Therapeutic Vaccines to Treat Chronic HPV Infection and Associated Cancer

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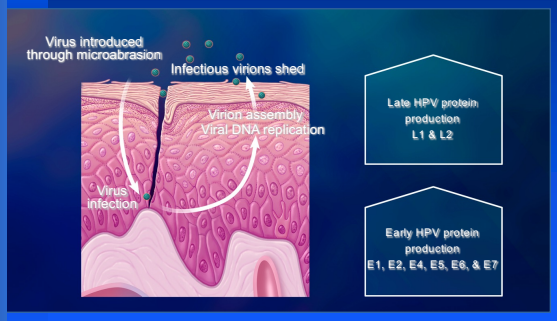
1

Outline

- HPV-related precancer and cancer
- Challenges with therapeutic vaccines
  - VGX-3100
  - Peptide vaccines
  - VTP-200
- New concepts

2

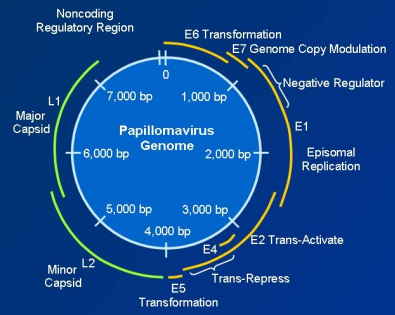
HPV Infection and Productive Life Cycle



Adapted from Doorbar J. *J Clin Virol.* 2005;32S:S7–S15.

3

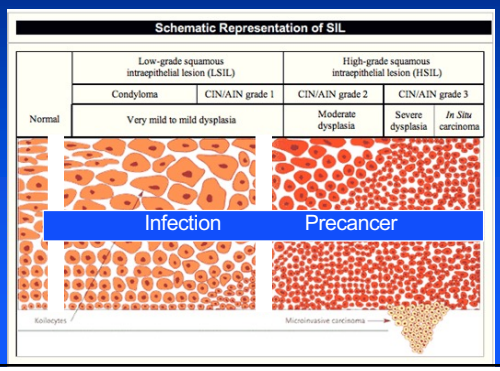
General Organization of a Papillomavirus Genome*,1



*Bars represent open reading frames. E = early region; L = late region; bp = base pair
1. Koutsky LA, Galloway DA, Holmes KK. *Epidemiol Rev.* 1988;10:122–163. Reprinted by permission of Oxford University Press.

4

2-tiered system: LSIL & HSIL



5

Immune response to HPV

- Cell-mediated immune response
  - Regression of warts preceded by infiltration of T cells
  - CD8 T cell-mediated cytotoxic T cell response
  - CD4 T cell helper cell activity is important as well
  - NK cells

6

Challenges associated with HPV therapeutic vaccines

- Sequestered compartment
- Low levels of viral proteins
- Poorly immunogenic viral proteins
- Immune escape
- Disease target: Cancer vs. HSIL
- Recruitment to studies: finding study participants with HSIL

7

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

J.M. Palefsky, J.Y. Lee, N. Jay, S.E. Goldstone, T.M. Darragh, H.A. Dunlevy, I. Rosa-Cunha, A. Arons, J.C. Pugliese, D. Vena, J.A. Sparano, T.J. Wilkin, G. Bucher, E.A. Stier, M. Tirado Gomez, L. Flowers, L.F. Barroso, R.T. Mitsuyasu, S.Y. Lensing, J. Logan, D.M. Aboulafia, J.T. Schouten, J. de la Ossa, R. Levine, J.D. Korman, M. Hagensee, T.M. Atkinson, M.H. Einstein, B.M. Cracchiolo, D. Wiley, G.B. Ellsworth, C. Brickman, and J.M. Berry-Lawhorn, for the ANCHOR Investigators Group*

