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Faculty of Medicine, Chulalongkorn University

World Health Organization

Models for Therapeutic HPV Vaccine: Preclinical study

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Challenges and Opportunities of HPV Therapeutic Vaccines

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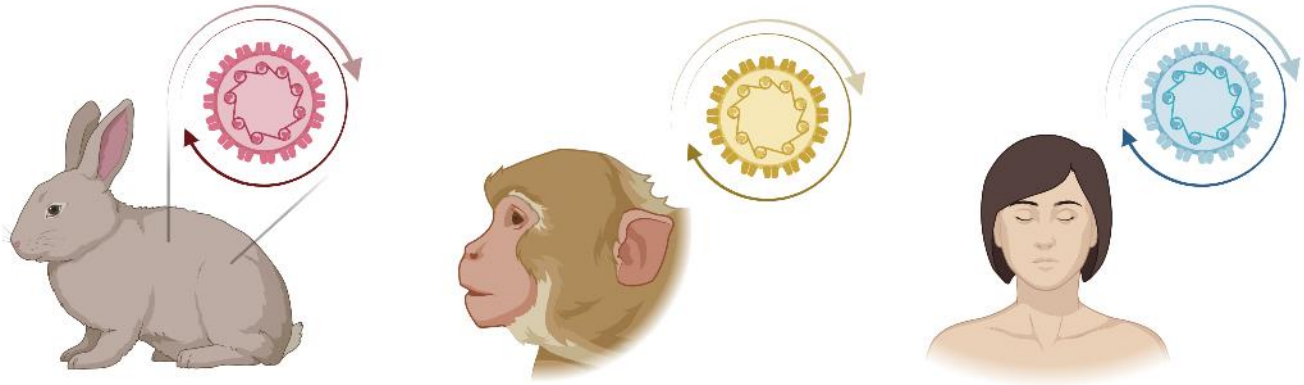
Human papillomaviruses

Species specific

- viruses only replicate and complete their life cycle in human



HPV genotypes

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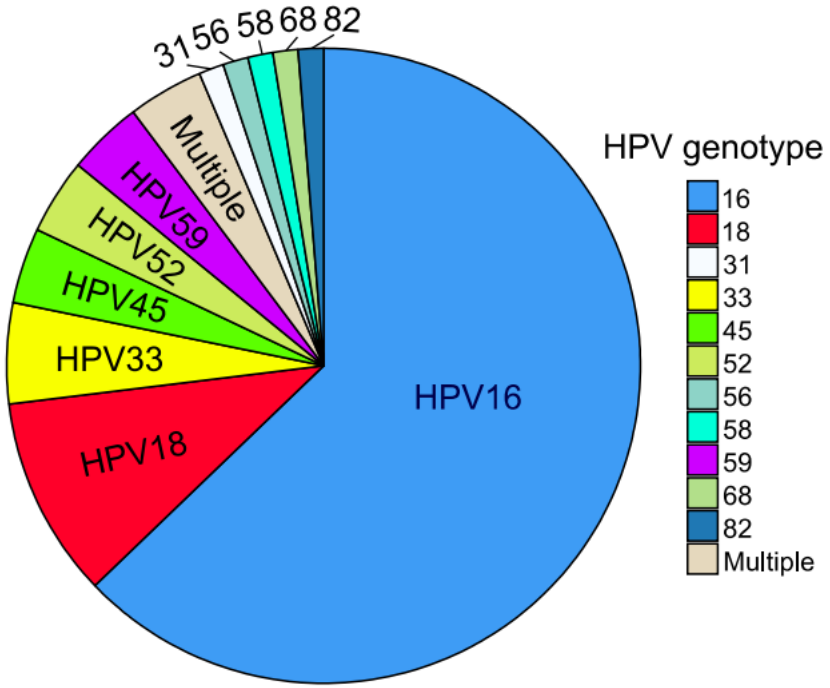
- Consists of more than **450 genotypes**
  - Divided into 2 groups
    1) **Low risk (LR)**: causing mainly genital warts
    2) **High risk (HR):** causing **invasive cancer**
       → ~15 types
       → **HPV16 and HPV18** are the two most common types, accounting for ~70%

