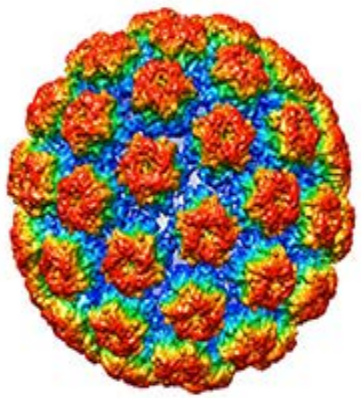
Cervical Cancer

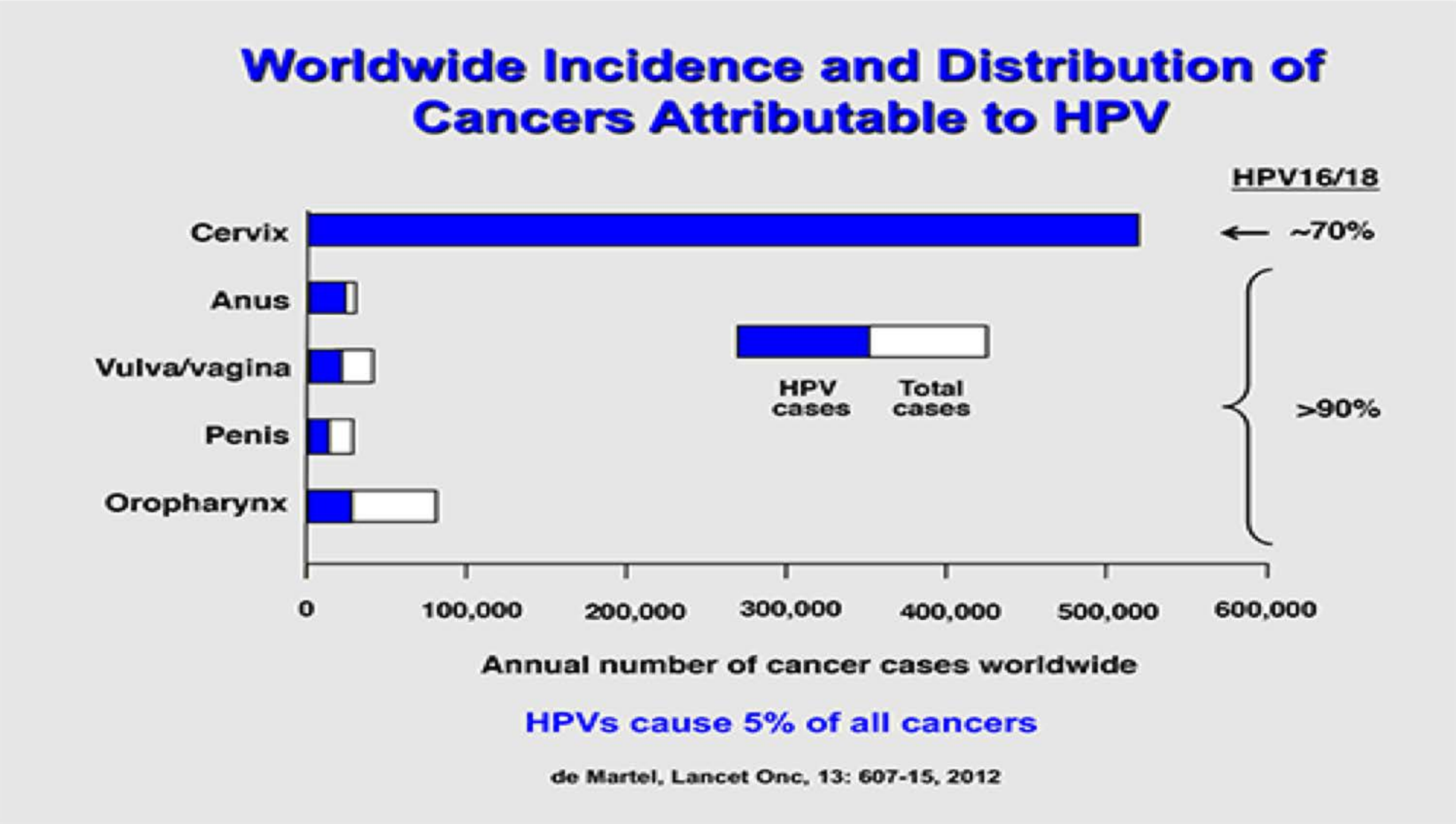
HPV Vaccines to Prevent Cervical Cancer and other HPV-associated Diseases

John Schiller, Center for Cancer Research, NCI

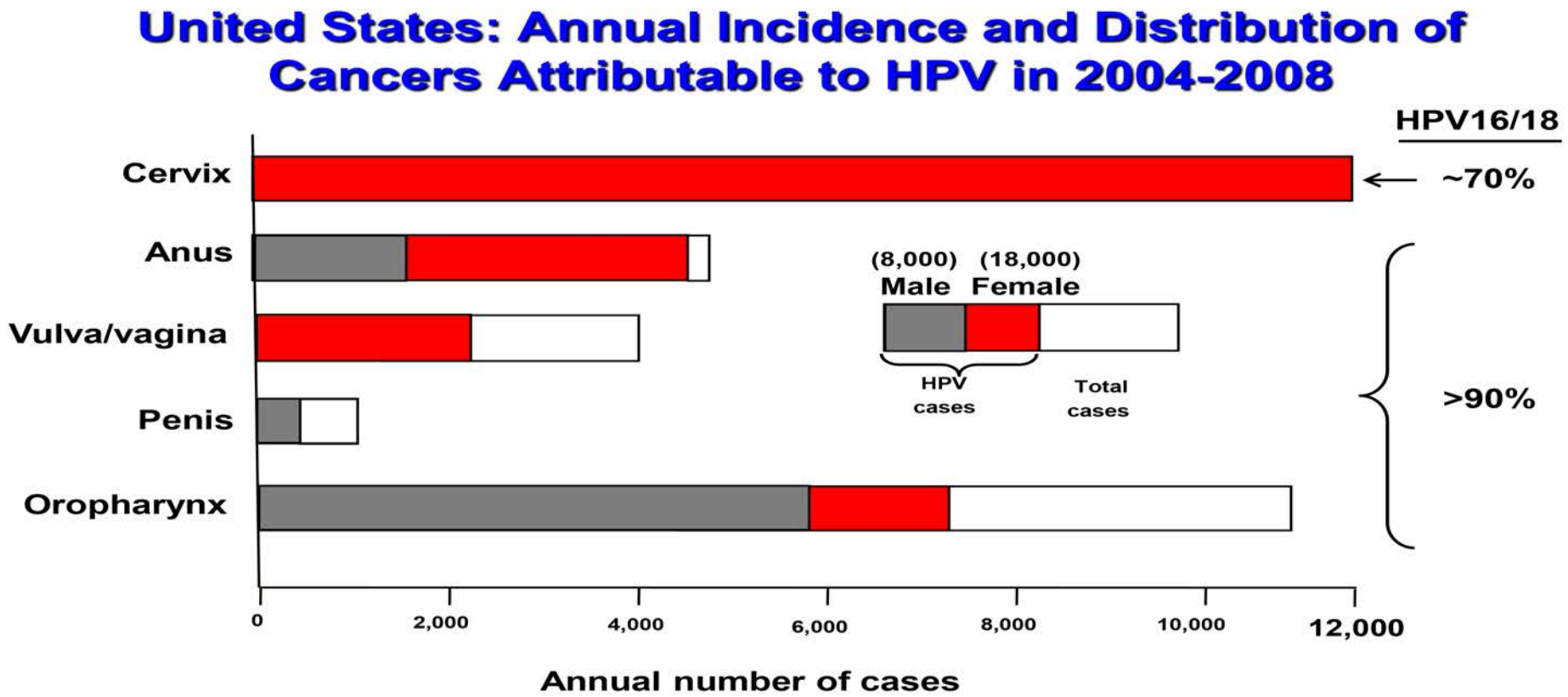


- HPV and Cancer
- Vaccine Efficacy/Effectiveness
- Key Implementation Issues
- Why they work so well

Cancers attributable to HPV



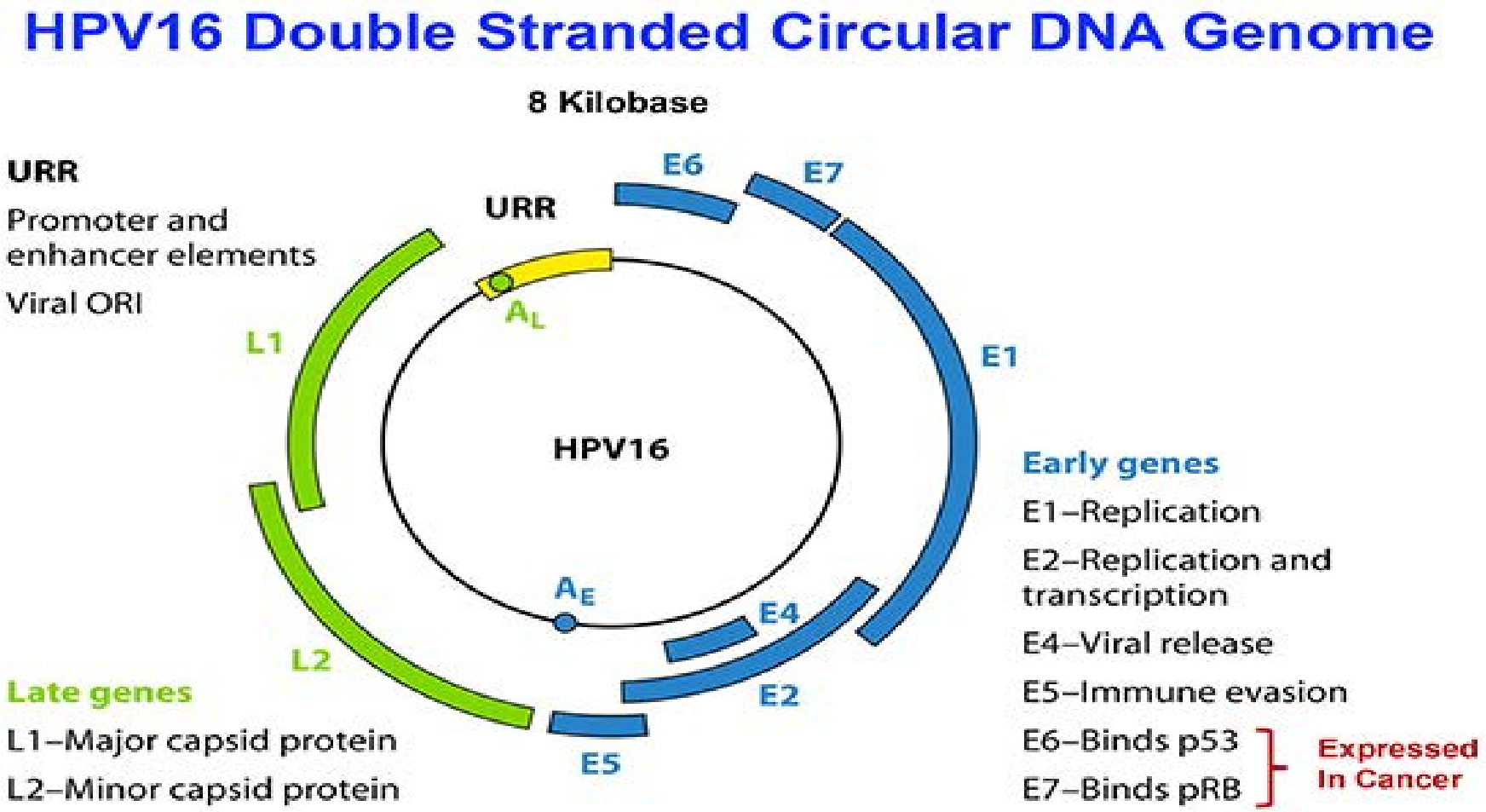
HPV cancers



- Pap screening has reduced the incidence of cervical cancer by ~ 80%
- Incidence of HPV-positive oropharynx cancer 1988-2004 increased 225%

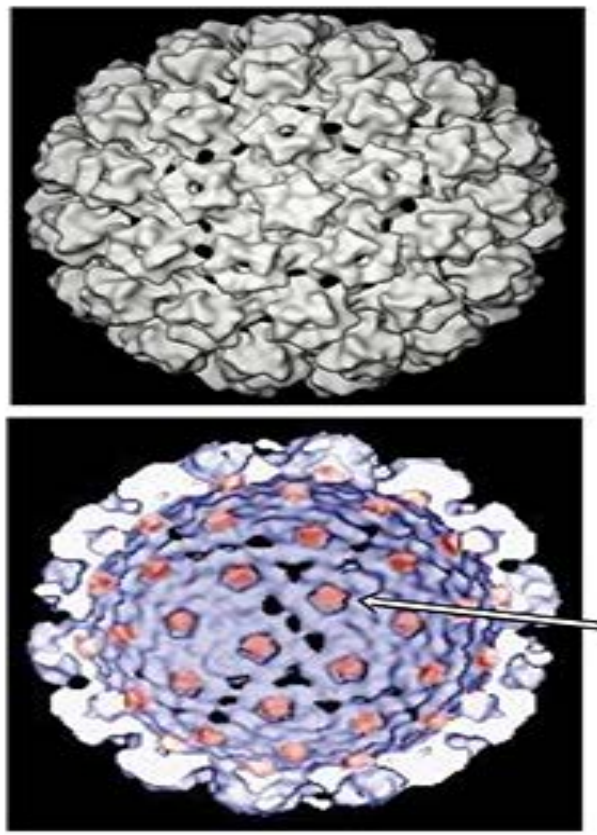
MMWR Weekly 61:253-80, 2012

HIV genome


HPV16 Double Stranded Circular DNA Genome
8 Kilobase
URR
Promoter and enhancer elements
Viral ORI
URR
E6
E7
E1
E2
E4
E5
L1
L2
A_L
A_E
HPV16
Early genes
E1–Replication
E2–Replication and transcription
E4–Viral release
E5–Immune evasion
E6–Binds p53
E7–Binds pRB
Expressed In Cancer
Late genes
L1–Major capsid protein
L2–Minor capsid protein

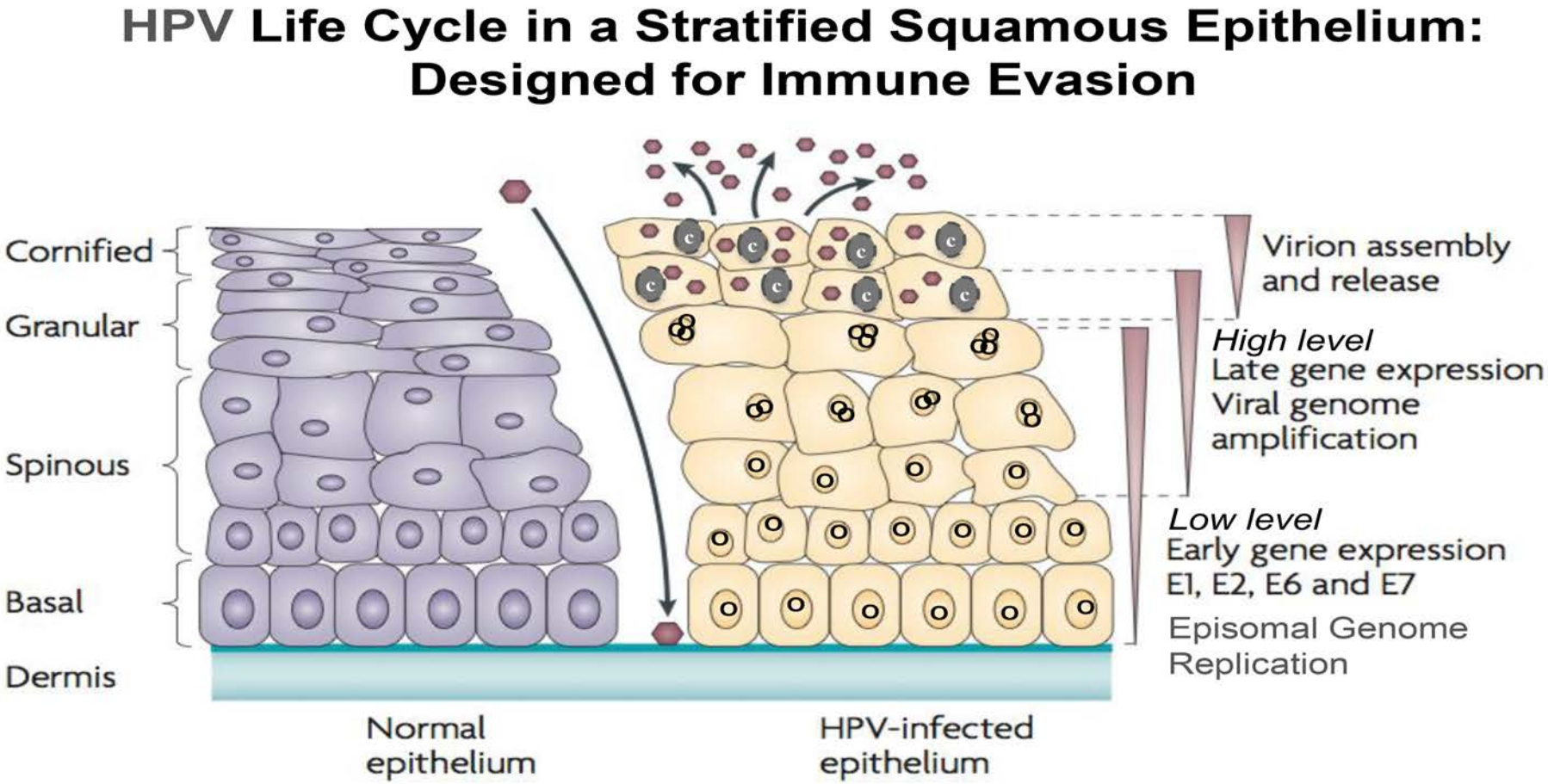
Virion

Papillomavirus Virion

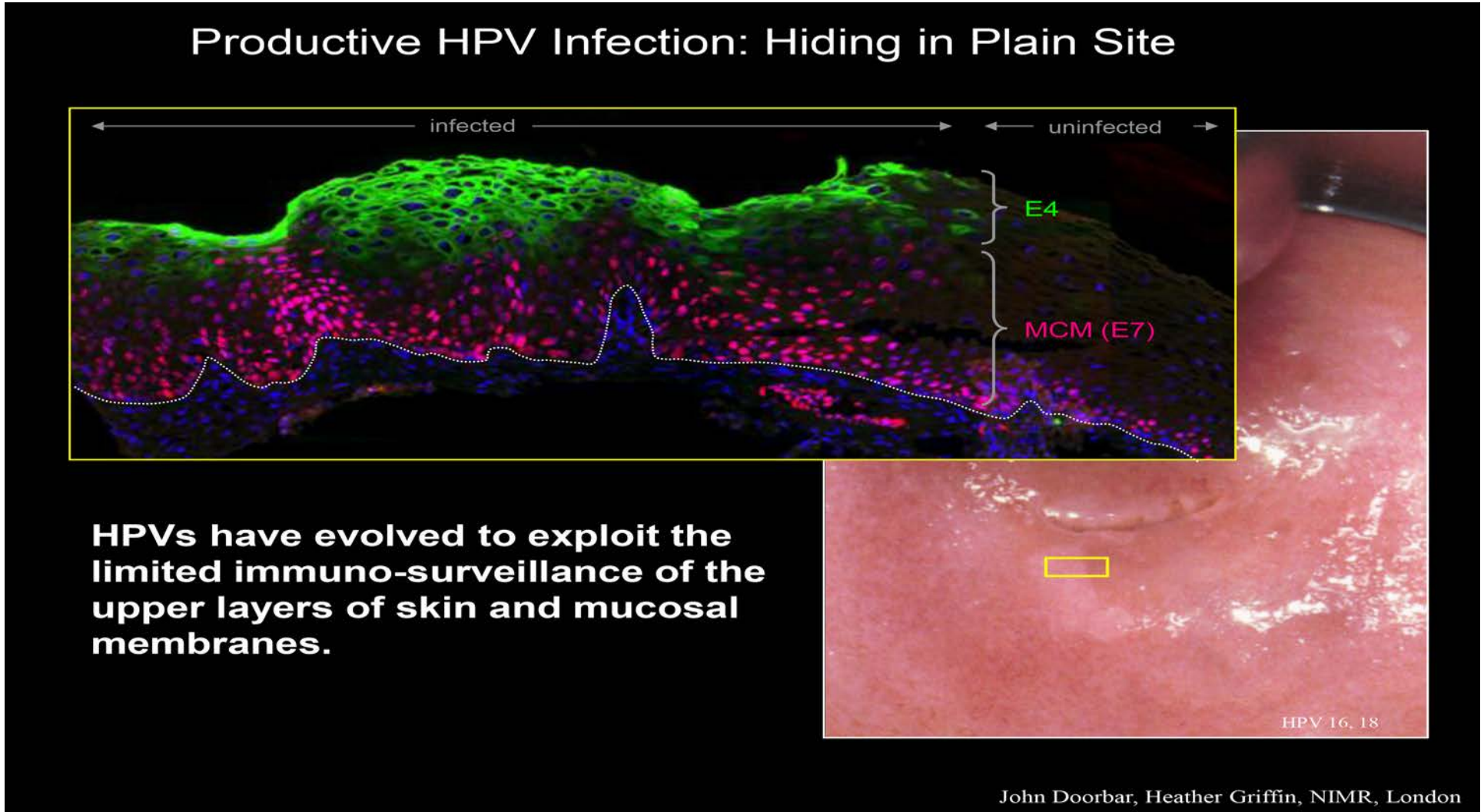


- Non-enveloped icosahedral shell formed by 72 pentamers of L1
- 60 nanometer diameter
- A second capsid protein L2 is present at up to 72 copies
- 8kb circular dsDNA genome (chromatinized)

