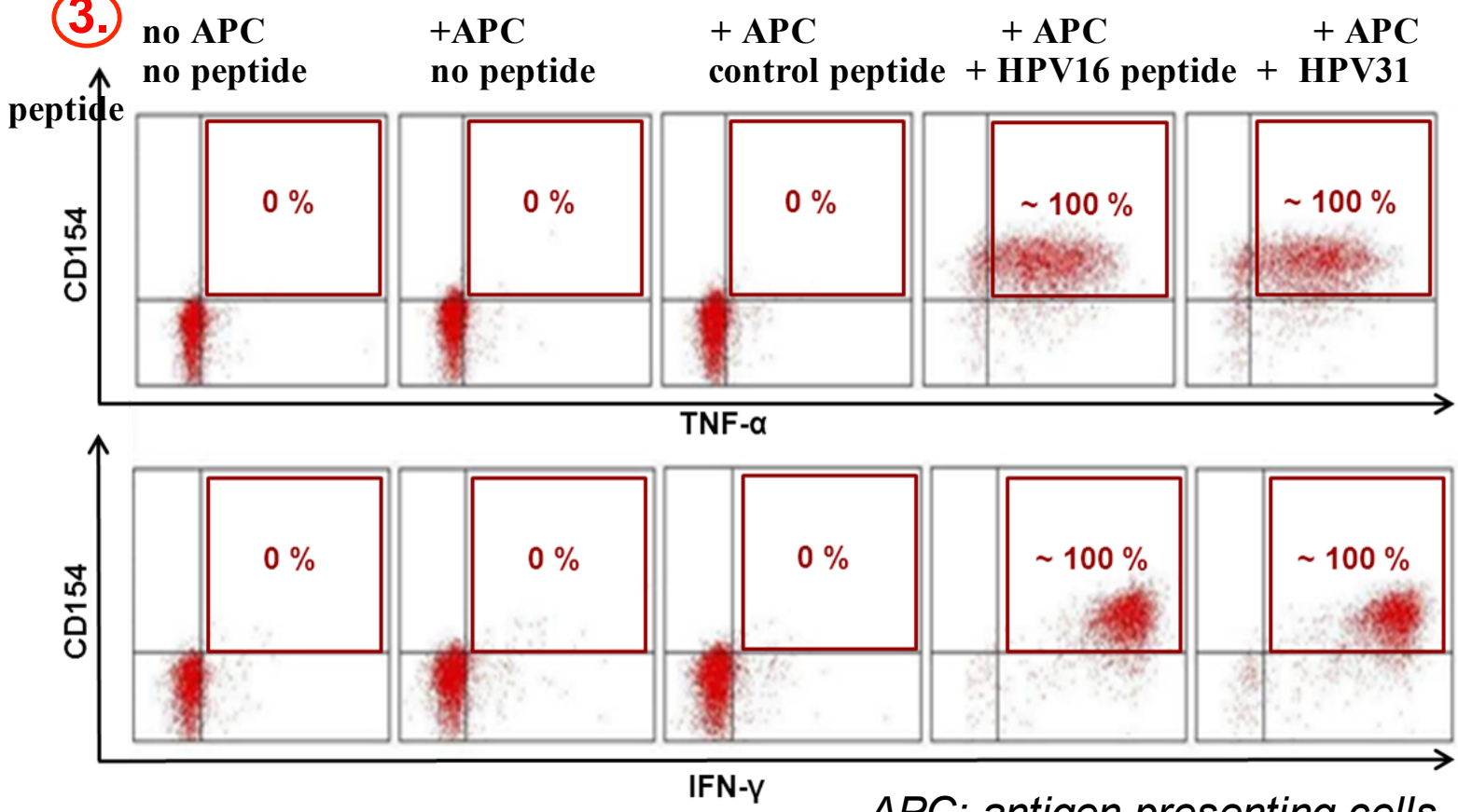
1. life cell gating



2. CD4 gating



3.