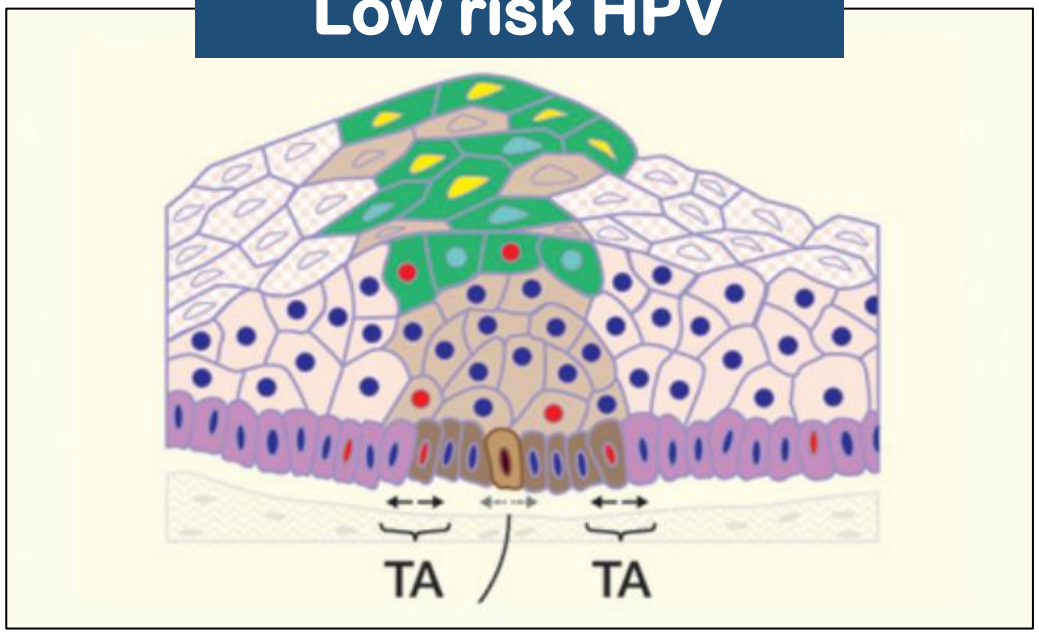


Express two potent oncoproteins, **E6 and E7**

Lulu Yu. et al. Int. J. Mol. Sci. 2022
Matthew J. Inkman et al. Scientific reports, 2020

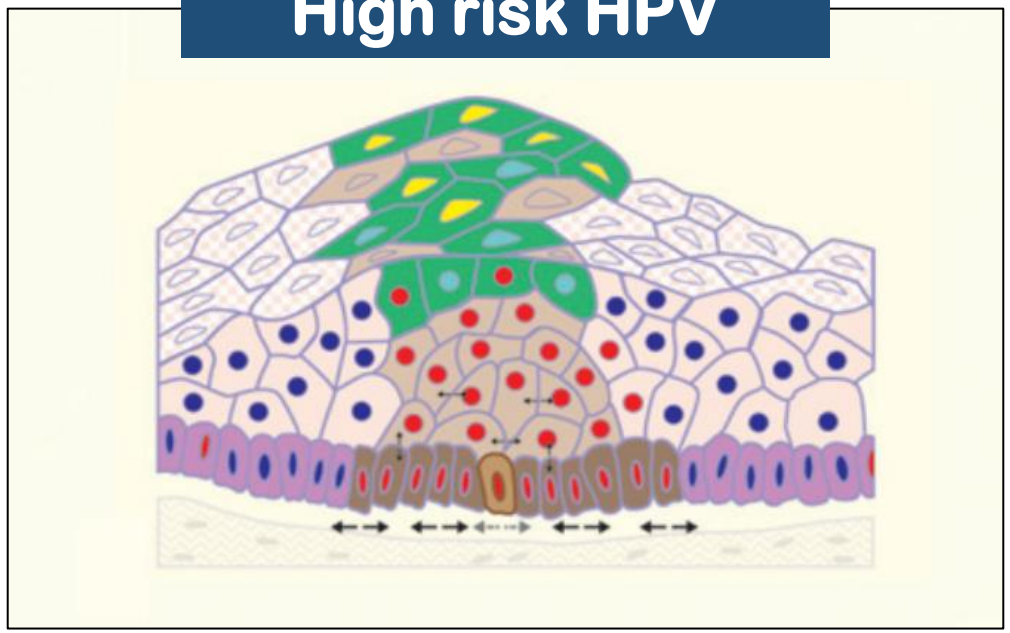
The ‘low-’ and ‘high-risk’ papillomaviruses (PVs) have different life cycle strategies

Low risk HPV



- Slow division of an infected stem-like cell maintains the lesion

High risk HPV



- E6/E7 proteins increase the proportion of proliferating cells
- **Easier to model in cell culture systems**

John Doorbar. J Pathol 2016

The most classically used preclinical tool for therapeutic HPV vaccine research "TC-1 Luc model"

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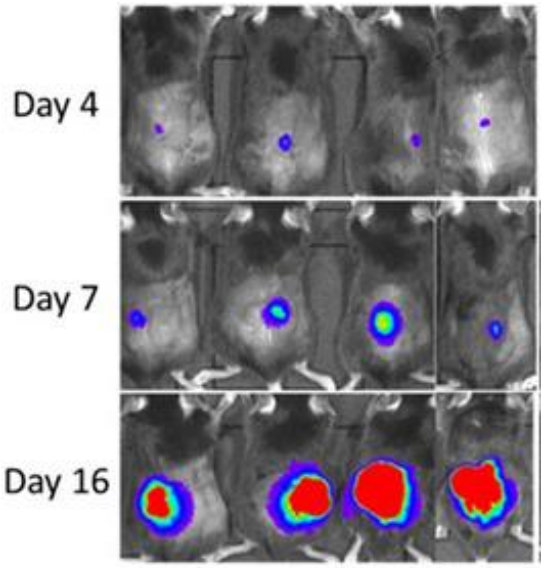
Features