HPV life cycle

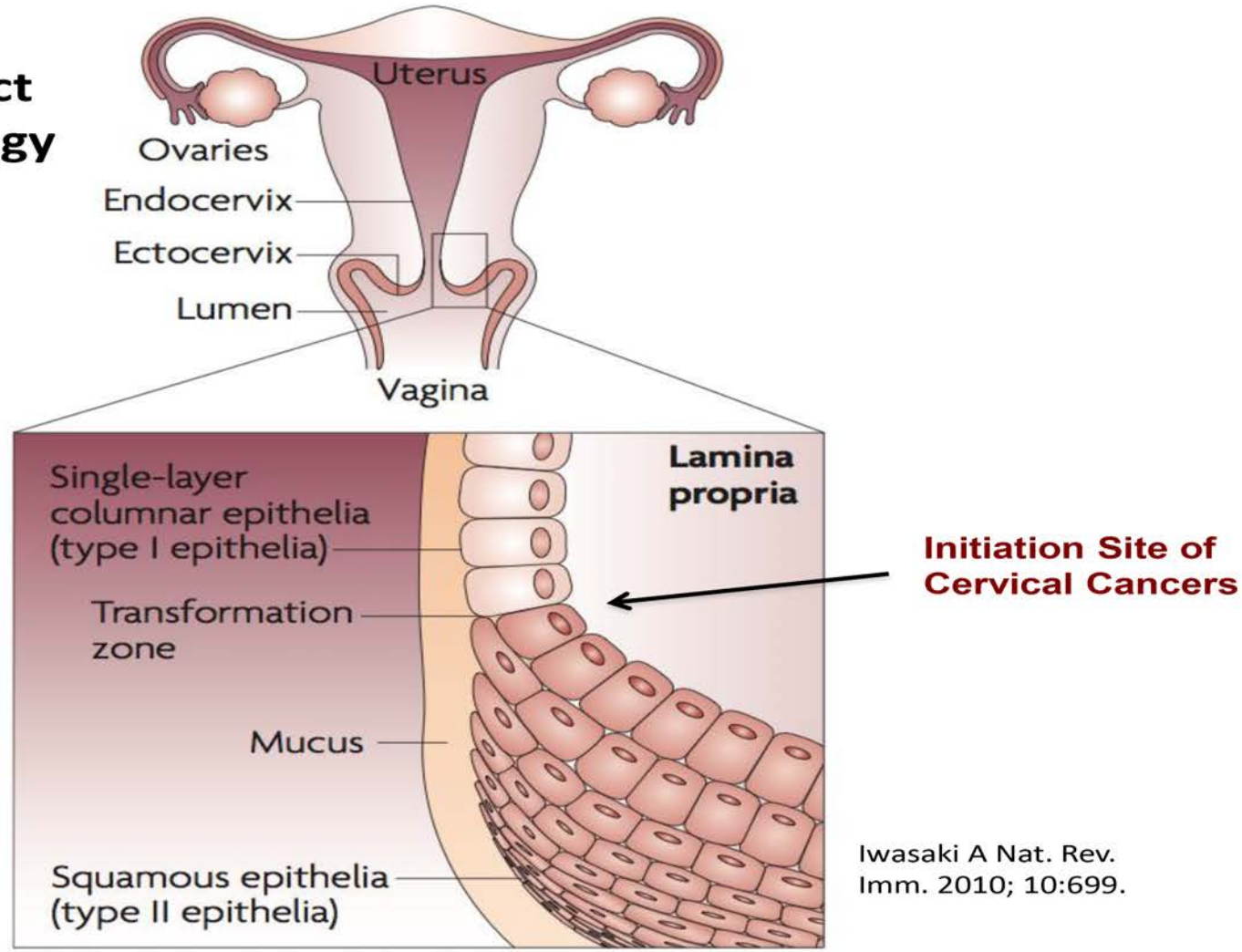


HPV infection



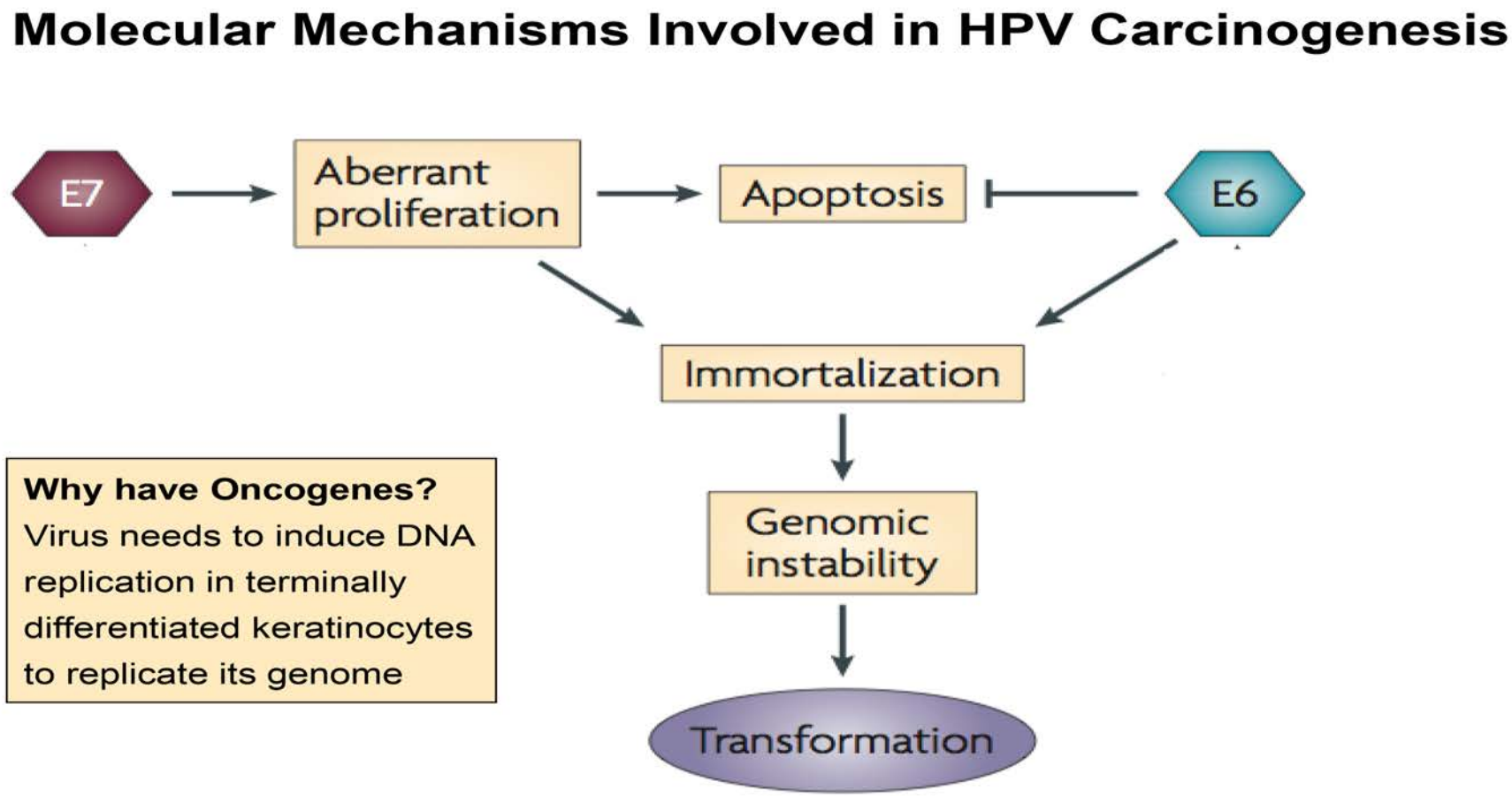
Cervical cancer

Female Reproductive Tract Anatomy & Histology



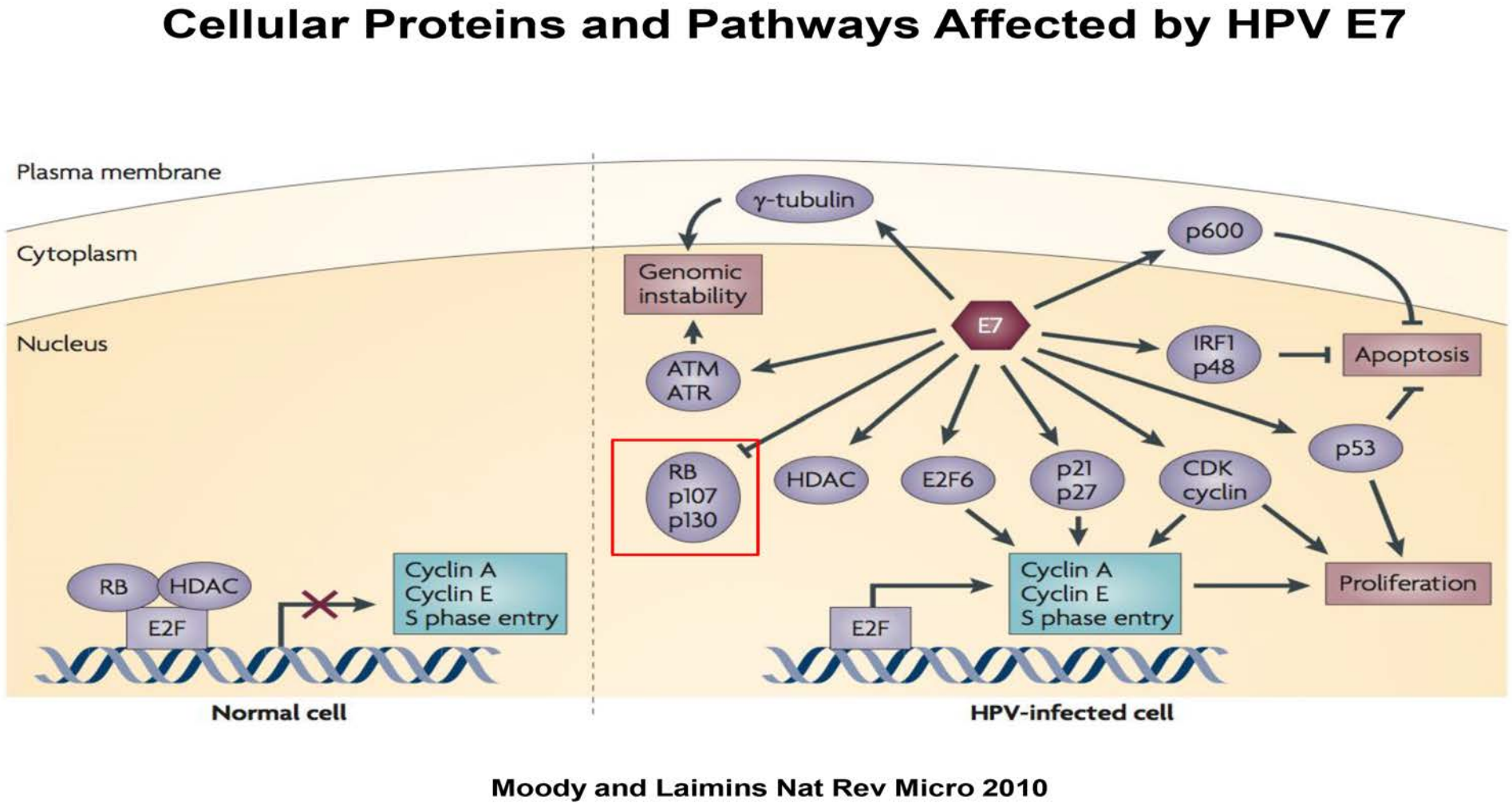
Iwasaki A Nat. Rev. Imm. 2010; 10:699.