APC: antigen presenting cells

Cross-reaction of HPV16 or 18 L1 specific T cell clones

Cervarix					
# reactive clones	TCR family	Specificity	cross-reactivity HPV31	HPV6	HPV11
6	13; 17	**1601**	+	-	-
3			-	-	-
1		**1602**	-	-	-
1		**1603**	-	-	-
2	17	**1605**	+	+	+
8		**1608**	-	-	-
4	5	**1609**	-	-	-
1		**1610**	+	-	-

Gardasil					
# reactive clones	TCR family	Specificity	cross-reactivity HPV31	HPV6	HPV11
1		**1601**	+	+	+
5	17; 21	**1603**	+	-	-
1	17	**1605**	-	-	-
2	17		+	-	-
1	22	**1609**	-	-	-

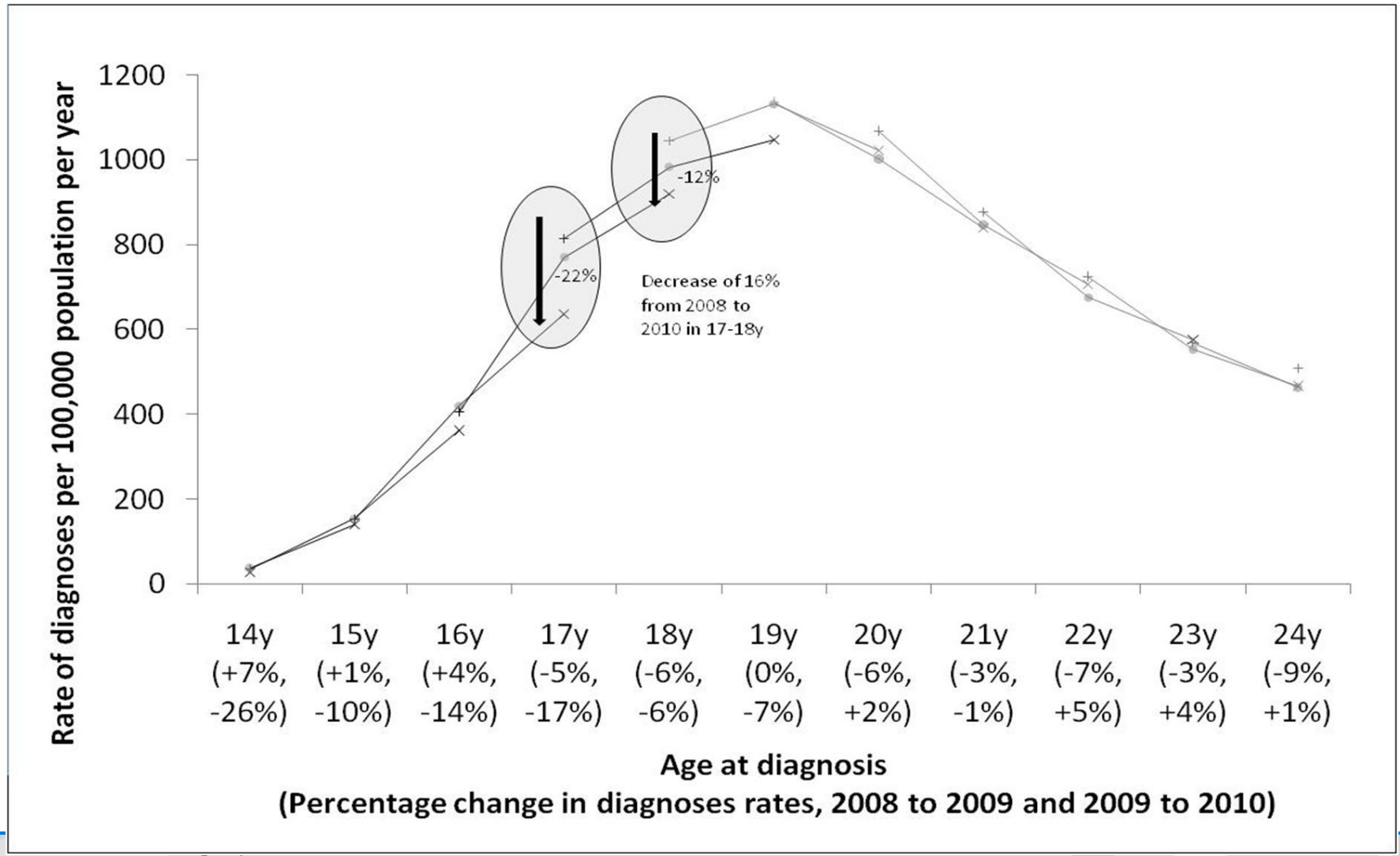
Cervarix					
# reactive clones	TCR family	Specificity	cross-reactivity HPV45	HPV6	HPV11
2	13	**1801**	-	-	-
1		**1802**	-	-	-

Gardasil					
# reactive clones	TCR family	Specificity	cross-reactivity HPV45	HPV6	HPV11
1		**1801**	+	-	-

Cross-reactive CD4+ T cells against homologous peptides of high risk and even low risk HPV types in both vaccine groups!