N ENGL J MED 386;24 NEJM.ORG JUNE 16, 2022

8

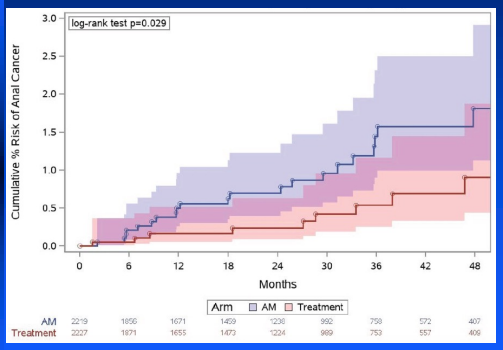
Results of the ANCHOR Study

- Median follow-up of 25.8 months, 57% reduction in anal cancer (95% CI 6% to 80%, chi-squared = 4.74, P=.029)

Palefsky JM et al. New Engl J Med 2022; 386: 2273-82

9

Kaplan-Meier curve of time-to-confirmed cancer cases



Palefsky JM et al. New Engl J Med 2022; 386: 2273-82

10

Vaccines against HNSCC

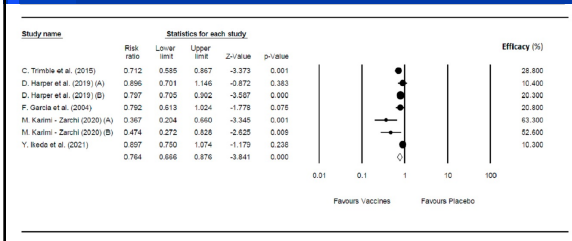
Vaccine	Targeting Antigens	Clinical Trial ID	References
		Peptide-based	
GL-0810/0817	MAGE-A3/HPV16	NCT00257738	Zandberg et al. 2015
DPX-E7 vaccine	HPV16-E7	NCT02865135	Karkada et al. 2013
HESPECTA	HPV E6	NCT02821494	Slingerland et al. 2016
ISA101	HPV16 E6/E7	NCT02426892	Kenter et al. 2008
Anti-MUC1	MUC1	NCT02544880	Weed et al. 2015
TAA peptides	LY6K, CDCA1, and IMP3	Phase II trial	Yoshitake et al. 2015
p16(INK4a) vaccine	p16	NCT01462838	Reuschenbach et al. 2016
		Nucleic acid–based	
INO-3112/INO-9012	HPV16 /18 E6/7	NCT02163057	Bauml et al. 2016
Allovectin-7	Restore HLA-B7 / β2	NCT00050388	Gleich et al. 2001
		Pathogen-based	
TG4001	HPV16 E6/7	NCT03260023	N/A
ADXS11-001	HPV16 E7	NCT02002182	Wallecha et al. 2012
TRICOM	CEA and/or MUC1	NCT00021424	N/A
		Cell-based	
CSC-DC	$ALDH^{high}$	Preclinical	Hu et al. 2016
DC vaccine	p53	NCT00404339	Schuler et al. 2014
MVX-ONCO-1	Autologous tumor cells	NCT02999646	Mach et al. 2016

Tan YS et al. Journal of Dental Research 2018, Vol. 97(6) 627–634

11

Meta-analysis

Vaccine efficacy against CIN 2/3 compared with placebo

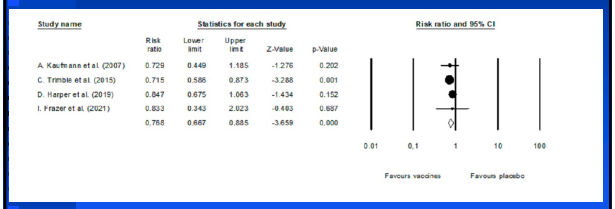


Ventura C et al. Vaccines 2022, 10, 1560. https://doi.org/10.3390/vaccines10091560

12

Meta-analysis

DNA clearance after vaccination compared with placebo



Ventura C et al. Vaccines 2022, 10, 1560. https://doi.org/10.3390/vaccines10091560

