National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Key Immunological Considerations For HPV mRNA Vaccine Development

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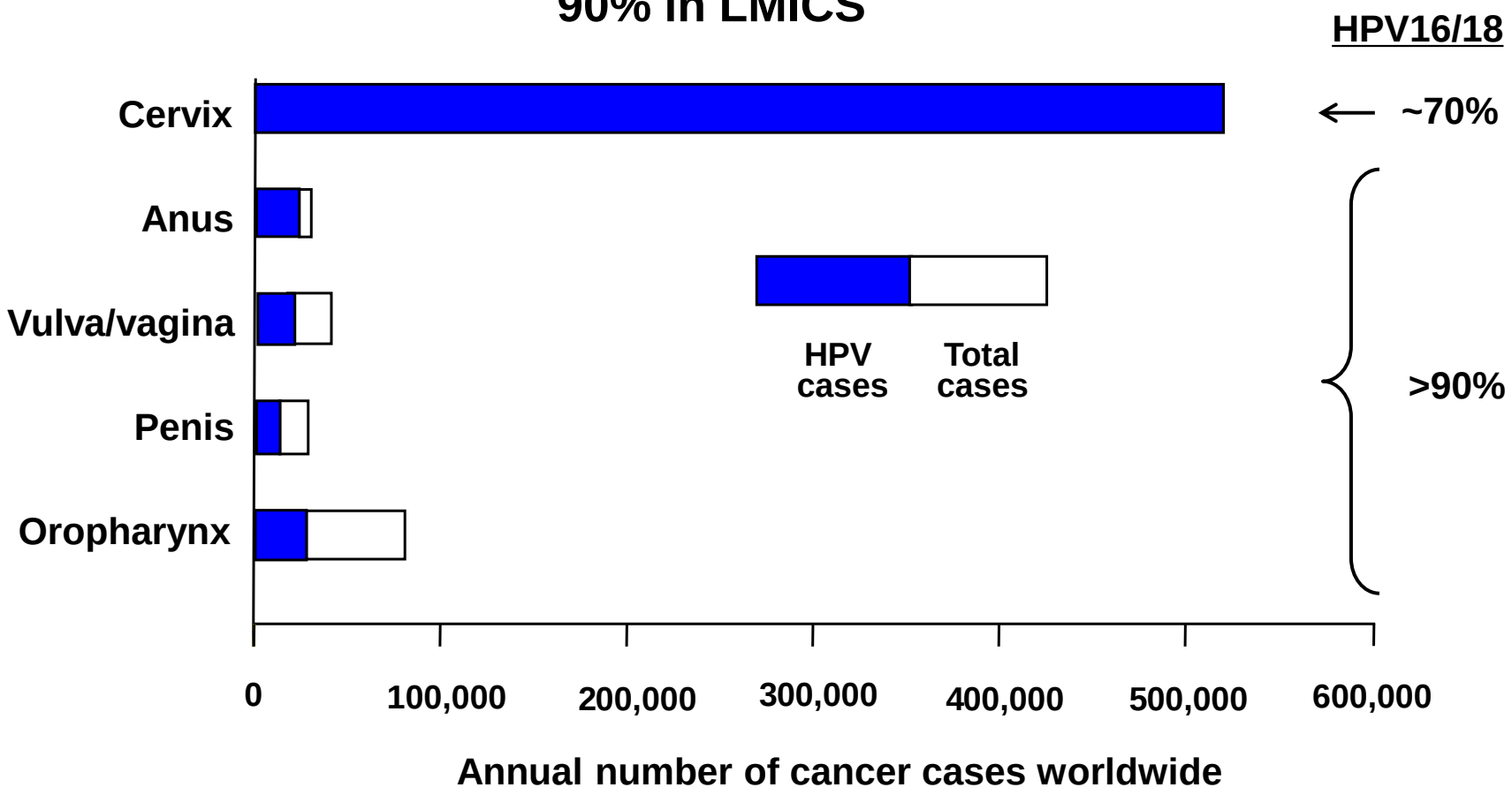
Worldwide Incidence of HPV-Associated Cancers And Attributable Fraction