England: Cervarix in organisiertem Programm (>80% Zielpopulation)

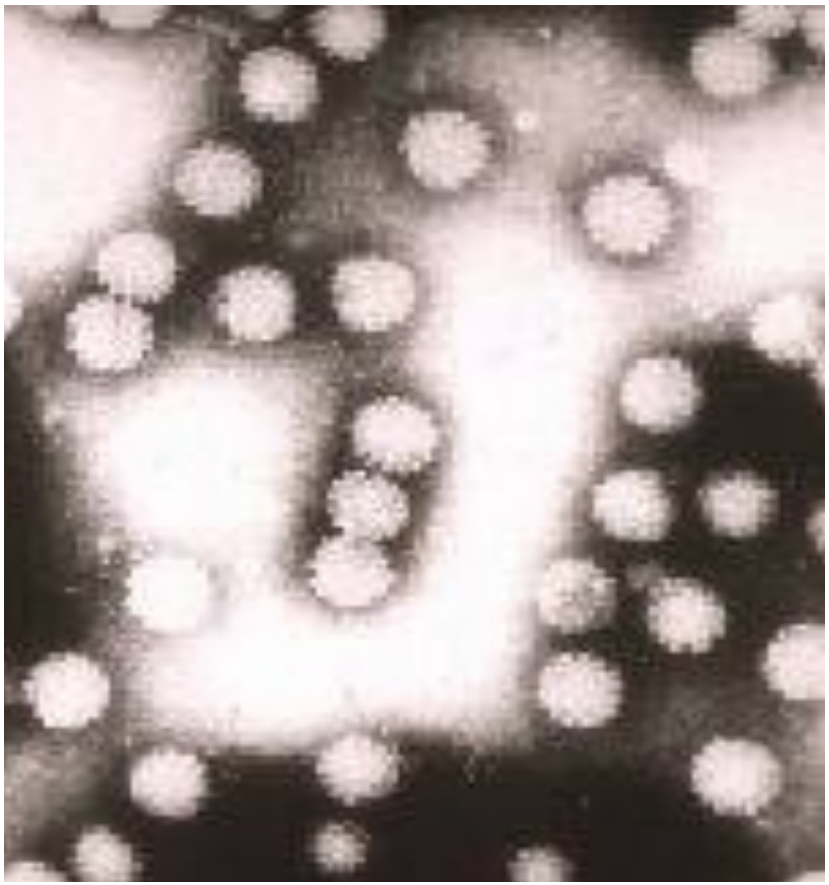
Rates of diagnoses at GUM clinics in England by year of age, birth cohort (linked data points) and year of diagnosis (shown by marker: + 2008, o 2009, and x 2010.) a) GW diagnoses at GUM clinics in females