HPV carcinogenesis

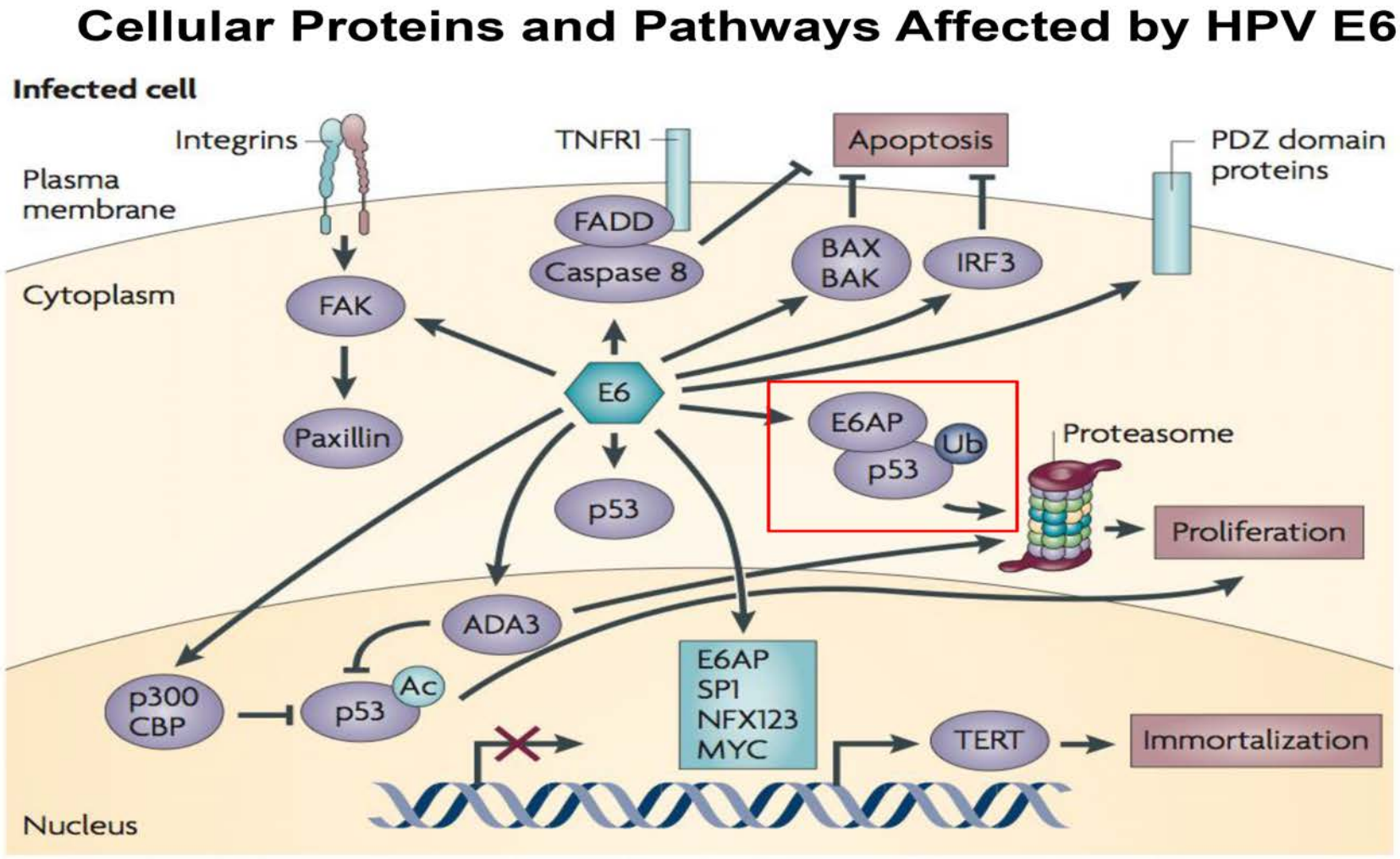


Moody and Laimins Nat Rev Micro 2010

Cellular proteins

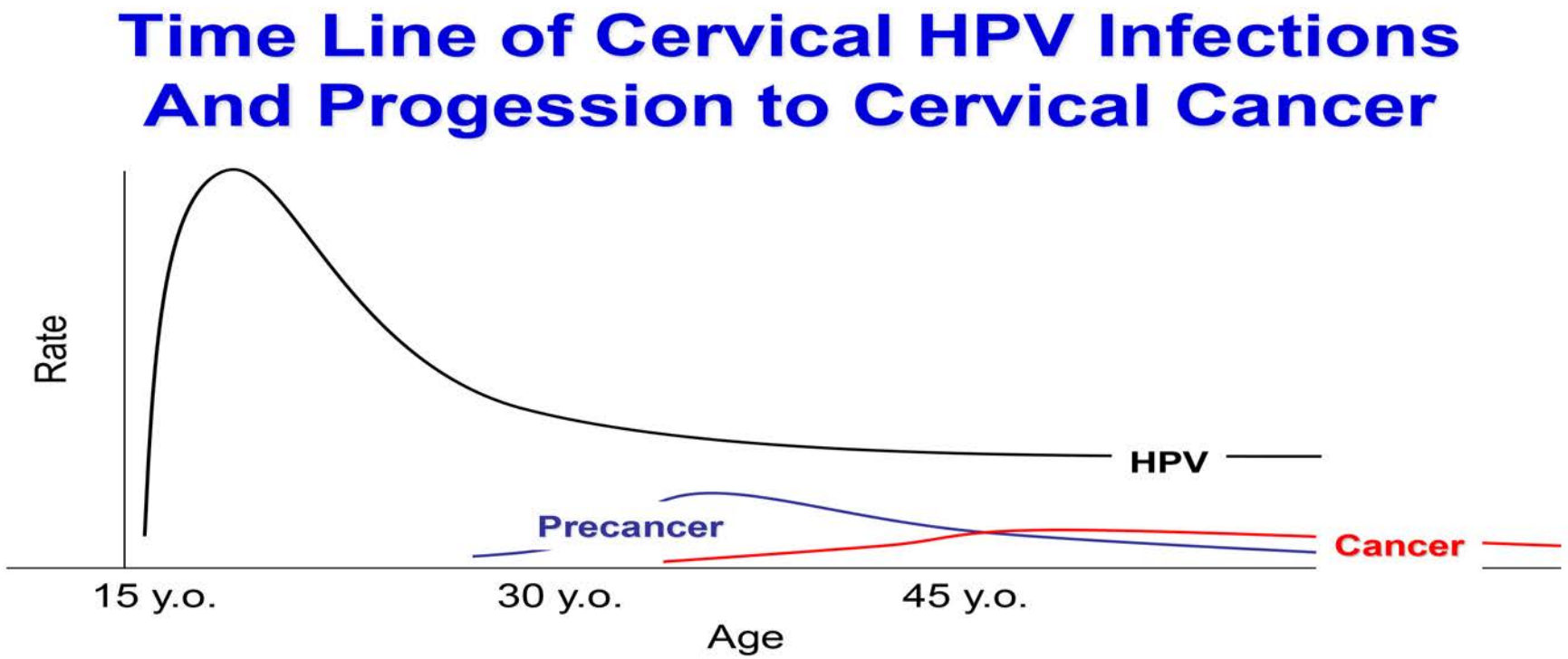


HPV pathways



Moody and Laimins Nat Rev Micro 2010

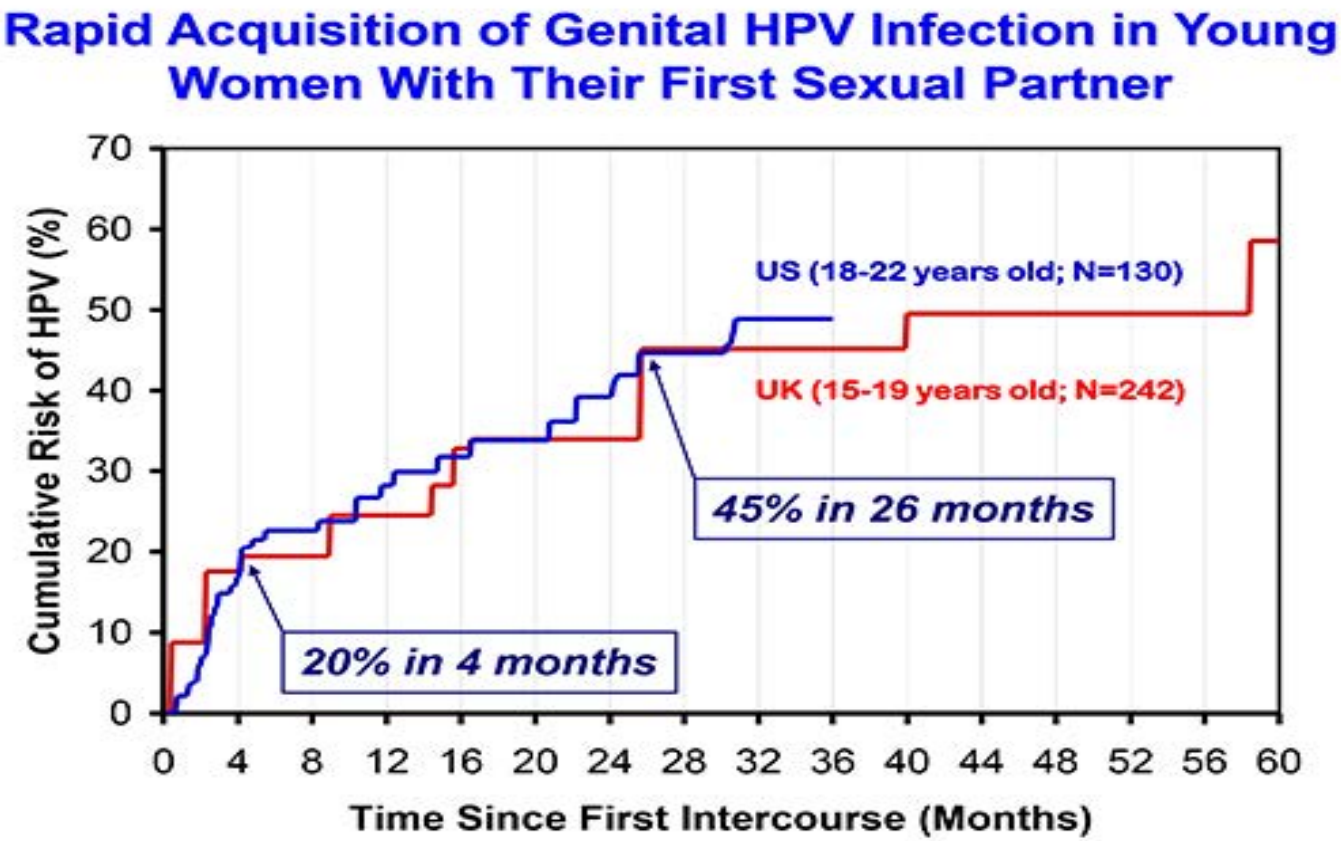
HPV infection time line



- **Lifetime incidence of genital HPV infection >80% in U.S.**
- **Most infections clear spontaneously, eliminating cancer risk for that infection.**
- **Persistent infection with a high-risk HPV, especially HPV16 or 18, is the single most important risk factor for progression to precancer and cancer.**

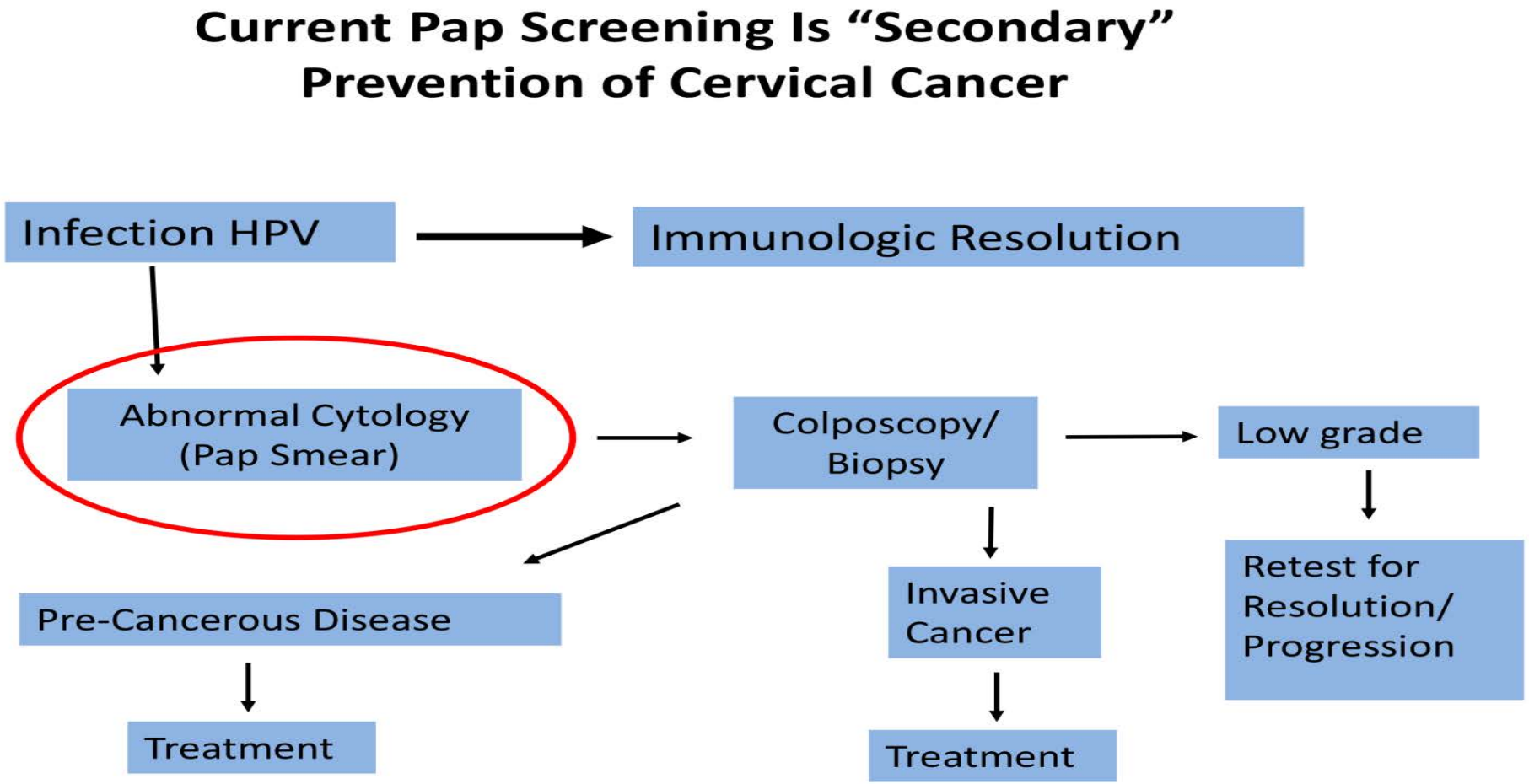
Adapted from Schiffman & Castle, New Eng J Med 353:2101-4, 2005

HPV infection

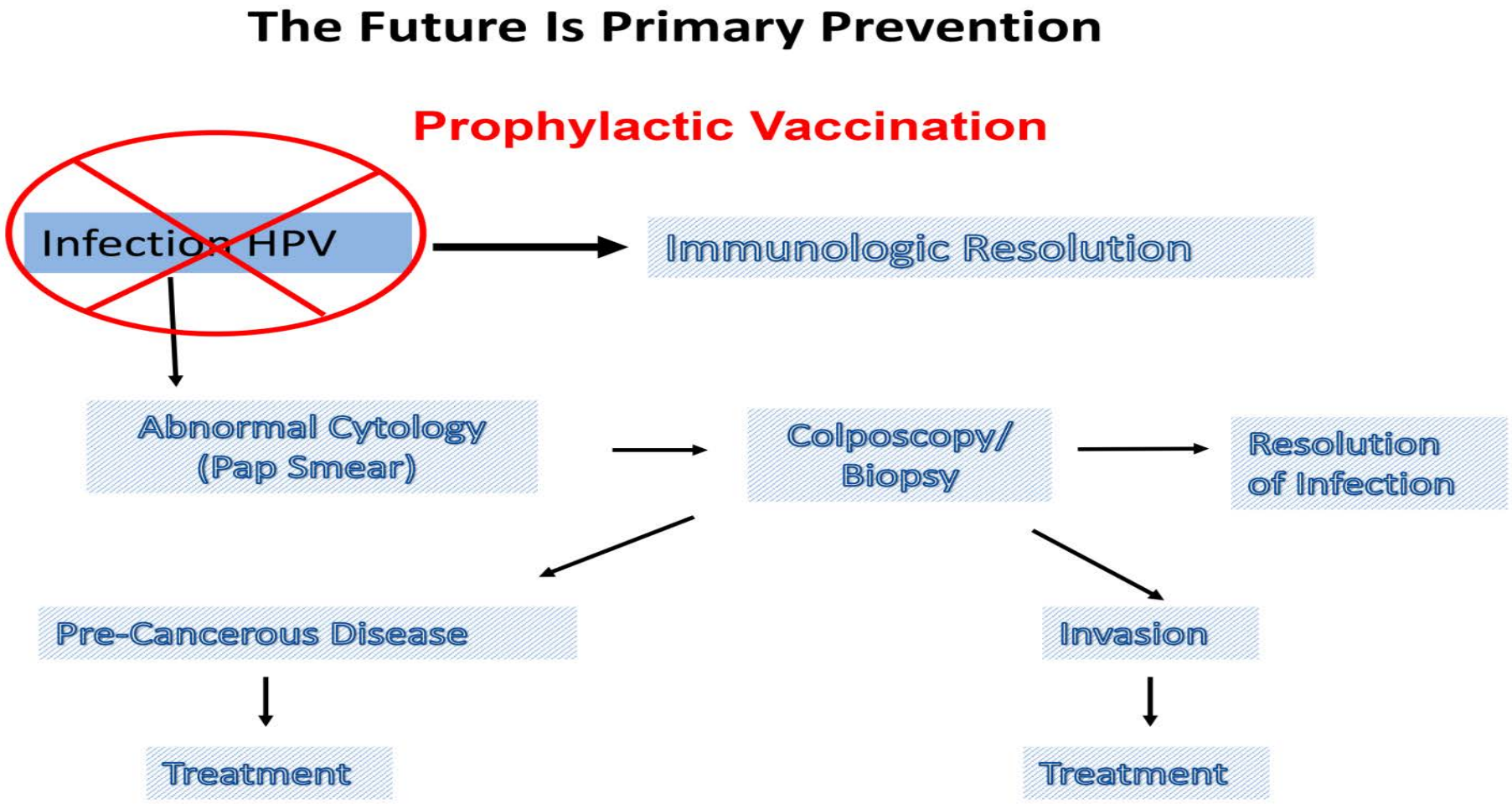


UK data adapted from *Collins et al, BJOG 109: 96-98, 2002* US data adapted from *Winer et al, J Inf Dis 197:279-282, 2008*

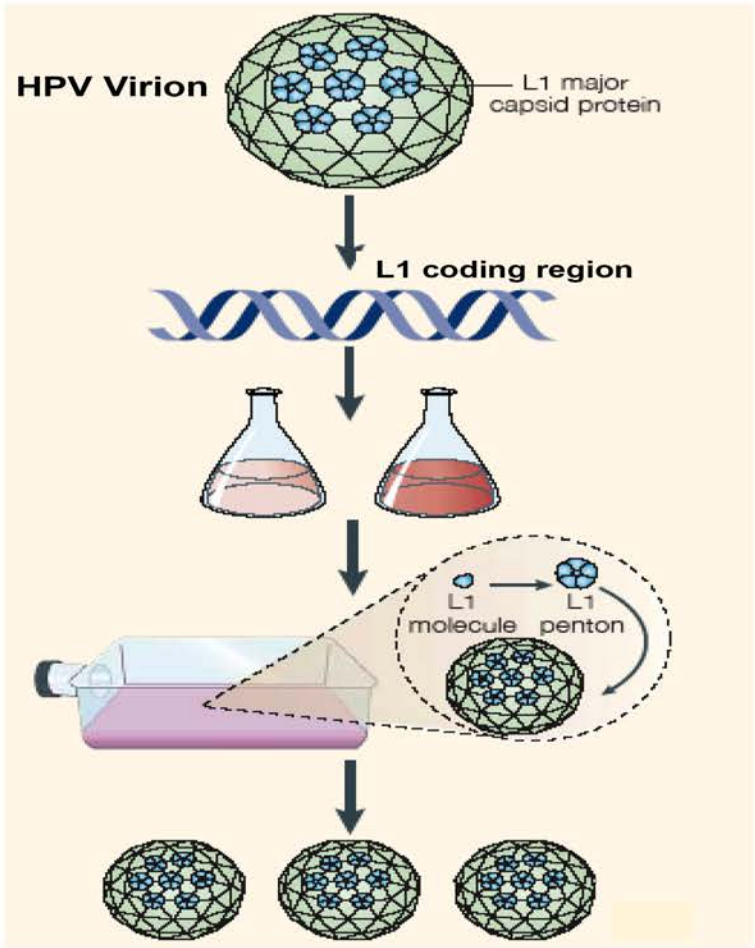
Pap screening



Primary prevention



Virus like particles



Prophylactic HPV Vaccines Are L1 Virus Like Particles (VLPs)

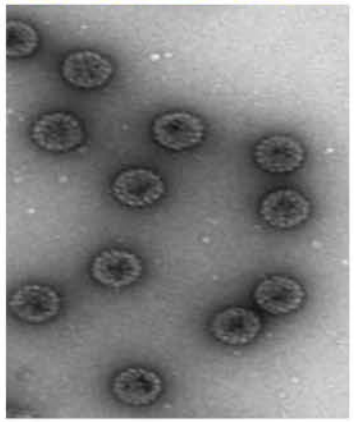
L1 Insertion into a Baculovirus Expression Vector

Production in Insect Cells

Spontaneous assembly of L1 into VLPs

Induce high titers of virion neutralizing antibodies

HPV16 L1 VLPs



Non-infectious, Non-oncogenic

Reinhard Kirnbauer et al. PNAS 1992

Three vaccines

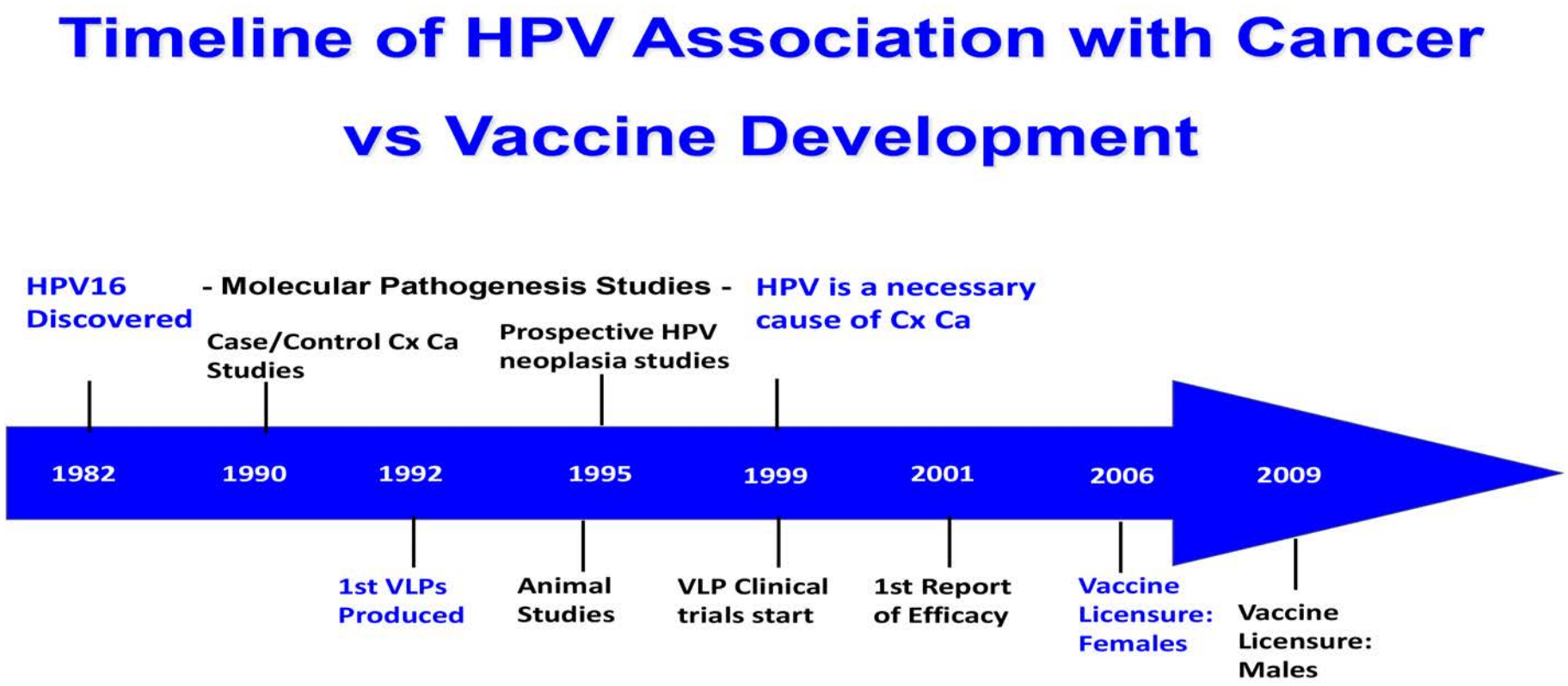
Three Distinct HPV L1 VLP Vaccines Have Been Commercialized

Name	Producer	VLP Types	Adjuvant	Production	Licensed
Cervarix	GSK	16,18	AS04*	Insect Cells	2007
Gardasil	Merck	16,18, 6,11	Alum	Yeast	2006
Gardasil-9	Merck	16,18,31, 33,45,52,58 6,11	Alum	Yeast	2014