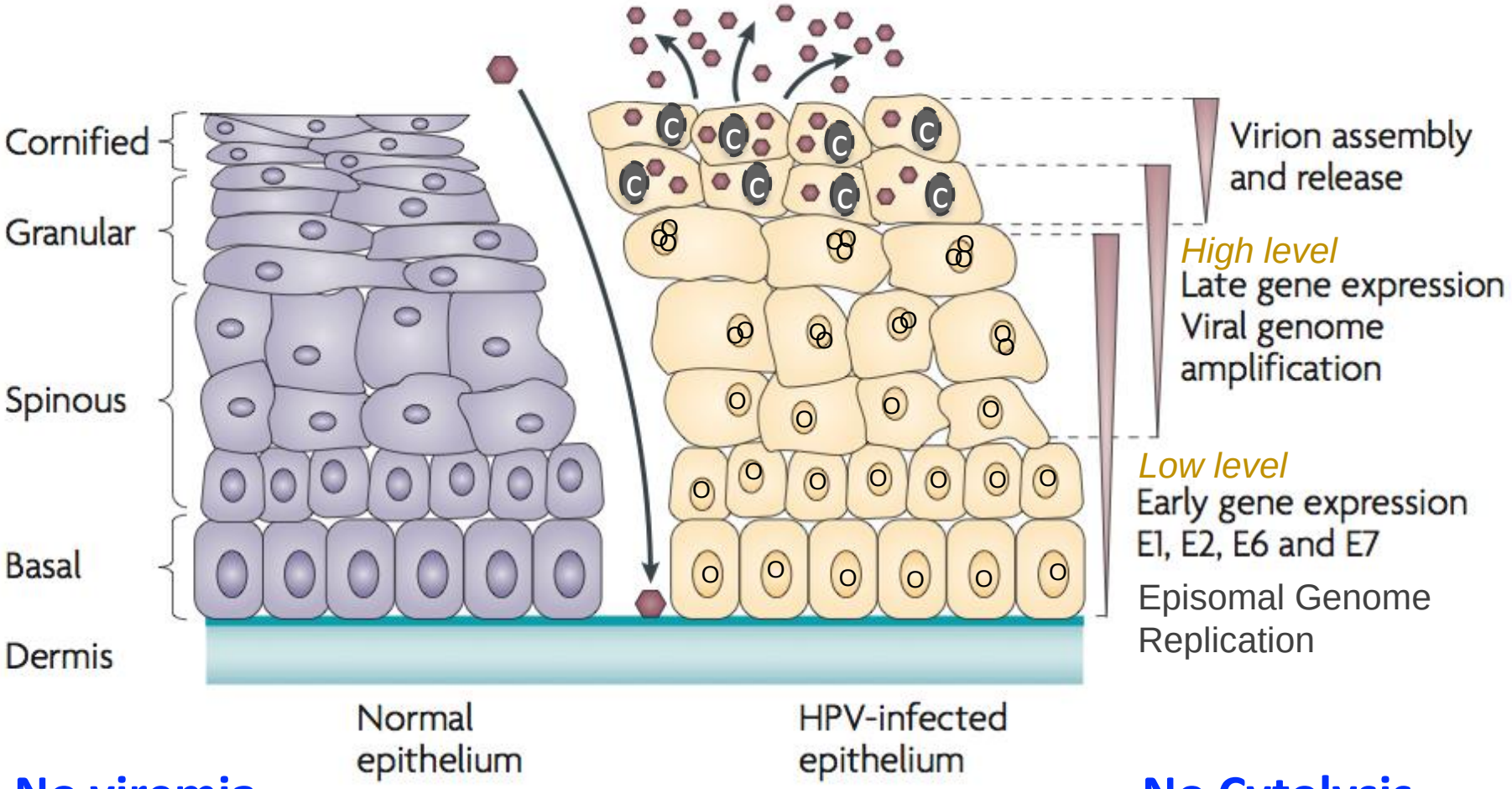
HPVs cause 5% of all cancers

90% in LMICS



A woman dies of cervical cancer every 2 minutes

HPV Life Cycle in a Stratified Squamous Epithelium: Designed for Immune Evasion



