Models for Therapeutic HPV Vaccine: Preclinical study

Presented by
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WHO/MPP mRNA Technology Transfer Programme
Regional meeting in South-East Asia Shangri-la hotel,
Bangkok, Thailand 31 Oct-1 Nov 2023
Challenges and Opportunities of HPV Therapeutic Vaccines

**Human papillomaviruses**

**Species specific**
- viruses only replicate and complete their life cycle in human
HPV genotypes

- 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

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

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

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
## Vaccine prototypes which using “TC-1 Luc model” in preclinical study

<table>
<thead>
<tr>
<th>Vaccine name</th>
<th>Vaccine type</th>
<th>Vaccine design</th>
<th>Results</th>
<th>Study start/Date of publication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tumor regression</td>
<td>Prevent tumor growth</td>
<td>Prevent tumor relapse</td>
<td></td>
</tr>
<tr>
<td>gDE7 mRNA-LNP</td>
<td>mRNA</td>
<td>HPV16 E7</td>
<td>✓</td>
<td>ND</td>
<td>2023</td>
</tr>
<tr>
<td>E7 RNA-LPX</td>
<td>mRNA</td>
<td>HPV16 E7</td>
<td>✓</td>
<td>ND</td>
<td>2019</td>
</tr>
<tr>
<td>ProCervix (also called GTL001)</td>
<td>recombinant proteins</td>
<td>HPV16/18 E7</td>
<td>✓</td>
<td>✓</td>
<td>2013</td>
</tr>
<tr>
<td>VGX-3100</td>
<td>DNA</td>
<td>HPV16/18 E6/E7</td>
<td>✓</td>
<td>✓</td>
<td>2008</td>
</tr>
</tbody>
</table>

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
VGX-3100
No better than placebo at improving lesion regression and viral clearance

Inovio's endpoint switcheroo backfires as phase 3 misses on new measure, hits on old
By Nick Paul Taylor · Mar 2, 2023 5:20am

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

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.

\(^{(2)}\) 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)

(3) Totain et al. Laboratory Animal Research (2023) 39:14
## Developing animal models in therapeutic HPV vaccine testing

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