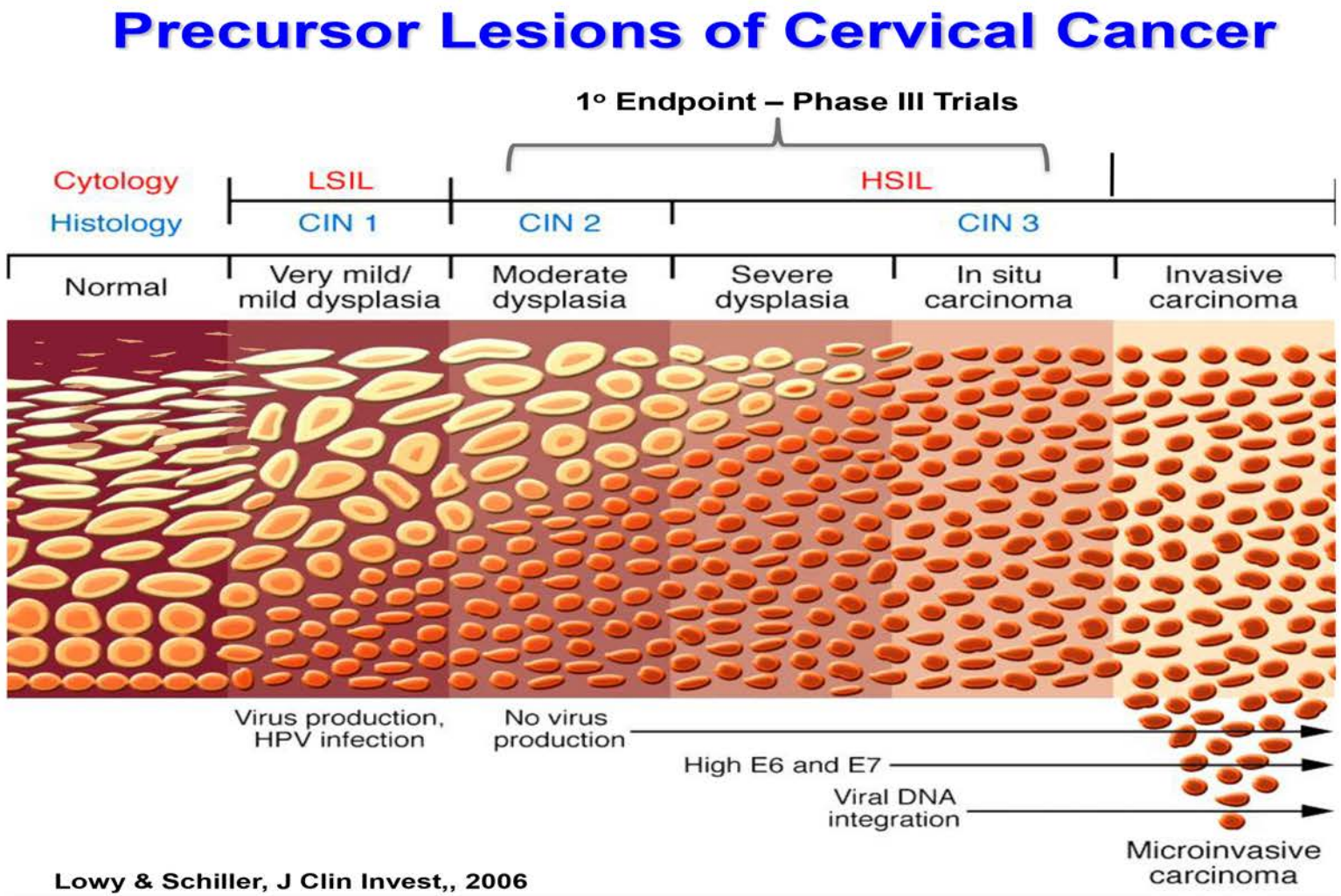
IM Injections at 0, 1 or 2, and 6 months
1, 6 months for <15 yrs in EU, and now in U.S.

* MPL First TLR Agonist Adjuvant to be FDA Approved

Timeline of HPV Association



Precursor Lesions



Efficacy of HPV Vaccine

Efficacy of HPV VLP Vaccines Against Incident Disease By *Vaccine-Targeted Types* in Randomized Trials

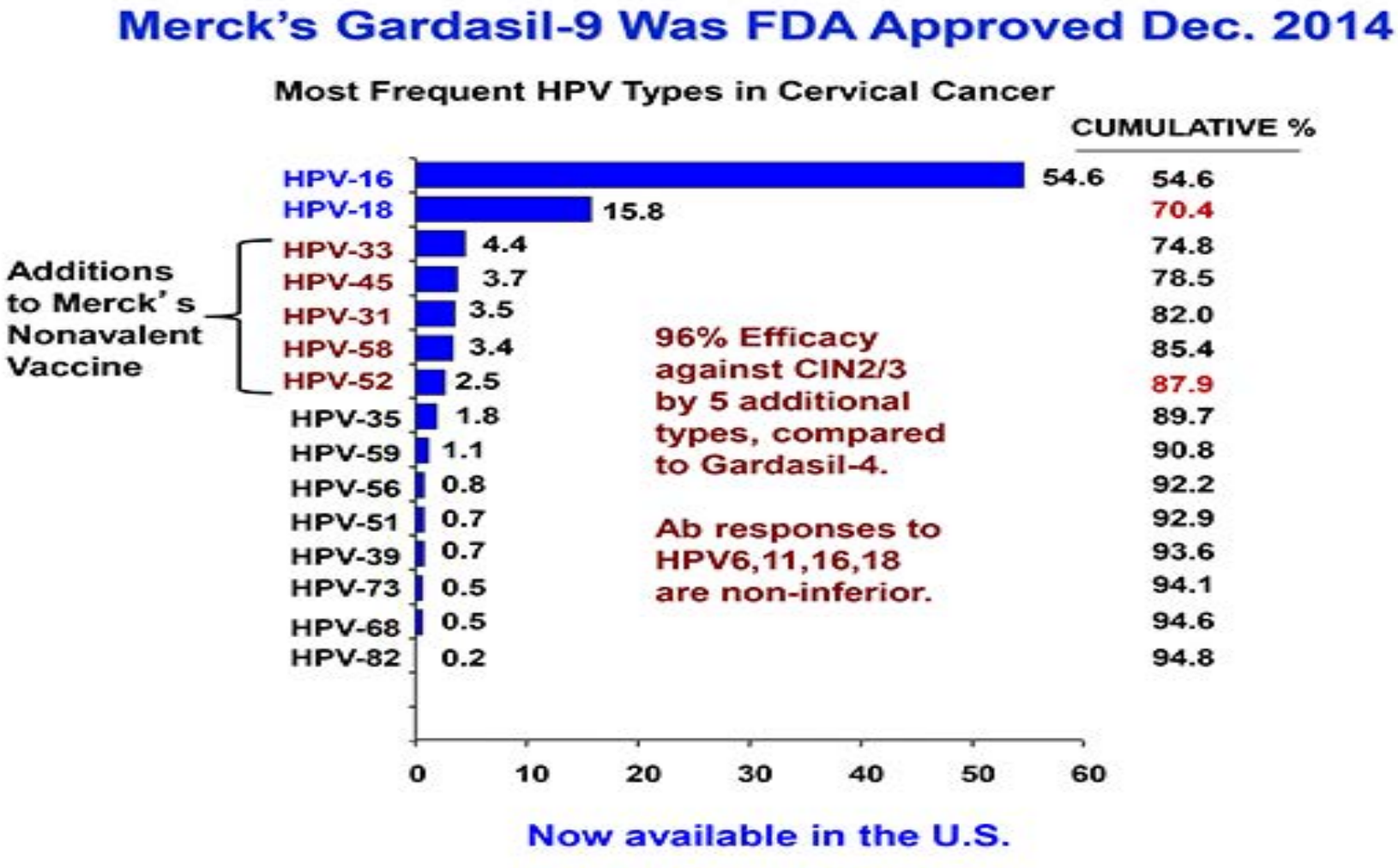
No gential HPV infection detected in at entry

End Point	Sex	Age	Vaccine	Efficacy (95% CI)
CIN III	Female	15-25	Cervarix	100% (90.5-100)
CIN III	Female	15-26	Gardasil	100% (85.5-100)
Genital Warts	Female	15-26	Gardasil	96.4% (91.4-98.4)
AIN	Male	16-26	Gardasil	77.5% (39.6-93.3)
Genital Warts	Male	16-26	Gardasil	89.4% (65.5-97.9)

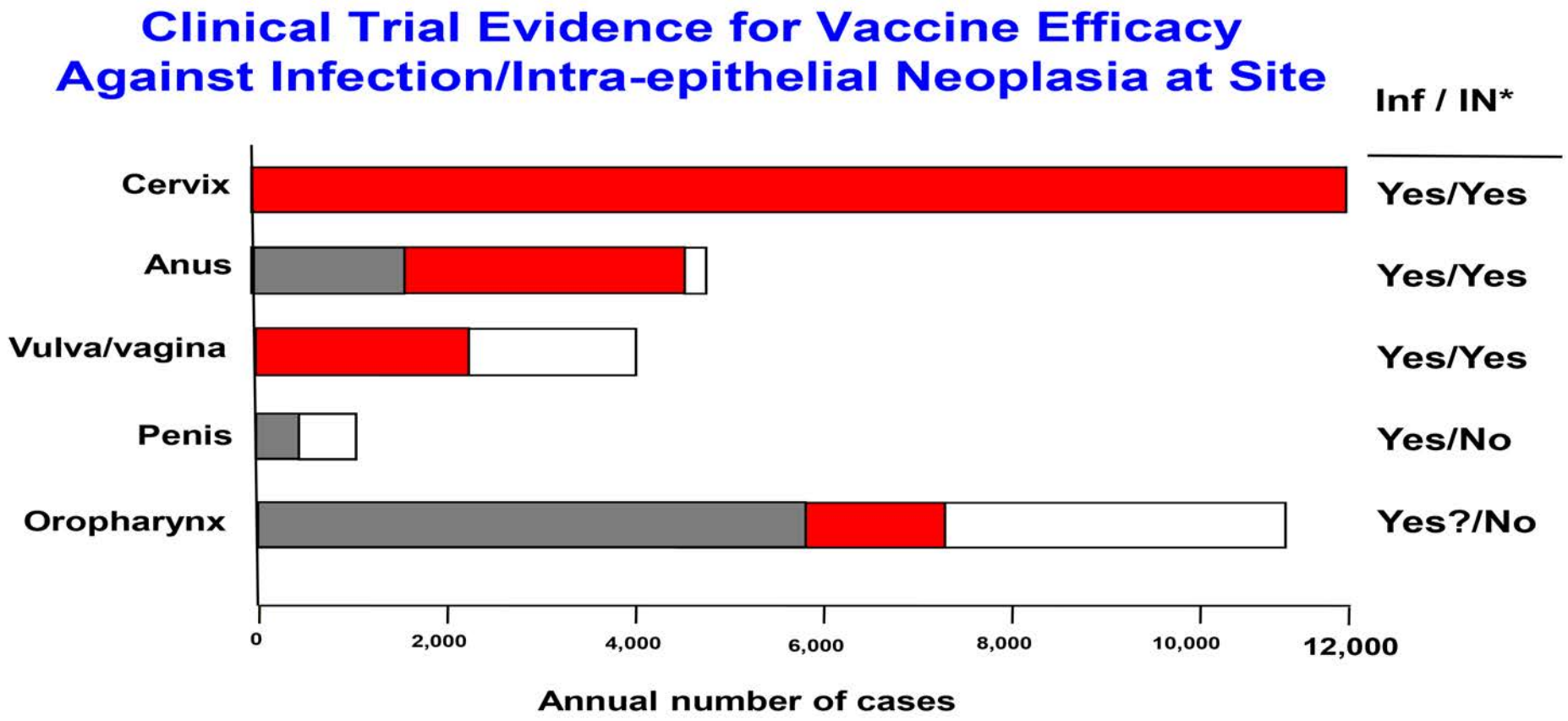
Data from Lehtinen Lancet Oncol 2011; Munoz JNCI 2010; Palefsky NEJM 2011; Giuliano NEJM 2011

CIN III: Cervical Intraepithelial Neoplasia Grade 3
AIN: Anal Intraepithelial Neoplasia of any grade

Gardasil-9


Merck's Gardasil-9 Was FDA Approved Dec. 2014
Most Frequent HPV Types in Cervical Cancer
CUMULATIVE %
HPV-16 54.6 54.6
HPV-18 15.8 70.4
HPV-33 4.4 74.8
HPV-45 3.7 78.5
HPV-31 3.5 82.0
HPV-58 3.4 85.4
HPV-52 2.5 87.9
HPV-35 1.8 89.7
HPV-59 1.1 90.8
HPV-56 0.8 92.2
HPV-51 0.7 92.9
HPV-39 0.7 93.6
HPV-73 0.5 94.1
HPV-68 0.5 94.6
HPV-82 0.2 94.8
Additions to Merck's Nonavalent Vaccine
96% Efficacy against CIN2/3 by 5 additional types, compared to Gardasil-4.
Ab responses to HPV6,11,16,18 are non-inferior.
0 10 20 30 40 50 60
Now available in the U.S.

Clinical Trial Evidence



MMWR Weekly 61:253-80, 2012

Protection from Initial Infection

Protection From Initial Infection

- Most Vaccinees never tested positive for HPV infection as measured by sensitive PCR Assays.
- “Breakthrough” infection tended to appear early in the trials suggesting that most were emergence of prevalent infection.
- Results imply that sterilizing immunity normally generated.

HPC vaccine

What the HPV Vaccines Don't Do

- They don't prevent infection or disease caused by most of the other HPV types that cause cervical cancer.
- They don't induce regression of established HPV infections or prevent progression of HPV-induced lesions.

Safety record

HPV VLP Vaccines Have an Excellent Safety Record

- Low grade and transient injection site reactions, particularly pain, are common.
- Systemic reactions, when they occur, are mild and self-limiting.
- Synocope (fainting) is sometimes observed (needle related).

Serious Adverse Events Following HPV Vaccination

Study	Vaccine	% Vaccine	% Control	Relative Risk (95% CI)
Future I	Gardasil	1.8%	1.7%	1.07 (0.71-1.60)
Future II	Gardasil	0.7%	0.9%	0.83 (0.56-1.24)
PATRICIA	Cervarix	7.5%	7.5%	1.00 (0.91-1.11)

No patterns of serious adverse events following immunization in trials or post-licensure surveillance that would suggest a causal relation to the vaccine.

Reviewed in: Macartney, Drug Saf 2013; 36:393-412; Sheller JAMA 2015; 313:54-61; Arnheim-Dahlstrom, BMJ 2013; 347, f5906.

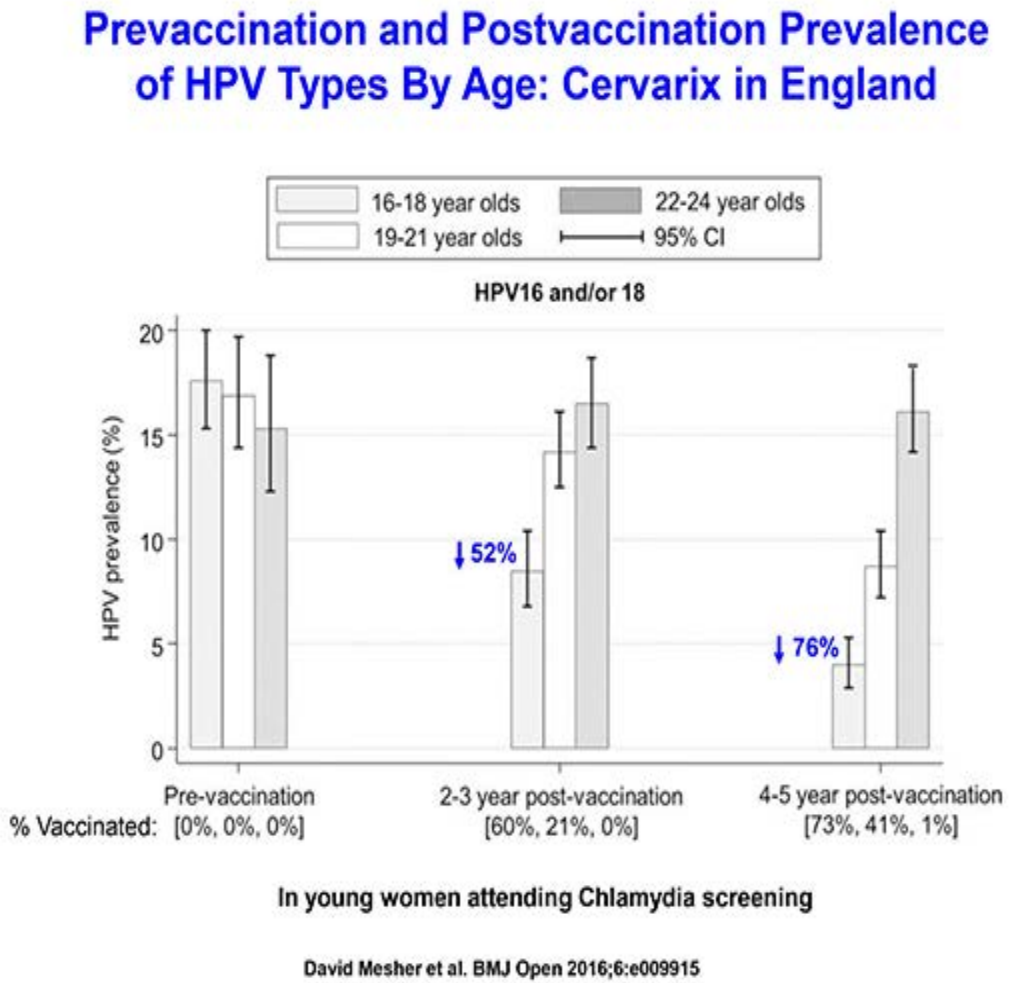
Vaccine effectiveness

Vaccine Effectiveness: Evidence From National Immunization Programs

Country	Type-Specific Infection		Genital Warts		Cervical Lesions
	Female	Male	Female	Male	Female
Australia	+	+	+	+	+
Britain	+		+		+
USA	+	+	+		+
Canada			+		+
Denmark			+	+	+
Sweden			+	+	+
France	+				
Spain			+		
Italy			+	+	
Israel			+	+	