No viremia

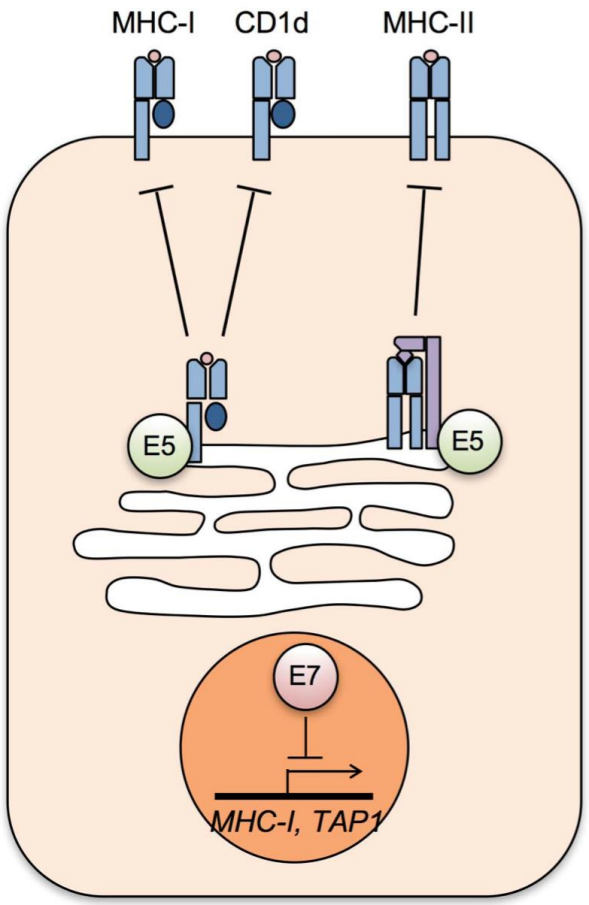
No Cytolysis

Moody and Laimins Nat Rev Micro 2010

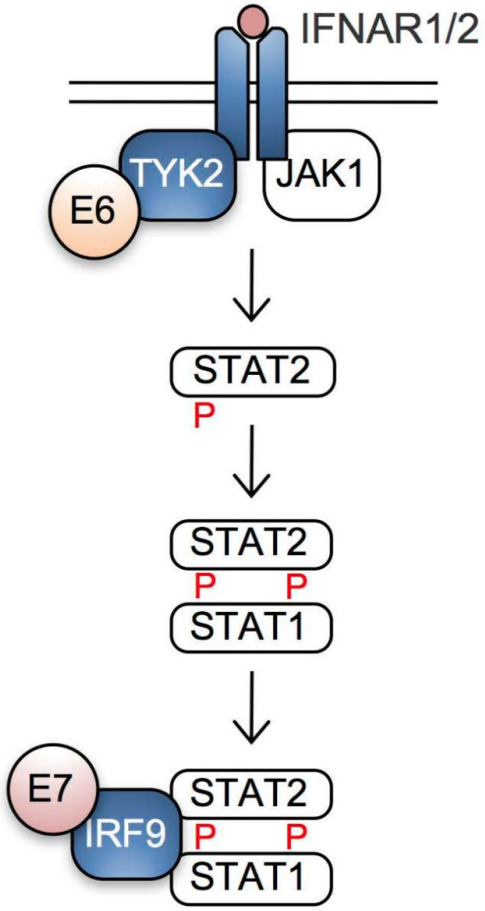
HPV Oncoproteins Inhibit Immune Responses