Soldan et al., IPVC, 2011 Berlin


Vielen Dank
impfen !!!
gegen HPV
impfen !!!
gegen HP

Human Papillomavirus



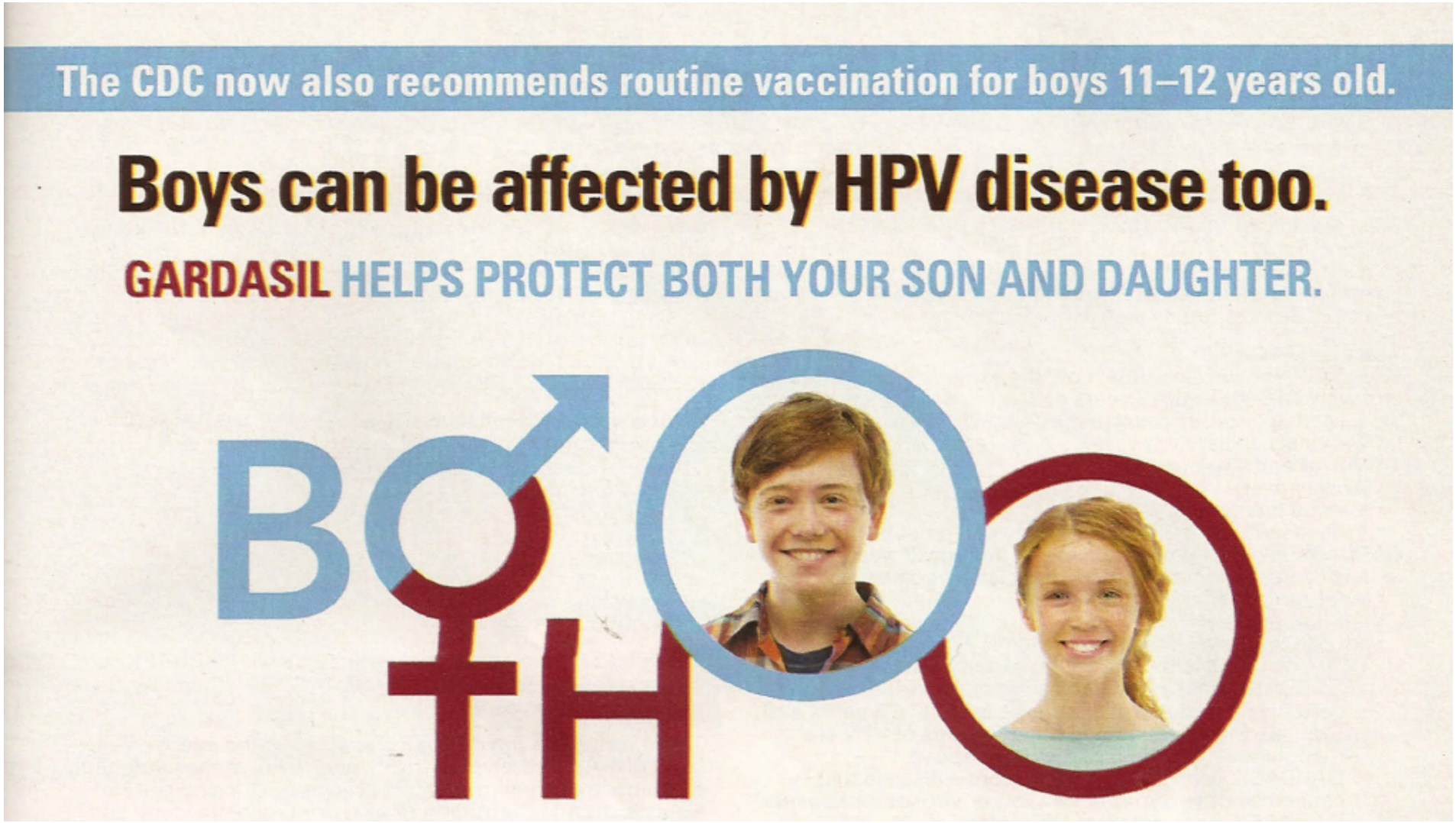
55 nm HPV particles
(1/20.000 mm)

Papillomaviridae
PV in every vertebrate species
>130 Human PV Types
cutaneous/mucosal Types

ca. 20 „high-risik“ HPV
in 99.7% of cervical cancers present

ca. 18 „low-risk“ HPV
in 90% Condylomata acuminata

Double stranded,
circular DNA genome, 8 kb



Update der S3 Leitlinie zur Impfprävention HPV assoziierter Neoplasien (Ende 2012)
Update STIKO Empfehlung (2013)

Landmark paper Hildesheim et al., AMA 2007

Future I&II

PATRICIA

Effect of Human Papillomavirus 16/18 L1 Viruslike Particle Vaccine Among Young Women With Preexisting Infection

A Randomized Trial

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Sholom Wacholder, PhD
Ana C. Rodriguez, MD
Diane Solomon, MD
M. Concepcion Bratti, MD
John T. Schiller, PhD
Paula Gonzalez, MD
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Silvia E. Jimenez, MBA
Douglas R. Lowy, MD
for the Costa Rican HPV Vaccine Trial Group

Context Viruslike particle human papillomavirus (HPV) vaccines were designed to prevent HPV infection and development of cervical precancers and cancer. Women with oncogenic HPV infections might consider vaccination as therapy.

Objective To determine whether vaccination against HPV types 16 and 18 increases the rate of viral clearance in women already infected with HPV.

Design and Setting Phase 3, masked, community-based randomized trial conducted in 2 provinces of Costa Rica.

Participants A total of 2189 women aged 18 to 25 years who were recruited between June 2004 and December 2005. Participants were positive for HPV DNA at enrollment, had at least 6 months of follow-up, and had follow-up HPV DNA results.

Intervention Participants were randomly assigned to receive 3 doses of a bivalent HPV-16/18 L1 protein viruslike particle AS04 candidate vaccine (n=1088) or a control hepatitis A vaccine (n=1101) over 6 months.

Main Outcome Measures Presence of HPV DNA was determined in cervical specimens by a molecular hybridization assay using chemiluminescence with HPV RNA probes and by polymerase chain reaction using SPF10 primers and a line probe assay detection system before vaccination and by polymerase chain reaction after vaccination. We compared rates of type-specific viral clearance using generalized estimating equations methods at the 6-month visit (after 2 doses) and 12-month visit (after 3 doses) in the 2 study groups.