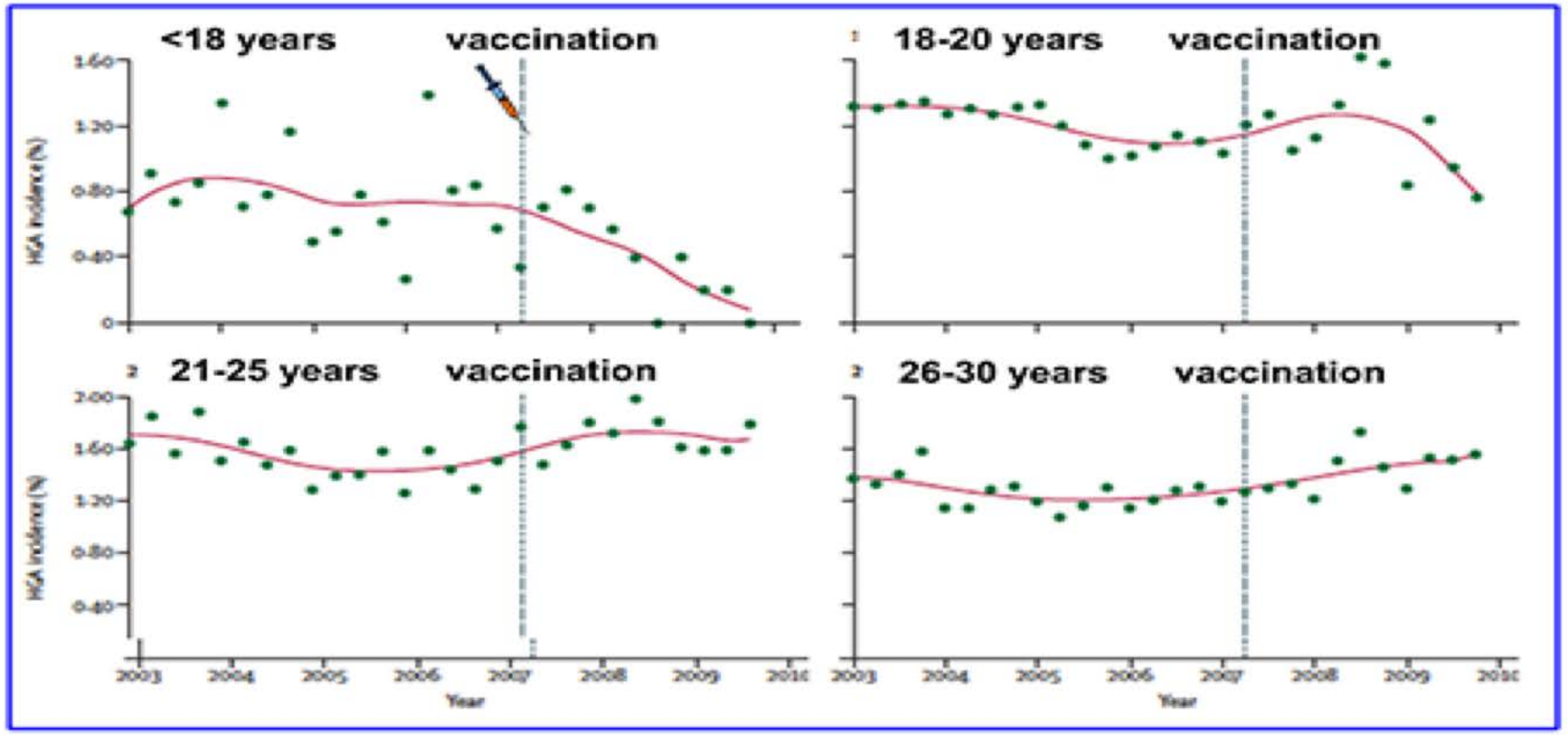
Drolet, Lancet Infect Dis 2015;15:565-580; Brotherton, Best Pract Res Clin Obst & Gyn, 2017

Vaccination



Reduction of CIN2+ cervical dysplasia

Effectiveness: Reduction in CIN2+ Cervical Dysplasia by Gardasil in Australia



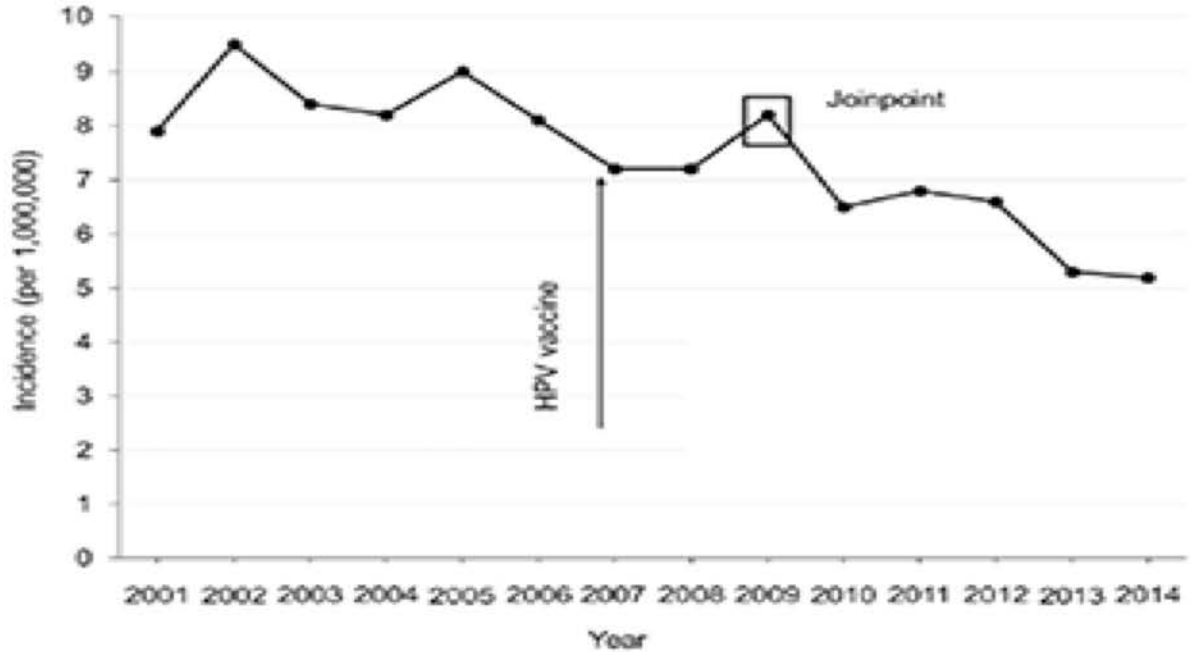
Brotherton et al, Lancet 377: 2085-92, 2011

Prevention of cervical cancer

Prevention of Cervical Cancer?

Annual Incident Rates of Cervical Cancer in U.S. Women 15-24 Years

A 29% decrease 2011-2014 vs 2003-2006



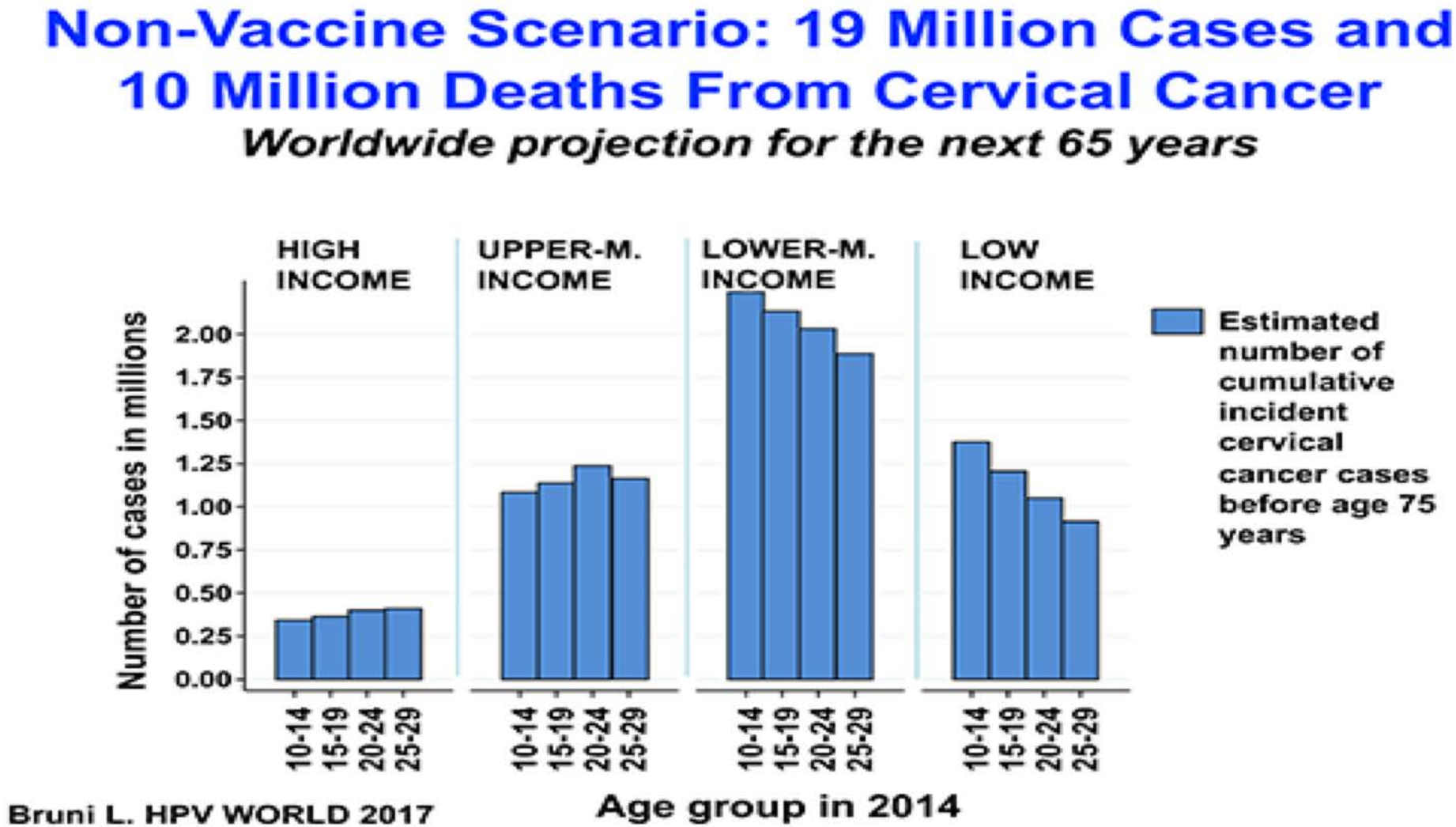
Guo et al Am J Prev Med 2018

HPV vaccines

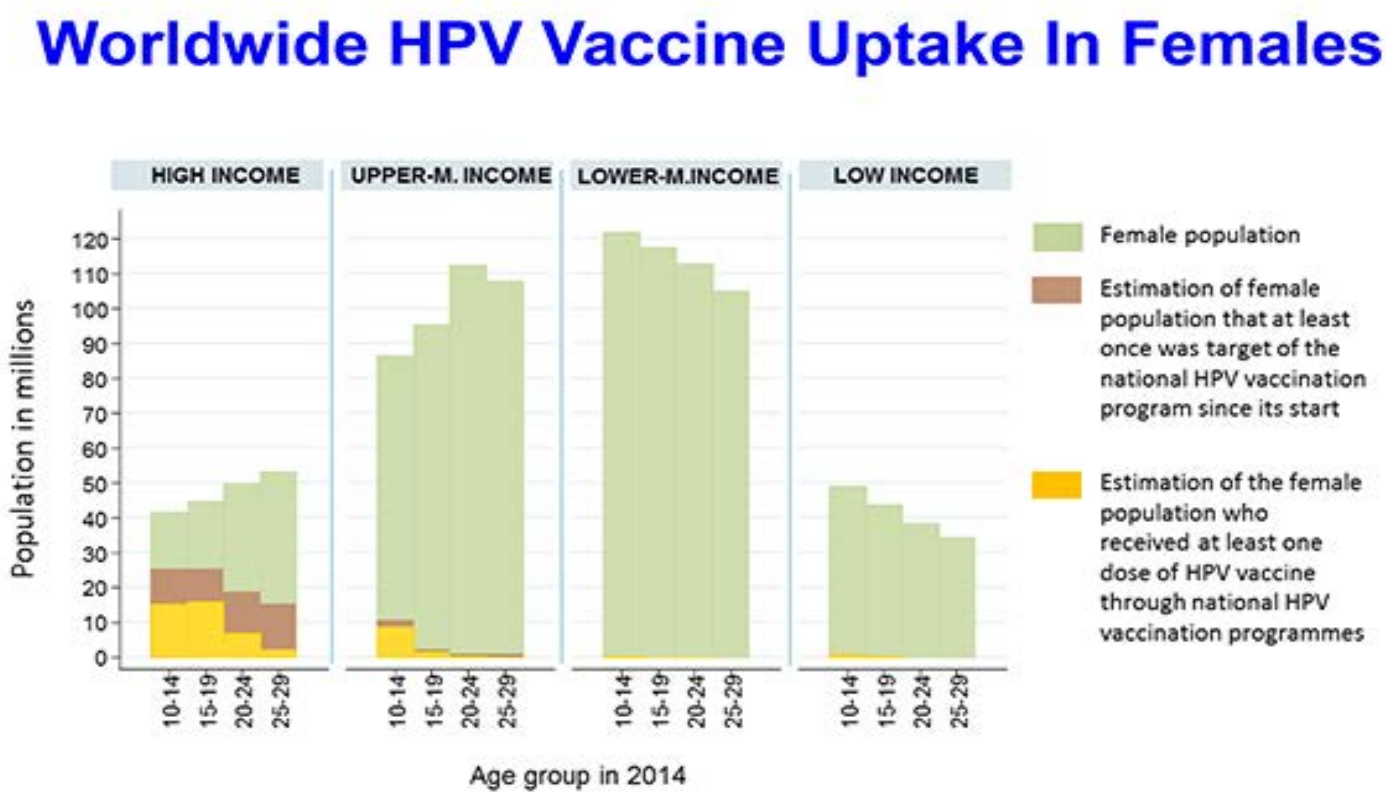
HPV Vaccines Are Now Established Products

- Commercially available for more than 10 years.
- Licensed in 82 countries.
- Over 270 million doses given globally.
- Increasing evidence of effectiveness in national immunization programs.

Non-vaccine scenario



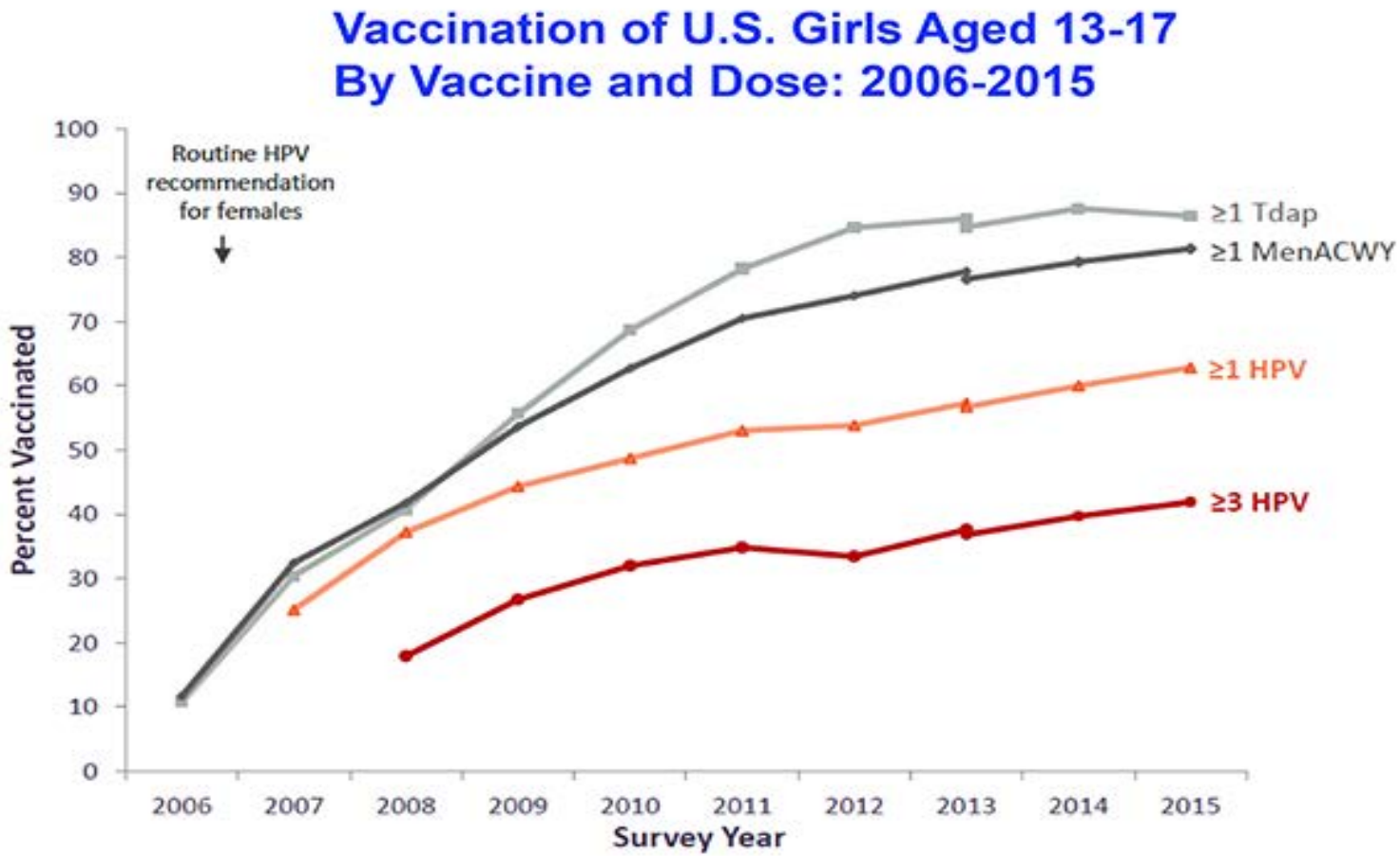
Worldvide HPV vaccine uptake



Only 3% of girls in lower and lower-middle income countries have been vaccinated

Bruni et al. Lancet Global Health2016; 4:3453-63

US girls vaccination rate



Reagan-Steiner et al. MMWR 2016

Increasing Uptake, Particularly in Low Resource Settings

Increasing Uptake, Particularly in Low Resource Settings

- **Both companies are committed to sale to GAVI at less than $5 per dose.**
- **Vaccine manufacture in emerging countries.**
- **Address vaccination hesitancy by education programs aimed families and health care providers.**
- **Deliver fewer than three doses.**

Post hoc analysis

Post Hoc Analysis of Cumulative HPV Infection Incidence Over 7 Years in the Costa Rican Cervarix Trial

	% Infected (95% CI)	
End Point	3 doses (N = 2043)	1 dose (N = 134)
HPV16/18	**4.3** (3.5-5.3)	**1.5** (0.3-4.9)
HPV31/33/45	**8.0** (6.9-9.3)	**8.2** (4.4-13.8)
Other Oncogenic*	**43.6** (41.5-45.8)	**39.6** (31.5-48.0)
Nononcogenic	**46.2** (44.0-48.3)	**44.0** (35.8-52.5)

* HPV types 35/39/52/52/56/58/59

M Safaeian et al, J Natl Cancer Inst, 110 (2), 2018

One dose clinical trial results

Other One Dose Clinical Trial Results

Cervarix:

4 year *post hoc* results PATRICIA trial showed similar efficacy for 1, 2 and 3 dose recipients.

Kreimer et al. Lancet Oncol 16:e424-5, 2015

Gardasil:

In an interrupted Indian cluster randomized trial, after 7 years, there was similar protection in young women receiving 1, 2, or 3 doses.

Sankaranarayanan et al. Vaccine, 2018, Epub Mar 15

Single dose HPV vaccination

Is It Time to Adopt Single Dose HPV Vaccination Programs?

These post-hoc findings provide insufficient evidence to generally promote implementation of single dose HPV vaccination programs.

Early adoption in low resource settings with a contingency plan to boost if needed might be justified.

One or two doses of the HPV vaccine

RCT of One or Two Doses of the HPV Vaccines in Costa Rica

- 4 Arms: 1 vs 2 dose Cervarix
  1 vs 2 dose Gardasil-9
- 5000 12-16 yr old females per arm.
- Primary endpoint: persistent HPV16/18 infection.
- Survey of HPV prevalence in age matched women in region.
- 4 year primary trial; long term follow up.
- NCI and Gates financed.

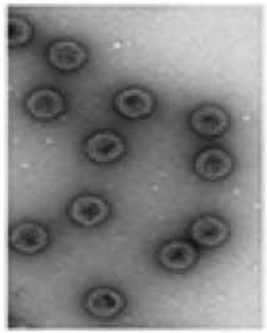
Clinicaltrials.gov identifier: NCT03180034

proyecto escuddo

Why do HPV VLP vaccines work so well?

Why Do HPV VLP Vaccines Work So Well?

- The vaccines are exceptionally good at inducing neutralizing antibodies.
- Infection mechanism make HPVs exceptionally susceptible to neutralizing antibodies.
- HPVs have DNA genomes so can't evolve rapidly to evade nAb responses.