Promotes virus persistence

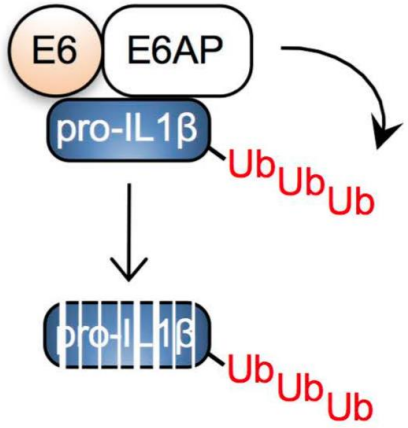
MHC Function



Interferon Signaling



Inflammation



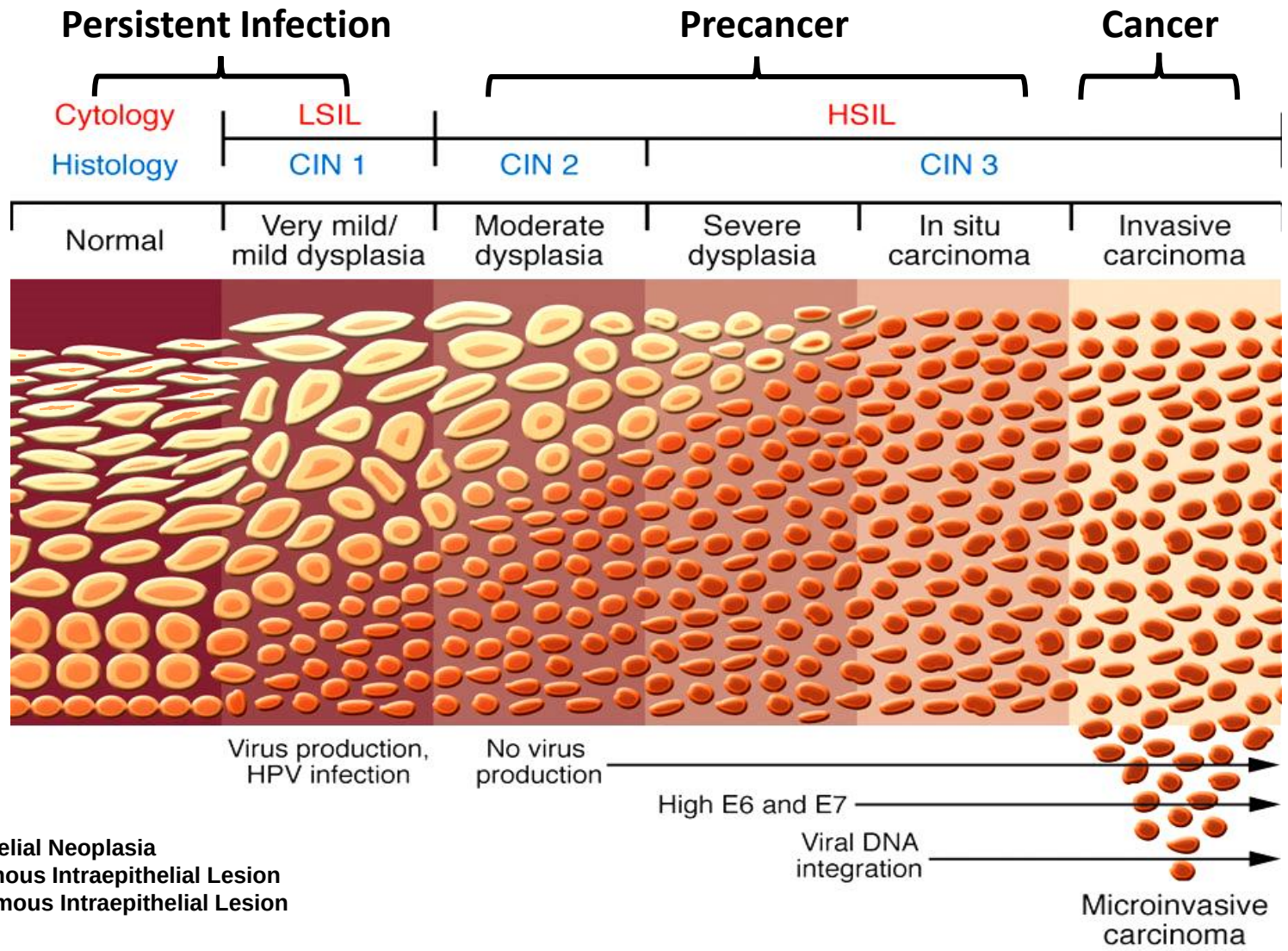
JA Westrich Virus Res 231:21-33, 2017

Exploiting mRNA Vaccine Technologies: Prophylactic or Therapeutic HPV Vaccines?

- ***Prophylactic vaccines:*** **current L1 VLP-based vaccines are so effective, even after a single dose, that there is little incentive to develop alternatives. mRNA encoding L1 would be a possibility, but issue with co-expression of different types generated mixed aggregates.**

- ***Therapeutic vaccines:*** **no commercial vaccines, large unmet need. Possible use of mRNA vaccines inducing T cells to viral early proteins.**

What Stage in HPV Carcinogenesis Should HPV Therapeutic Vaccine Target?