- By Dr. T.C. Wu (Johns Hopkins University, Baltimore, MD, USA)
- Derived from primary lung epithelial cells of C57BL/6 mice
- Expressed HPV16 E6 and E7 oncogenes and firefly luciferase, which allows for the monitoring of tumor growth
- Can apply to *in vitro* and *in vivo* study



Mice bearing TC1-Luc cell induced tumors

Vivek Verma1 et al.
Oncotarget, Vol. 7, 2016.

Y.-H. Lee et al. / Journal of Controlled Release 199 (2015)

Vaccine prototypes which using "TC-1 Luc model" in preclinical study

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Present

Vaccine name	Vaccine type	Vaccine design	Results			Study start/Date of publication	Status
			Tumor regression	Prevent tumor growth	Prevent tumor relapse		
gDE7 mRNA-LNP	mRNA	HPV16 E7	✓	ND	✓	2023	Preclinical study
E7 RNA-LPX	mRNA	HPV16 E7	✓	ND	✓	2019	Preclinical study
ProCervix (also called GTL001)	recombinant proteins	HPV16/ 18 E7	✓	✓	✓	2013	Phase II
VGX-3100	DNA	HPV16/18 E6/E7	✓	✓	✓	2008	Phase III

Past

ND: Not determined

Limitations of TC-1 cells

- Only be used in C57BL/6N mice
- Being a tumor model but not a model for infection
- Not represent the complexity of the cell types that can be transformed by HPV
- Unavailable for other HPV serotypes

Totain et al. Laboratory Animal Research (2023) 39:14

VGX-3100

No better than placebo at improving lesion regression and viral clearance

ProCervix or GTL001

In phase II clinical trial NCT01957878, the GTL001 wasn't superior to placebo in viral clearance. In general, the future of protein-based vaccines relies upon the enhancement of immunogenicity and T-cell response through adjuvant and fusion protein strategies.

Developing animal models in therapeutic HPV vaccine testing

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C3 cells

Features

- Tumor cell line generated by immortalization and transfection of B6 mouse embryonic cells with the complete HPV16 genome
- Expresses the full HPV16 genome [1]

Limitation

- More difficult to treat by vaccine approaches than TC-1 cells by intrinsic resistance mechanisms such as the Qa-1/NKG2A axis [2]

mEER cells [3]

Features

- Mouse tonsil-derived epithelial expressing HPV16 E6 and E7 genes
- Have advantages in terms of better translation toward human HNSCC

Limitation

- Only be used in C57BL/6N mice this genetic background
- Not being suitable for studies on pre-malignant or persistent infections.

(1) M. C. W. Feltkamp et al. Eur. J. Immunol. 1993
(2) Van Montfoort N et al. Cell, 2018
(3) Stephanie Dorta-Estremera et al. Cancer Res, 2018

Another potential animal models

Cotton-tail rabbit PV (CRPV)

- Present the E1, E2, E6 or E7 encoding DNA vaccines could elicit therapeutic efficacy
- The *Sylvilagus floridanus* papillomavirus 1 (SfPV1) rabbit model has been used to investigate effective targets for therapeutic purposes [1]

Macaca fascicularis papillomavirus type 3 (MfPV3)

- Has a close phylogenetic and phenotypic relationship to HPV16 [2]
- Can be used for prevalent or persistent genital infection

Beagle dogs

- Canine immune system and immune responses are more similar to humans
- Modify the dogs' cells expressed HPV16 E7 by using a lentiviral vector [3]

(1) Nancy M. Cladel et al. Phil. Trans. R. Soc. B, 2018.
(2) Chen Z et al. Front Microbiol (2019)
(3) Totain et al. Laboratory Animal Research (2023) 39:14

Developing animal models in therapeutic HPV vaccine testing

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Models	Species	Immunogens	Suite for tumor model	Suite for persistent infection	Closely to human immune response / great translation toward human
TC-1 cells	C57BL/6N mouse	HPV16 E6/E7	+	-	-
C3 cells	C57BL/6N mouse	Full genome HPV16	+	-	-
mEER cells	C57BL/6N mouse	HPV16 E6/E7	+	-	+
Cotton-tail rabbit PV		High risk HPVs	+	+	+
Macaca fascicularis PV type 3		HPV16	-	+	+++
Beagle dogs		High risk HPVs	-	+	++

Research gap

Tumor model

- Which animal models are suitable for testing tumor regression efficacy ?
- Is tumor model in mice suitable for go no go to clinical study?

Persistent infection and precancerous models

- Which animal models are suitable for persistent infection and precancerous models?