HPV16 L1 VLPs

Provides plausibility for HPV VLPs as the first subunit vaccine to induce long term protection after a single dose

Antibody responses to VLPs

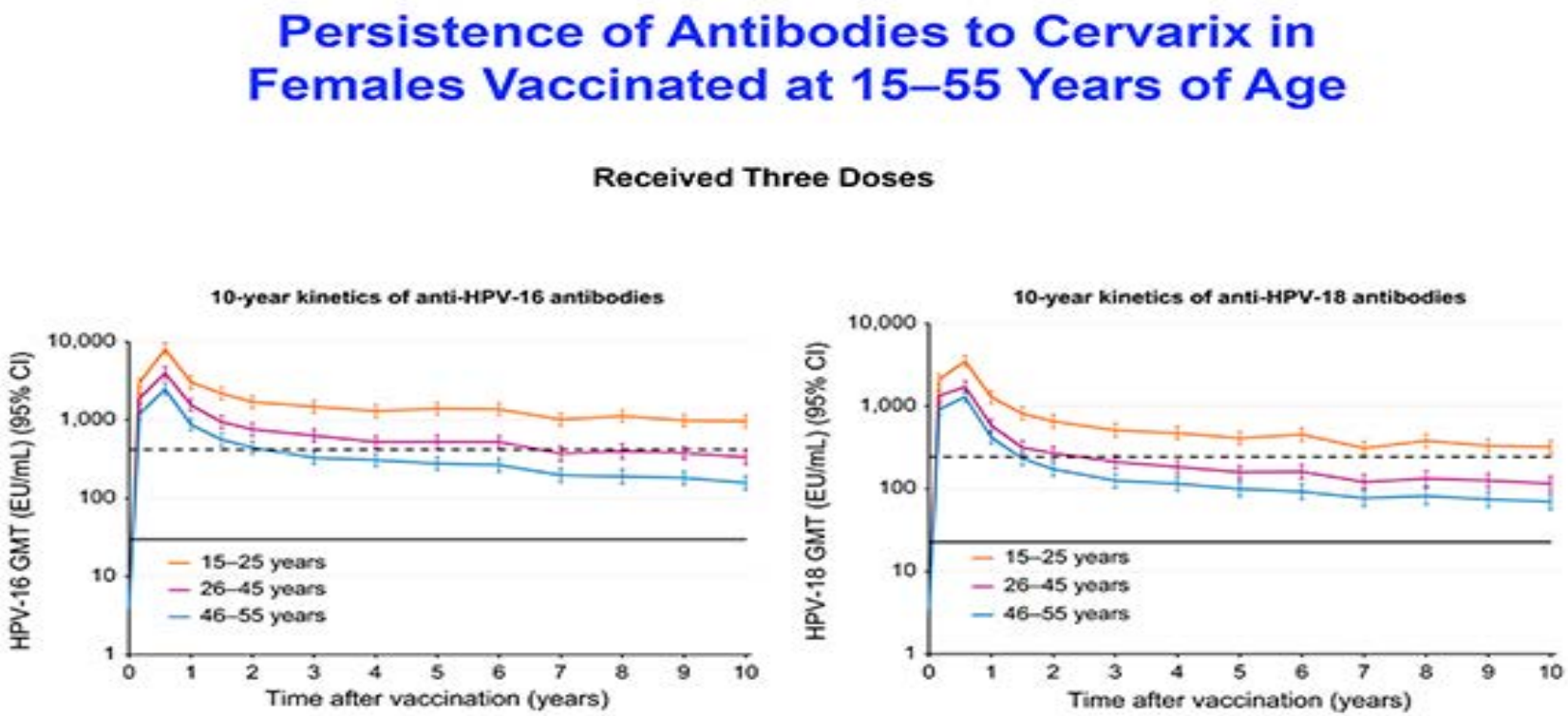
Consistency of Antibody Response to VLPs

Percent of Women Serocoverting to Individual HPV VLPs in Merck VLP Vaccine Gardasil*

HPV6	99.8%
HPV11	99.8%
HPV16	99.8%
HPV18	99.5%

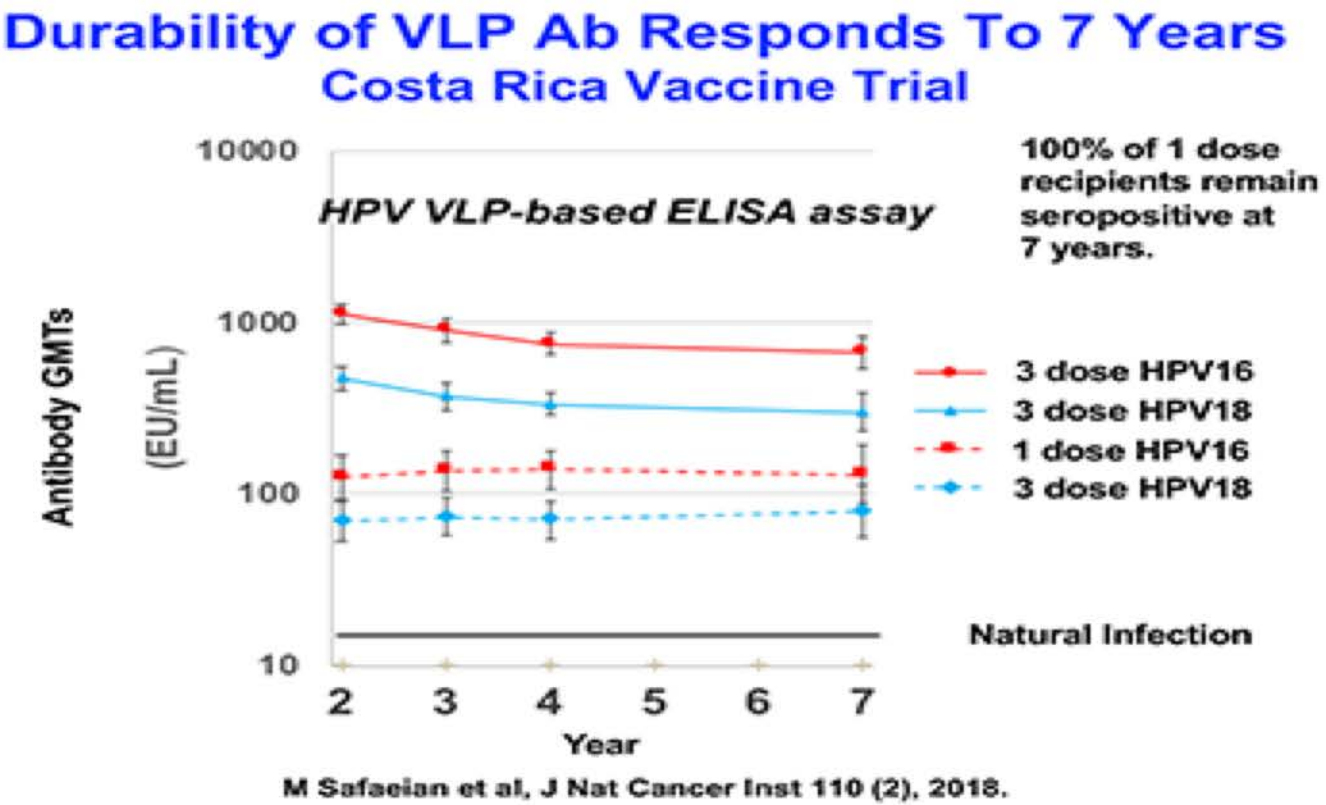
*4666 women vaccinated 3 times by intramuscular injection

Persistence of antibodies

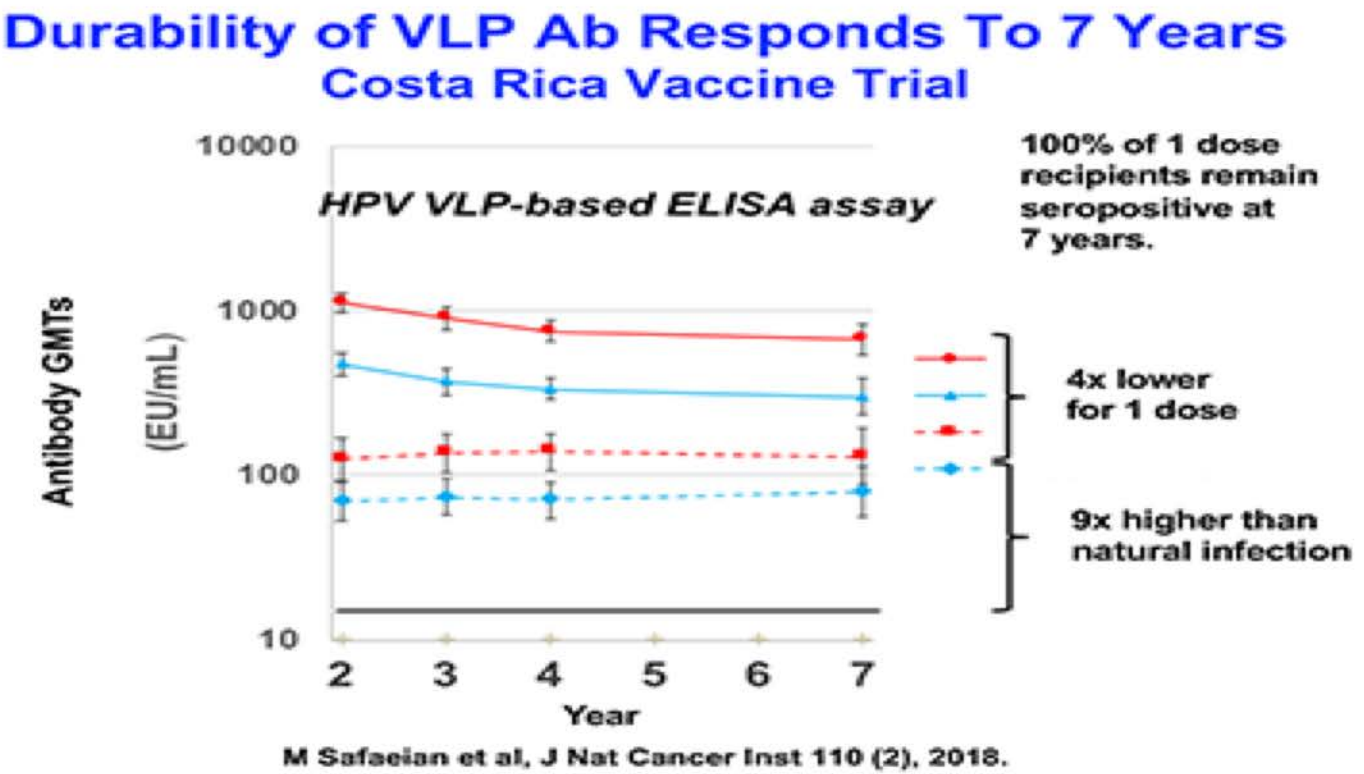


Cancer Medicine
5 OCT 2017 DOI: 10.1002/cam4.1155

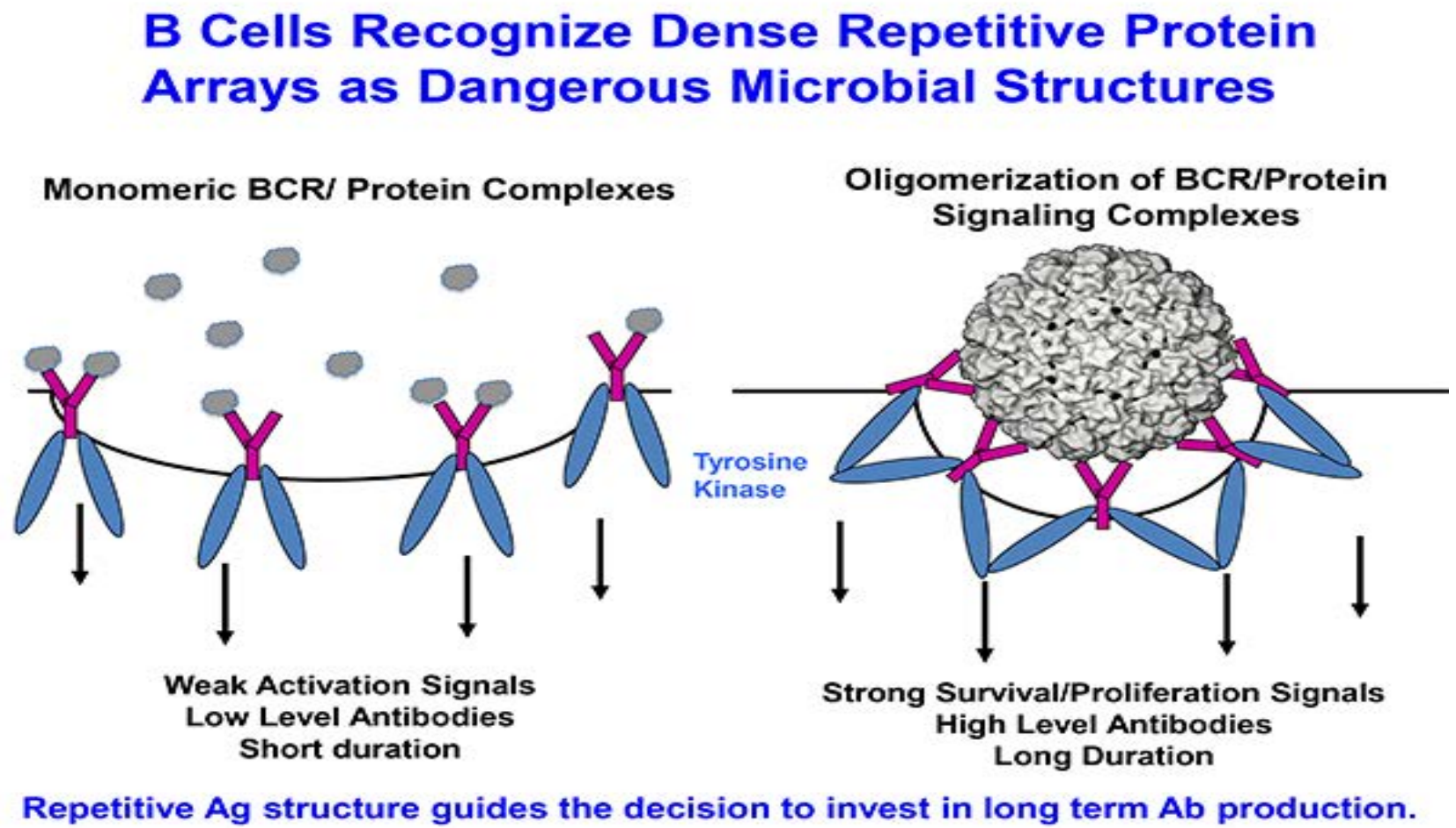
Durability of VLP Ab response



VLP Ab response



B cells recognize dense repetitive protein arrays



Repetitive antigen display

VLPs Have Highly Repetitive Antigen Display

B cells specifically recognize particulate antigens with epitope spacing of 50-100Å as foreign.

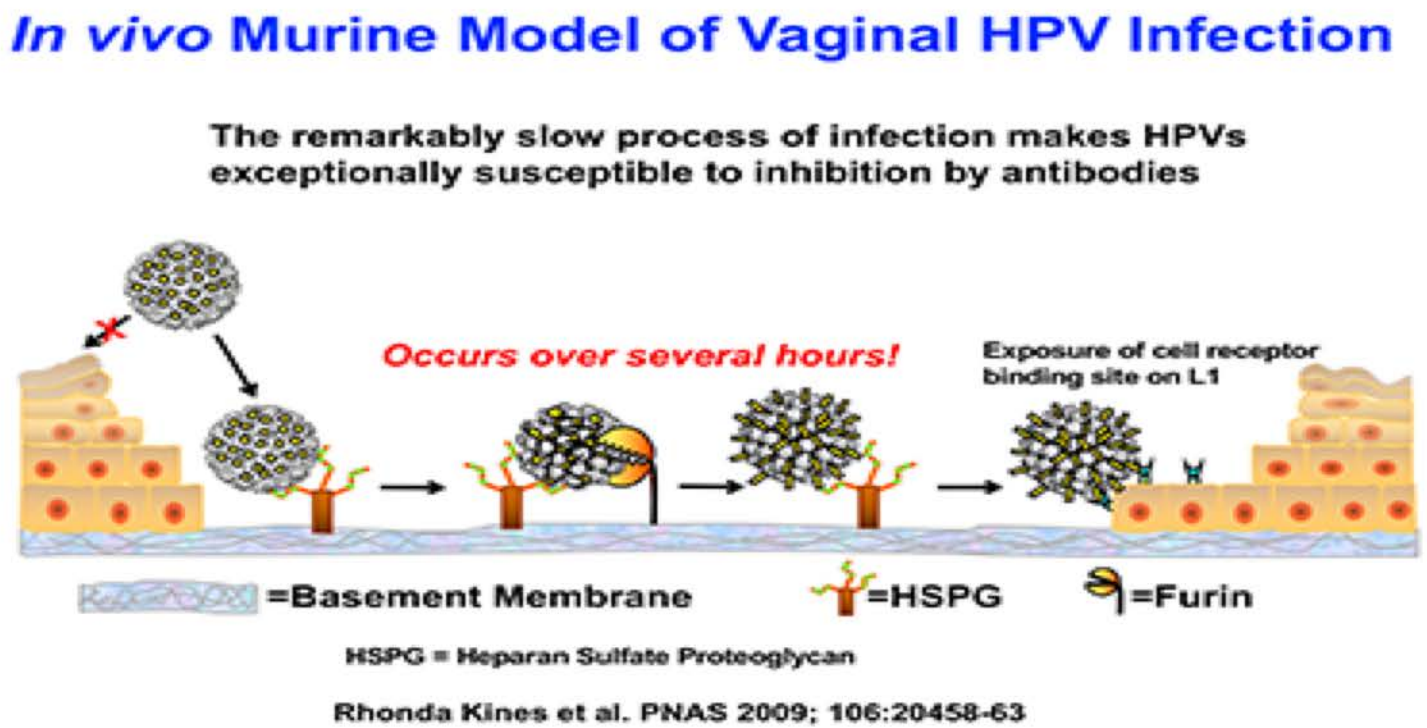
This epitope spacing is commonly found on microbial surfaces, e.g. virus major capsid protein or bacterial pili.

Protein complexes with this spacing rarely occur in vertebrate animals.

So BCRs have evolved as antigen specific pattern recognition receptors.

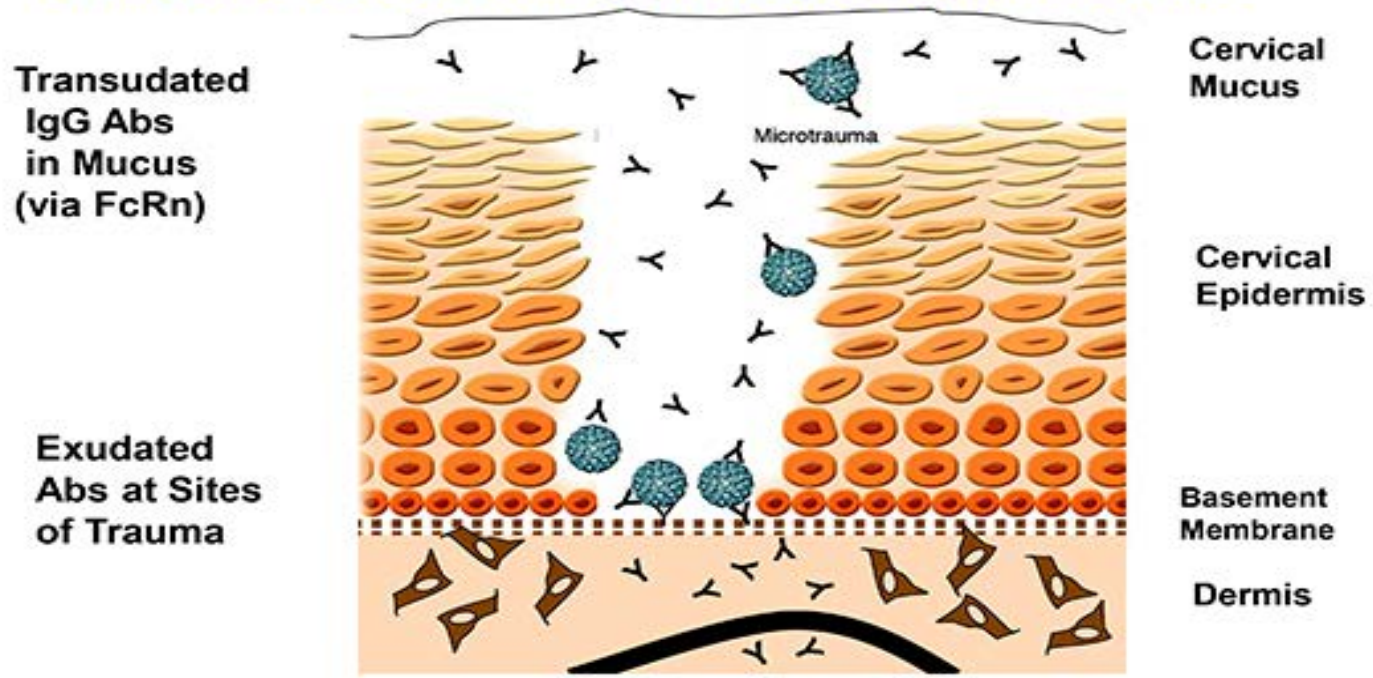
Bachmann et al. Science 1993; 262: 1448

Vaginal HPV infection



Cervix Ab response

How Could IM Injection of a VLP Vaccine Induce a Protective Ab Response at the Cervix?