CIN = Cervical Intraepithelial Neoplasia
LSIL = Low grade Squamous Intraepithelial Lesion
HSIL = High grade Squamous Intraepithelial Lesion

Targeting Cancer

Pro:

- It's what kills women, so would have the largest public health impact.
- Fewest women would need to be treated.
- Straight forward path to licensure.
- Greatest tolerance for adverse events.

Con:

- Tumors have undergone selection for immune escape mechanisms.
- No cancer vaccine against a tumor-restricted antigen has worked to date, despite extensive efforts.
- But ongoing Ph I/II BioNTech HPV16 E6/E7 mRNA + anti-PD1 in $HPV16^{+}$ H&N Ca.

Targeting High Grade Dysplasia/Precancer

Pro:

- Current focus of most companies, so investment is substantial.
- A acknowledged “treatable” disease state, so regulatory approve likely.
- Clinical trials relatively small and well defined.

Con:

- Could not replace screenings since it’s needed to identify target population.
- High bar: current excisional/ablative treatments work reasonably well.
- These long standing lesions, especially CIN3, have probably already undergone immune selection.

Targeting Persistent High Risk HPV Infections

Pro:

- There is no competing standard of care.
- Large target population in countries with HPV DNA screening.
- Amenable to mass vaccination, so could potentially substitute for screening in adult women (perhaps in conjunction with 1D VLP vaccination). WHO and BMGF interested.
- More antigens to target, e.g. E1 and E2, in addition to E6,E7.
- Less likely that the infections will have undergone immune escape so vaccine is more likely to be effective.

Targeting Persistent HR HPV Infection

Con:

- **Intervention needs to be safe enough for treating an infection with an ~ 90% rate of spontaneous “clearance” by 2 yrs.**
- **Efficacy trials would have to be large.**
- **Licensure based on time to “clearance”, not percent of ultimately cleared infections?**
- **Post-licensure demonstration of CIN2+ prevention?**
- **Limited corporate interest to date.**

General Overview of Therapeutic HPV Vaccines

- Wide variety of vaccines: peptide, protein, DNA, RNA, vectors.
- Mostly based on parenteral administration of E6/E7 viral antigens and aim to generate systemic CD8+ CTL responses.
- No or limited clinical data for most candidates.
- Most clinical trials target high grade dysplasia; some cancer.
- Few randomized placebo controlled efficacy trials.
- No licensed vaccines to date, because of limited efficacy.

Recent Therapeutic HPV Vaccine Clinical Trials

Vaccine	Antigens	Strategy	Phase
VB10.16	16 E6/E7-MIP-1α	DNA	I/II
GX-188E	16/18 E6/E7	DNA	II
VGX-3100	16/18 E6/E7	DNA	IIb
DNAE7 + TA-HPV	16E7 + 16/18 E6/E7	DNA prime/ Vaccinia boost	I
ISA101	16 E6/E7	Syn long peptide	I/II
GTL001	16/18 E7	Protein fusion w/B. pertussis ad cyclase	II
TG4001	16 E6/E7	MVA	II
VTP-200	E1/E2/E4/E5/E6/E7 peptides 16/18/31/52/58	Chimp Adeno/ MVA	I/II

Why Haven't Therapeutic HPV Vaccines Been More Effective?

To be effective a therapeutic vaccine must:

- **Induce enough of the right effector cells: $CD8^+$ CTLs? Cytokine producing $CD4^+$ cells?**
- **The key effectors must efficiently traffic into the intraepithelial lesion.**
- **Overcome/evade the local immunosuppressive environment and selection of immune escape mechanisms in the transformed cells.**
- **Has the field been too narrowly focused on the 1st requirement?**

Could an mRNA Vaccine Overcome These Obstacles?

To be effective a therapeutic vaccines must:

- **Induce enough of the right effector cells: $CD8^+$ CTLs? Cytokine producing $CD4^+$ cells?**
  Maybe? Are the T cell responses substantial better than those induced by viral vectors?

- **The key effectors must efficiently traffic into the intraepithelial lesion. Unlikely, if delivered systemically. Induction of Trms could be key. Mucosal delivery?**

- **Overcome/evade the local immunosuppressive environment and selection of immune escape mechanisms in the transformed cells. Unlikely, if delivered systemically.**

Conclusion

Oncogenic HPVs may not be exceptionally attractive targets for future mRNA-based vaccine development.