13

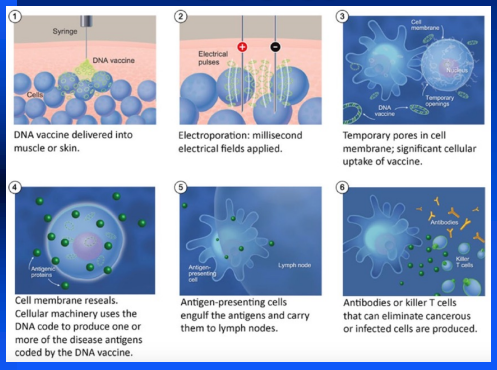
VGX-3100 Phase 2b in CIN 2/3

- VGX-3100 contains DNA plasmids for expression of HPV-16 E6/E7 (pGX3001) and HPV-18 E6/E7 (pGX3002) antigens
- Drug is injected intramuscularly (IM) using electroporation

Trimble CL et al. Lancet Oncol 2015; 386: 2078-88

14

VGX-3100



Bauml J et al. Ther Adv Med Oncol 2016, Vol. 8(3) 168–175

15

VGX-3100 Phase 2b in CIN2/3

- (48·2%) of 114 VGX-3100 recipients and 12 (30·0%) of 40 placebo recipients had histopathological regression (percentage point difference 18·2 [95% CI 1·3-34·4]; p=0·034)

Trimble CL et al. Lancet Oncol 2015; 386: 2078-88

16

VGX-3100 Phase 2b in CIN2/3: duration of response

- For VGX-3100 recipients who regressed at 6 months following study treatment completion Pap testing showed no HSIL recurrence at 18 months
- 91% (32/35) VGX-3100-treated women, whose cervical HSIL regressed at 6 months had no detectable HPV16/18 at 18 months following treatment completion

_Bhuyan P et al. Hum Vaccin Immunother. 2021 May 4;17(5):1288-1293.

17

VGX-3100 Phase 2b in CIN2/3: immune correlates of response

- Patients treated with VGX-3100 who had lesion regression had a statistically significant >2-fold increase in CD137+perforin+CD8+ T cells specific for the HPV genotype causing disease
- Increases in cervical mucosal CD137+ and CD103+ infiltrates were observed only in treated patients
- Perforin+ cell infiltrates were significantly increased >2-fold in cervical tissue only in treated patients who had histologic CR

Morrow MP et al. Clin Cancer Res. 2018 January 15; 24(2): 276–294

18

VGX-3100 Phase 3 studies

- Data from a phase III trial (the REVEAL 1 Study) reported 23.7% of 131 patients responded with HSIL regression and HPV clearance, while 11.3% of 62 patients in the placebo group did so at week 36
- REVEAL 2 is in progress

19

VGX-3100 Phase 2b in AIN 2/3

- AIDS Malignancy Consortium study of 72 PLWH
- Addition of fourth dose (week 0,4, 12 and 24)

20

ISA101 peptide vaccine

- Direct administration of peptides derived from HPV proteins predicted to be antigenic
- Taken up by dendritic cells (DC)
- Presented in association with the major histocompatibility complexes (MHC) class I, class II, or both of human leukocyte antigen (HLA)

21

ISA101 Overlapping E6/E7 peptide vaccine

- At 12 months of follow-up of women treated for VIN, 15 of 19 patients had clinical responses (79%), with a complete response in 9 of 19 patients (47%)

Kenter GG et al. New Engl J Med 2009; 61:1838-1847

22

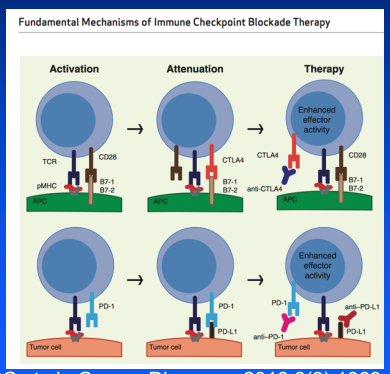
ISA101 overlapping peptide vaccine

- Post hoc analyses suggested that patients with a complete response at 3 months had a significantly stronger interferon-γ–associated proliferative CD4+ T-cell response and a broad response of CD8+ interferon-γ T cells than did patients without a complete response