- VLP-specific IgG in women's cervical mucus after IM vaccination: but 10-100X less than in serum - *Nardelli et al. JNCI, 2003*
- Cervicovaginal HPV infection in a mouse model requires epithelial trauma: *Roberts et al., Nat Med, 2007*

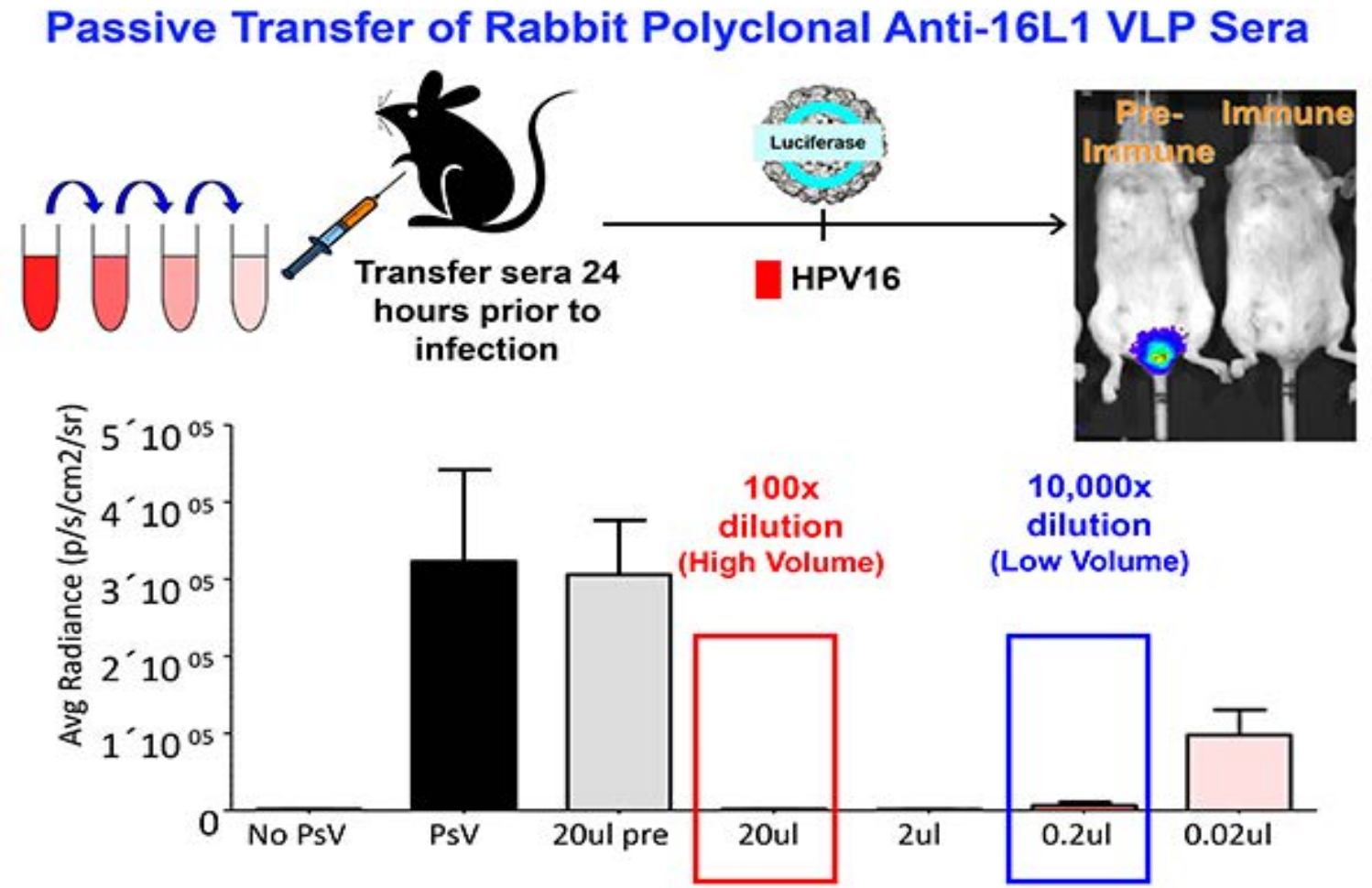
Antibody titers and protection

Antibody Titers and Protection

Are the plateau titers after vaccination near the minimum needed for protection?

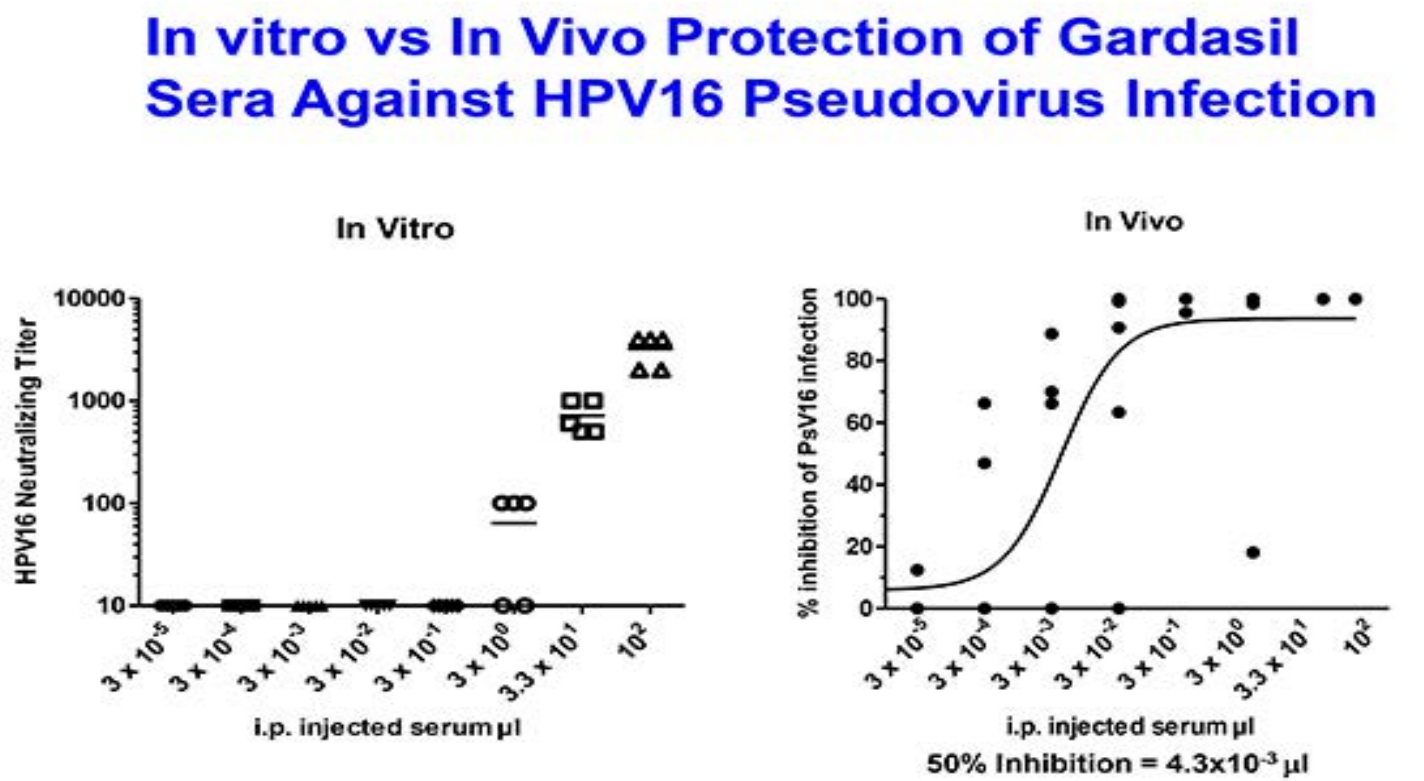
Will the 4-fold difference between Ab titers after three vs one dose influence long-term protection?

Passive transfer

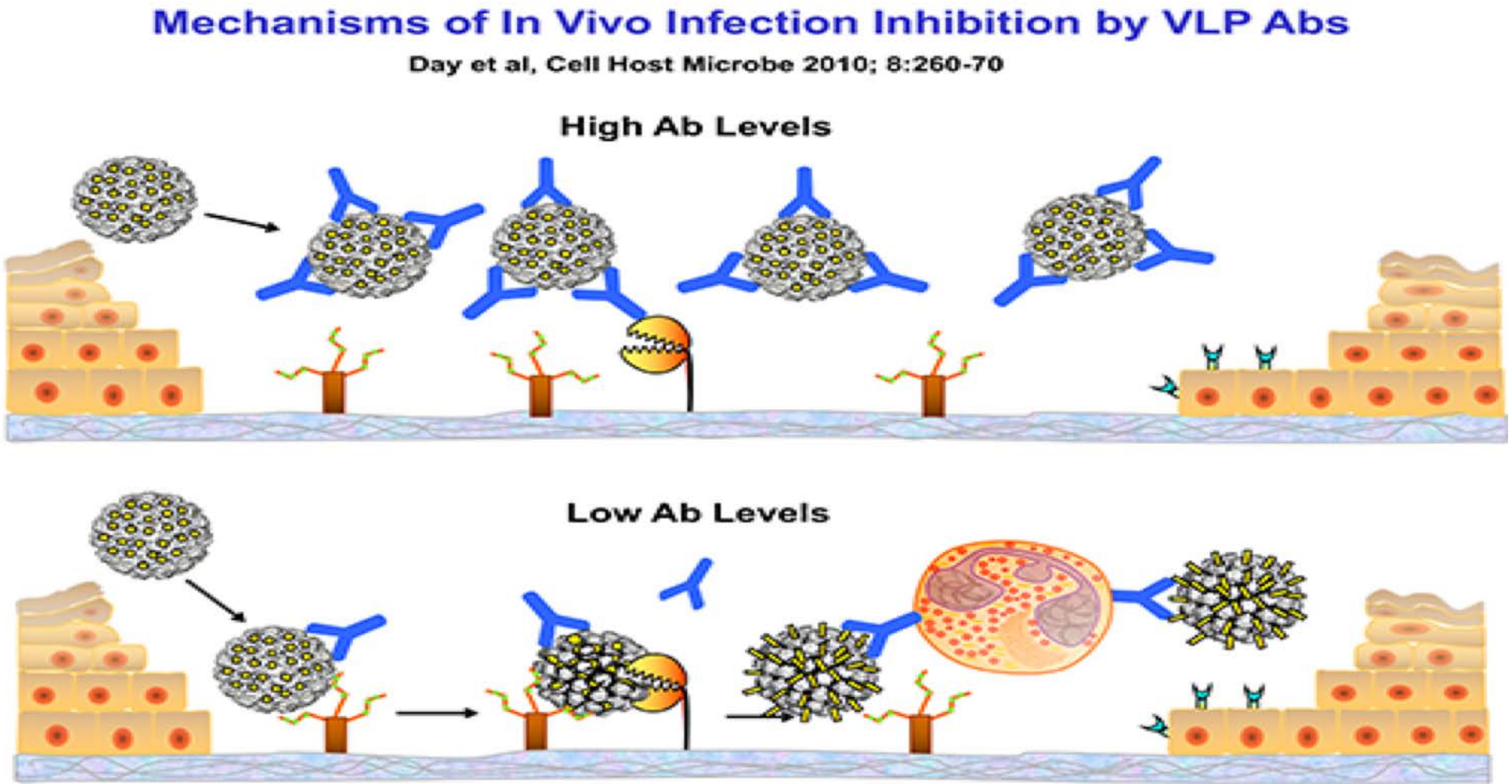


* Challenged with HPV16. See no protection from infection when challenged with HPV45

Gardasil sera protection



Mechanisms of in vivo infection



Conclusions

Conclusions

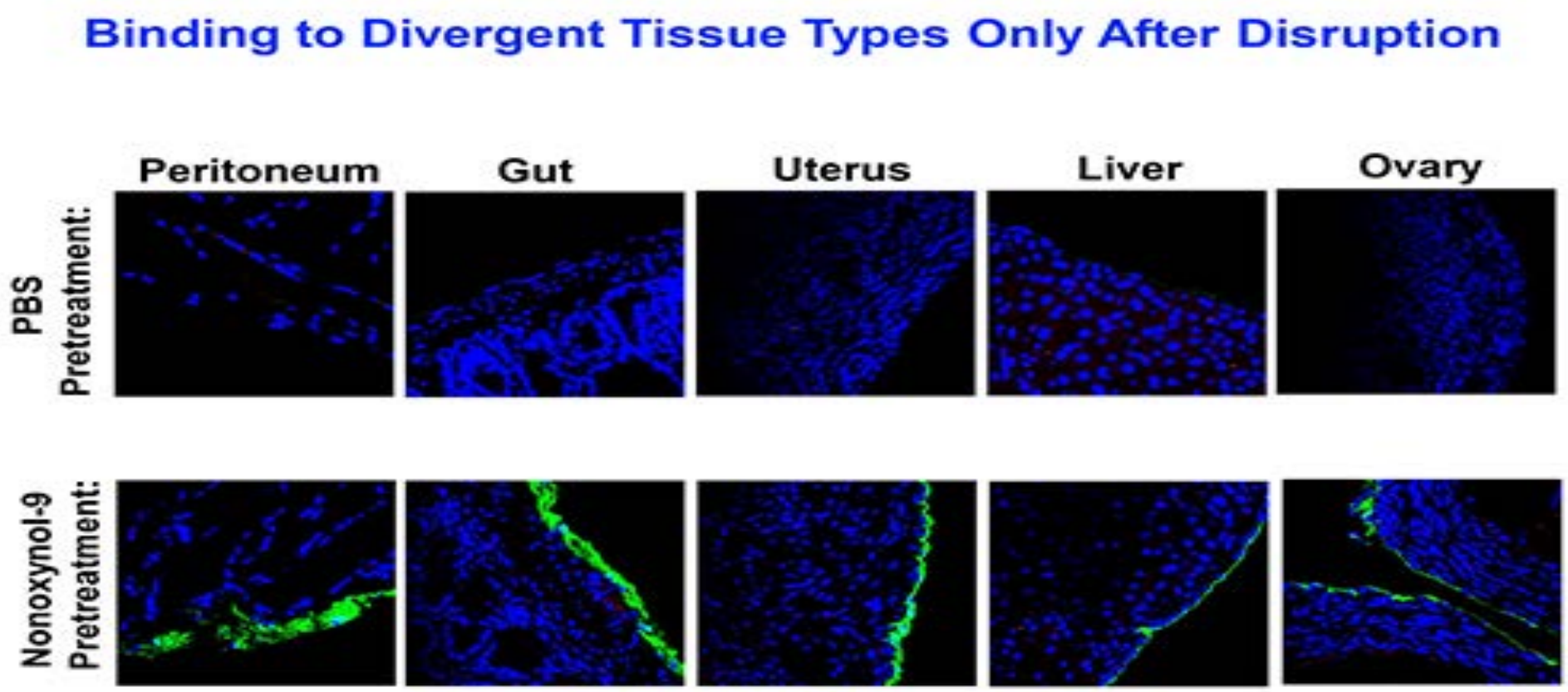
- The HPV VLP vaccines are very effective at preventing incident infection and disease by the vaccine types.
- Because the VLPs are exceptionally potent induces of neutralizing antibodies and the virus is exceptionally susceptible to inhibition by antibodies.
- The vaccines have great potential for reducing the burden of HPV-induced cancer worldwide.
- The primary challenge now is to see that the vaccines reach the individuals most in need of them.
- Demonstrating sustained efficacy of a single dose in a RCT could transform implementation programs.

Exploiting HPV's unexpected infection mechanism

Exploiting HPV's Unexpected Infection Mechanism For Cancer Therapy

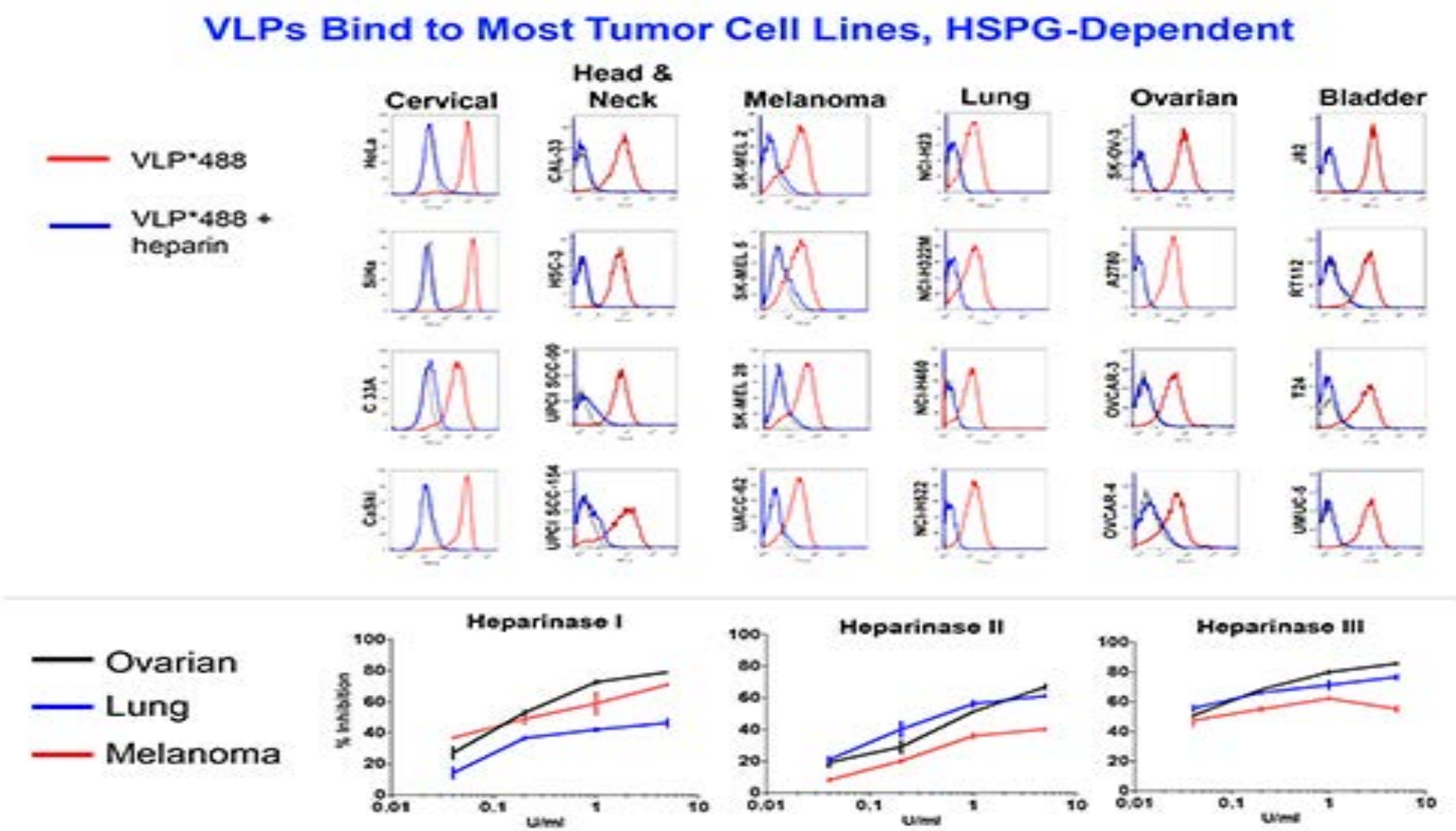
- HPV capsids don't bind or infect normal intact tissues: they lack the necessary HSPG modifications.
- Surprisingly, they do bind and infect most cancer cells: they evolve HSPG modifications that mimic those normally found only the basement membrane.
- So HPV VLPs can be used as "guided missiles" to deliver cytotoxic agents to tumors.