Results There was no evidence of increased viral clearance at 6 or 12 months in the group who received HPV vaccine compared with the control group. Clearance rates for HPV-16/18 infections at 6 months were 33.4% (82/248) in the HPV vaccine group and 31.6% (95/298) in the control group (vaccine efficacy for viral clearance, 2.5%; 95% confidence interval, –9.8% to 13.5%). Human papillomavirus 16/18 clearance rates at 12 months were 48.8% (86/177) in the HPV vaccine group and 49.8% (110/220) in the control group (vaccine efficacy for viral clearance, –2.0%; 95% confidence interval, –24.3% to 16.3%). There was no evidence of a therapeutic effect for other oncogenic or nononcogenic HPV categories, among women receiving all vaccine doses, among women with single infections, or among women stratified by the following entry variables: HPV-16/18 serology, cytologic results, HPV DNA viral load, time since sexual debut, *Chlamydia trachomatis* or *Neisseria gonorrhoeae* infection, hormonal contraceptive use, or smoking.

Conclusion In women positive for HPV DNA, HPV-16/18 vaccination does not accelerate clearance of the virus and should not be used to treat prevalent infections.

Trial Registration clinicaltrials.gov Identifier: NCT00128661

JAMA. 2007;298(7):743-753 www.jama.com

KNOWLEDGE THAT INFECTION with 1 of approximately 15 oncogenic human papillomavirus (HPV) types is required for the development of cervical cancer has permitted primary prevention efforts via vaccination.[1] Two vaccines based on HPV L1 protein viruslike particles (VLPs) are undergoing evaluation in large-scale clinical trials.[2-5] One vaccine (Gardasil) is a quadrivalent HPV-16/18 cervical cancer candidate vaccine that contains VLPs from 2 oncogenic HPV types, HPV-16 and HPV-18, and also contains VLPs from HPV types 6 and 11, which are not involved in cervical cancer pathogenesis but are linked to benign genital warts. This vaccine has been approved

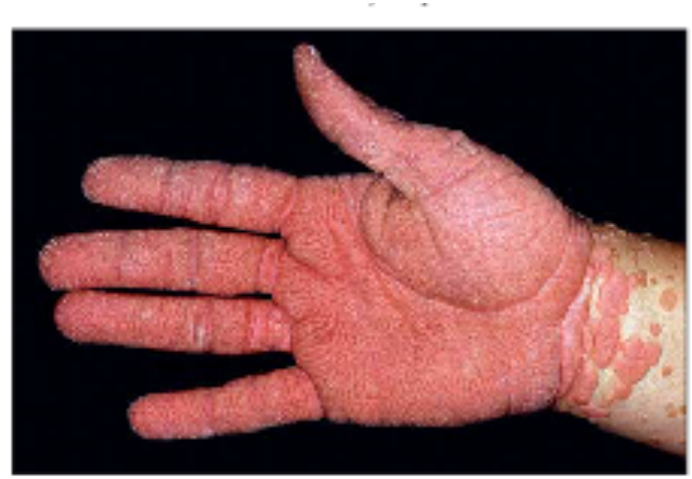
For editorial comment see p 805.

Author Affiliations and a complete list of the investigators of the Costa Rican HPV Vaccine Trial Group appears at the end of this article.
Corresponding Author: Allan Hildesheim, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, Ste 550, Rockville, MD 20852 (Hildesha@exchange.nih.gov); Rolando Herrero, MD, PhD, Proyecto Epidemiológico Guanacaste, Torre La Sabana, 300 Oeste del ICE, Piso 7, Sabana Norte, San José, Costa Rica (Rherrero@amnet.co.cr).

Comparable result with our 2nd WHIM patient

1 SCID patient, BM transplanted, chimeric (?)

2 published cases
- Handisurya et al., 2010
- Kreuter et al., 2010



Potential mechanisms

1) **Induced antibodies prevent intraepithelial reinfection**
Recurrence after therapy is reduced
Residual disease will be present

2) Resident CD4 T cells secrete cytokines like IFN-g, TNF-a, et al.,
that have a direct effect on keratinocytes, induce apoptosis

3) Immunity is skewed toward an inflammatory response with activation of LHC, T cell induction (e.g. E6-specific!), influx into lesion,
control of the disease

<u>Need to collect more data and initiate registration of results</u>

Acknowledgments

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Tina Kube
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German Cancer Center
Michael Pawlita
Ute Koch

Thank you