Kenter GG et al. New Engl J Med 2009; 61:1838-1847

23

Immune checkpoint inhibitors



Wei SC et al. Cancer Discovery 2018;8(9):1069-1086

24

ISA101 and nivolumab

- 22 patients with metastatic HNSCC, one with anal and one with cervical cancer
- Overall response rates was 33% (8/24), higher than the target of 30%, with one patient showing a CR and seven patients a PR

Glisson B. et al. Ann Oncol 2017;28

25

•ISA 101 and nivolumab-updated data

- Twenty-four patients were followed for a median of 46.5 months
- The median duration of response was 11.2 months
- The rates of OS at 2 and 3 years were 33% (95% CI, 18.9% to 58.7%) and 12.5% (95% CI, 4.3% to 36%), respectively
- Higher expression of immune response, inflammatory response and interferon-signaling pathway genes were correlated with clinical response ($p<0.05$)

De Sousa LG. et al. Journal for ImmunoTherapy of Cancer 2022;**10**:e004232

26

VTP-200

A multi-genotype therapeutic vaccine for pre-invasive high risk human papillomavirus disease

27

VTP-200

- HPV 16/18/31/52/58
- E6/E7/E1/E2/E4/E5 gene segments of 9-52 aa joined end to end
- Prime-boost vaccine that uses two non-replicating viral vectors, chimpanzee adenovirus Oxford 1 (ChAdOx1) and modified vaccinia virus Ankara (MVA)
- Phase 1 of first-in-human studies complete
- ChAdOx1-HPV 2 x 10^{10} viral particles prime and MVA-HPV 1 x 10^{8} pfu boost

28

VTP-200 for HSIL

- Study will include 150 women LWH with cervical HSIL
  - 100 will be treated with a therapeutic HPV vaccine and 50 will be given placebo
- Study will include 150 men or women LWH with anal HSIL
  - 100 will be treated with a therapeutic HPV vaccine and 50 will be given placebo

29

TCR-engineered T cells targeting E7 for patients with metastatic HPV-associated epithelial cancers

- A high-avidity TCR that targets HPV-16 E7 through recognition of the E711–19 epitope complexed with HLA-A*02:01
- Human T cells genetically engineered to express this TCR (E7 TCR-T cells) engage and kill HPV+ tumor cell lines in vitro and mediate regression of HPV+ tumor xenografts in vivo

Nagarsheth NB et al. Nat Med. 2021 March ; 27(3): 419–425

30

TCR-engineered T cells targeting E7 for patients with metastatic HPV-associated epithelial cancers

- Autologous peripheral blood mononuclear cells (PBMCs) were obtained by leukapheresis
- PBMCs were stimulated with OKT3 and IL-2
- Cells were transduced with MSGV1 gamma-retrovirus encoding the E7 TCR
- A secondary expansion step utilizing stimulation with irradiated allogeneic feeder cells, OKT3 and IL-2 was performed. The total manufacturing time was 23 days

Nagarsheth NB et al. Nat Med. 2021 March ; 27(3): 419–425

31

TCR-engineered T cells targeting E7 for patients with metastatic HPV-associated epithelial cancers

- Phase I clinical trial of E7 TCR-T cells for patients with metastatic HPV-associated cancers
- Robust tumor regression was observed with objective clinical responses in 6 of 12 patients, including 4 of 8 patients with anti-PD-1 refractory disease
- Engineered T cells can mediate regression of common carcinomas
- Studies of non-responders reveal immune editing as a constraint on the curative potential

Nagarsheth NB et al. Nat Med. 2021 March ; 27(3): 419–425

32

Summary

- Better treatments are needed for HPV-related cancer
  - Therapeutic vaccines
  - Combine with checkpoint inhibitors

33

Summary- important considerations

- Choice of disease target
  - Treat HSIL- anal
  - Treat HPV infection?
- Broaden target antigens
- Combine with immune modulators-checkpoint inhibitors?
- Newer approaches: TCR-engineered T cells targeting E7

34