Binding to divergent tissue types

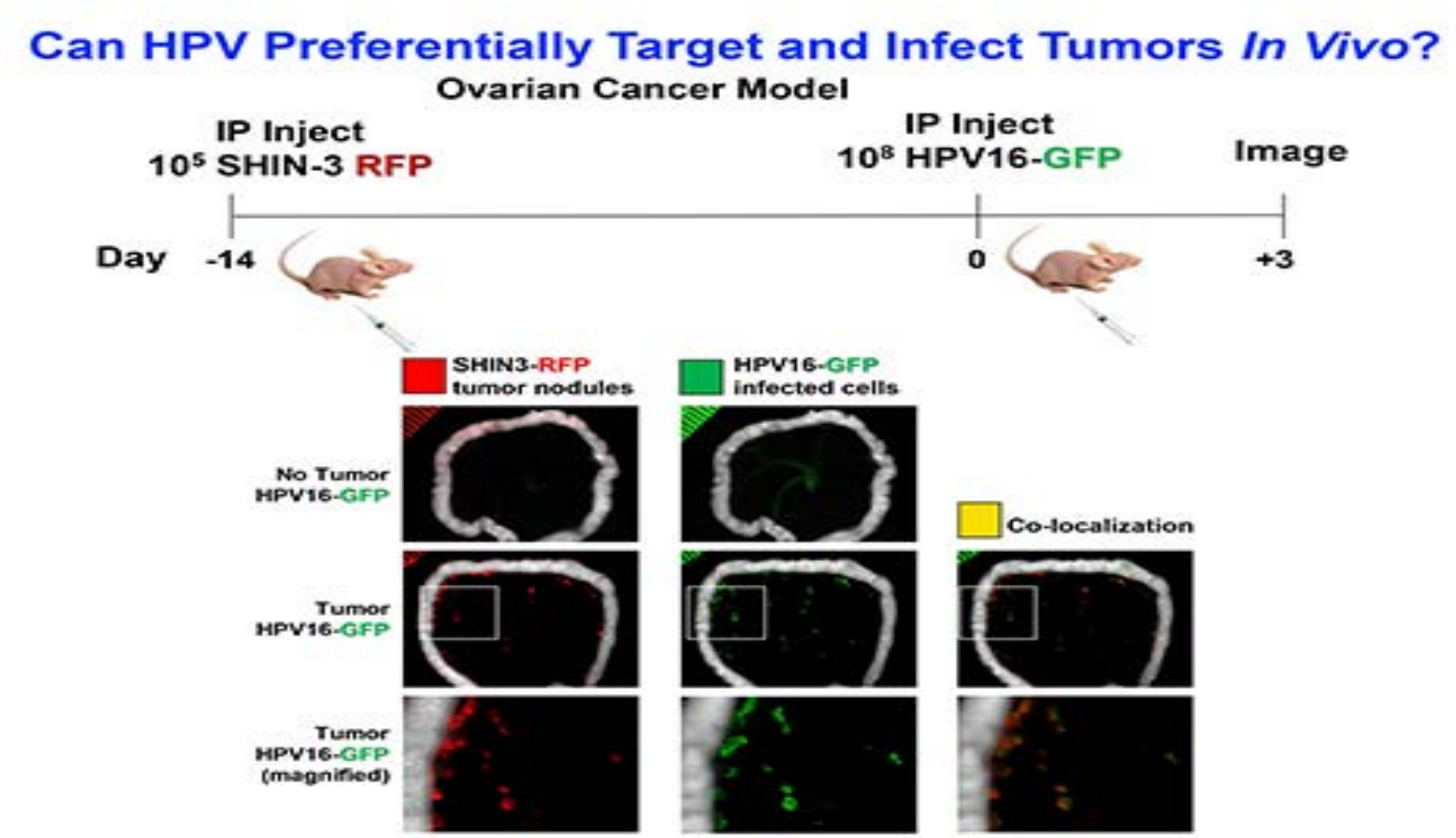


Kines and Cerio, et al. IJC 2016

VLPs bind to most tumor cell lines



Can HPV infect tumors in vivo?



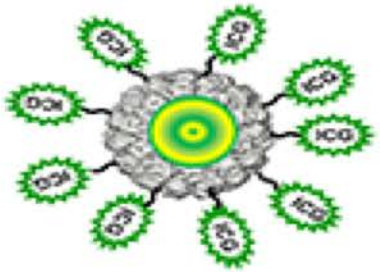
HPV capsids for cancer

Applications for HPV Capsids for Cancer

A collaboration with Aura BioScience

Imaging

- Dye (e.g. ICG, FITC, IR)
- Radio label



Drug/Cytotoxin Delivery

- Attached/encapsidated drug (eg. Doxorubucin, topotecan)
- Nucleic acid delivery expressing toxins/suicide gene (e.g. TK)

Direct killing

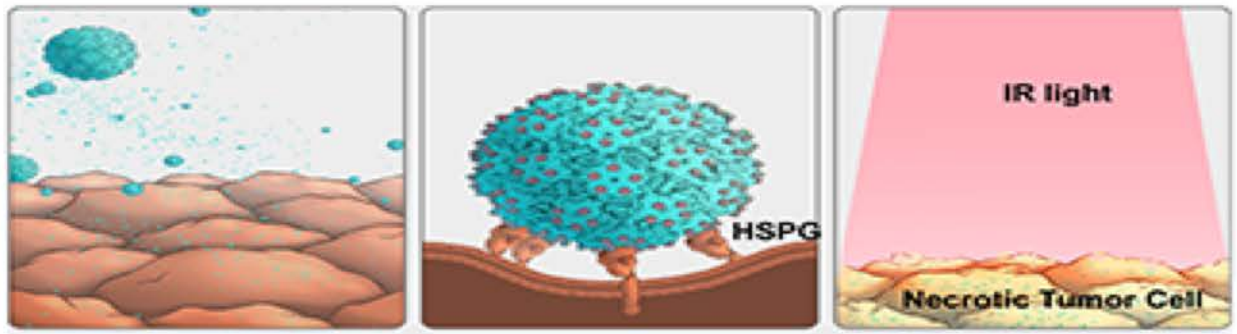
- Radio label
- NIR dye

HPV VLP-IR700 conjugates

HPV VLP-IR700 Conjugates: Dual Specificity for Cancer Therapy

Cytotoxic only if:

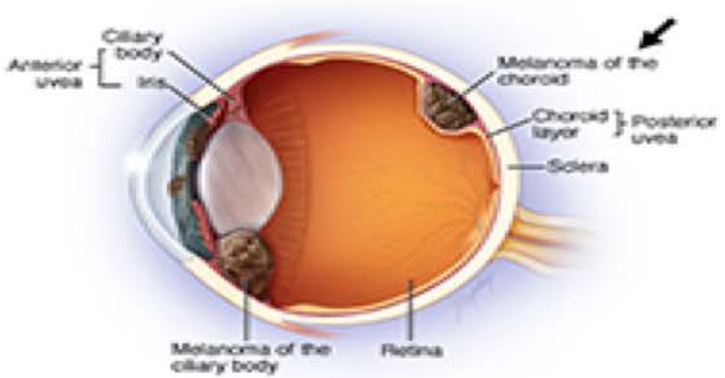
- **Bound to the cell surface**
- **Illuminated with infrared light**

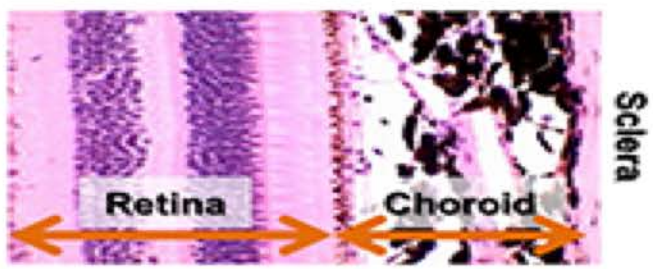


Occular/uveal melanoma

Ocular/Uveal Melanoma as a 1st Target for HPV VLP-IR700

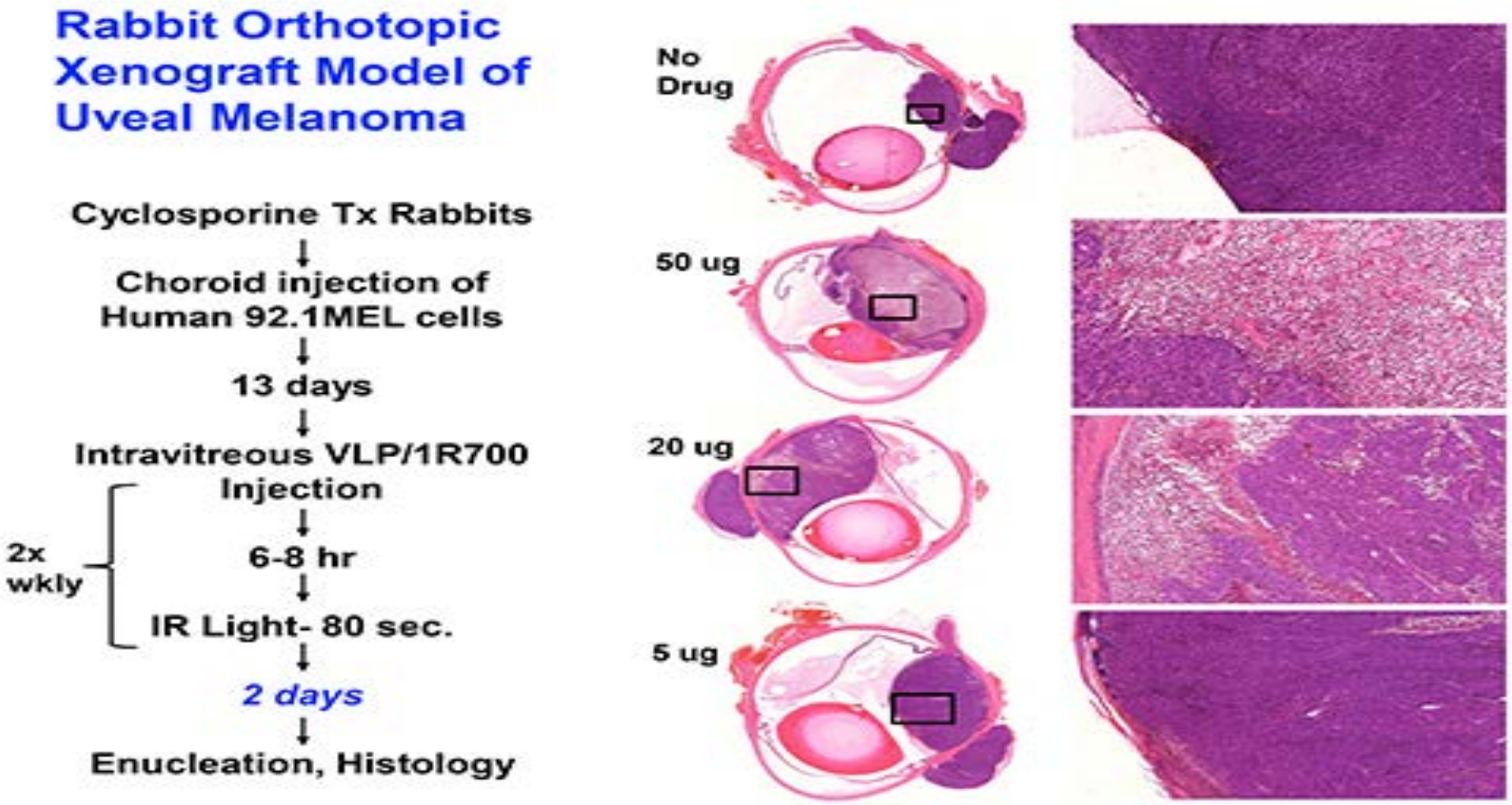
- **Often deadly due to liver metastases.**
- **Treatment is brachytherapy, often leads to long-term retinal damage and vision loss. Alternative is enucleation.**
- **Permits noninvasive access by laser.**
- **A rabbit model have been developed with intrachoroid implantation of human OM cell lines.**





A collaboration with Aura BioScience

Xenograft model of uveal melanoma



Xenograft model of uveal melanoma

Rabbit Orthotopic Xenograft Model of Uveal Melanoma

Cyclosporine Tx Rabbits

↓

Choroid injection of Human 92.1MEL cells

↓

13 days

↓

Intravitreous VLP/1R700 Injection

↓

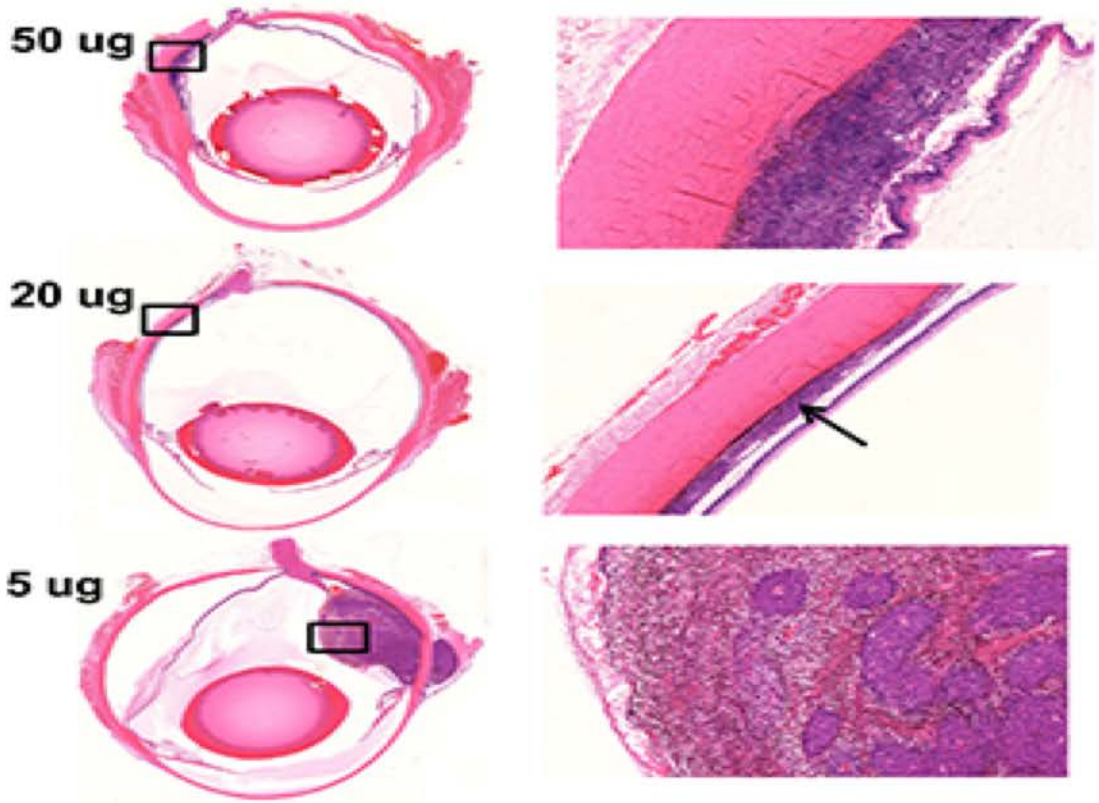
2x wkly: 6-8 hr → IR Light- 80 sec.

↓

8-9 days

↓

Enucleation, Histology

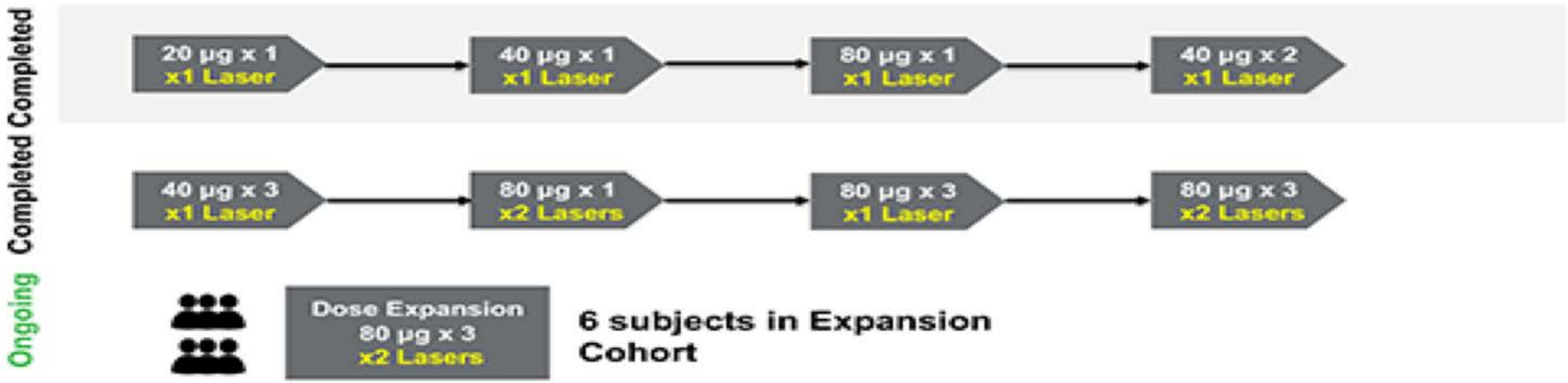


Clinical trial of uveal melanoma

A Phase Ib/2 Clinical Trial of Uveal Melanoma

Dosing parameters

- Drug Dose (20µg, 40µg, 80µg)
- Frequency of treatments (1, 2 or 3 weekly intravitreous injections)
- Laser administrations (1 or 2 applications separated by 30 min.)



Sponsored by Aura BioScience

Preliminary clinical trial results

Preliminary Clinical Trial Results

- 24 patients treated to date
- No related severe adverse events, or dose limiting toxicities
- Pre-treatment vision preserved in all patients followed at 6 months or longer
- Drug Related Adverse events mild to moderate :
  - Mild/Moderate Anterior Chamber Inflammation (N = 16/24)
  - Mild/Moderate Posterior Chamber Inflammation (N = 15/24)
  - Mild/Moderate Transient Increases in IOP (N = 9/24)
  - Appearing after 2-4 weeks, suggesting adaptive immunity
  - Managed with standard treatment and resolved without clinical sequelae

Most optimistic projection for the technology

A broadly applicable, “off the shelf” cancer therapy. What cancer should be tried next?

Key Collaborators

Key Collaborators

Present Members of the Lab:

Doug Lowy	Cindy Thompson	Tara Berman
Patricia Day	Susana Pang	Lukas Bialkowski
Nicolas Cuburu	Carla Cequeira	Alex Bell

Past Members of the Lab:

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Chris Buck	Reinhard Kirnbauer
Jeff Roberts	Rhonda Kines
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Aura Biosciences: Eli de los Pinos, Rhonda Kines, Steve Monk