Novel Immunotherapy Generates Robust HPV-Specific T-Cell Responses and Shows Efficacy in a HPV16 Tumor Model

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ABSTRACT 402

The poster layout was updated post-presentation to reflect revised branding; all scientific content remains unchanged.

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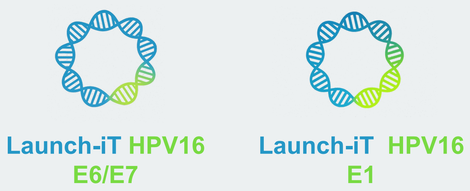
Introduction and Aim

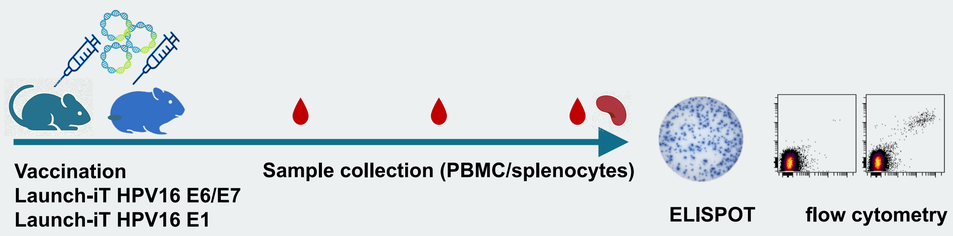
- Launch-iT is a clinically validated therapy utilizing live attenuated yellow fever (YF) viral vectors that deliver novel antigens encoded in a DNA plasmid.
- Aligning with the WHO preferred product characteristics for therapeutic HPV vaccines[1], AstriVax is developing Launch-iT immunotherapy to intervene early in high-risk cervical HPV infections:
  - Nearly all cervical cancers result from infection with a high-risk (hr) HPV strain[2], which can be detected soon after infection using available PCR tests[3].
  - Women with hrHPV infections presenting normal cytology or low-grade squamous intraepithelial lesions (LSIL) often face long waiting periods for spontaneous clearance before treatment is initiated[4], which can cause psychological distress and increase the risk of disease progression.
  - HPV-mediated immune suppression, which may reduce vaccine efficacy, typically arises during the high-grade squamous intraepithelial lesion (HSIL) stage[5].
  - The robust and sustained immune responses generated by Launch-iT are expected to be effective against persistent HPV infections.
- Launch-iT HPV16 candidates encode the early HPV16 proteins E6, E7 and E1:



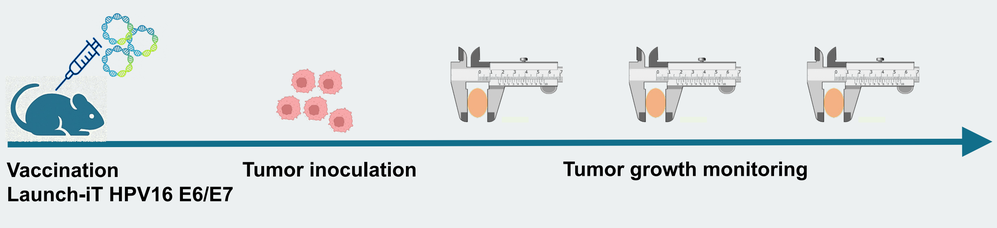
- Here, we present data on the immunogenicity of Launch-iT HPV16 and its ability to protect against HPV16 antigen-expressing tumor cell challenges in animal models.

Methods

- Launch-iT HPV16 candidates were assessed in interferon receptor type I knockout (*ifnar*$^{-/-}$) mice and Syrian hamsters, both of which are animal models permissive to replication of the yellow fever live-attenuated viral vector.
- Vaccinations were performed through a single intradermal injection containing 10 µg of Launch-iT HPV16 E6/E7 or 10 µg of Launch-iT HPV16 E1.
- Immunogenicity studies in the *ifnar*$^{-/-}$ mouse model and in the hampster model focused on the measurement of HPV-specific T-cell responses by IFNγ ELISPOT. In the *ifnar*$^{-/-}$ mouse model, immune responses were further characterized by flow cytometry to evaluate the polyfunctional capacity of HPV-specific T cells and to evaluate their phenotype.



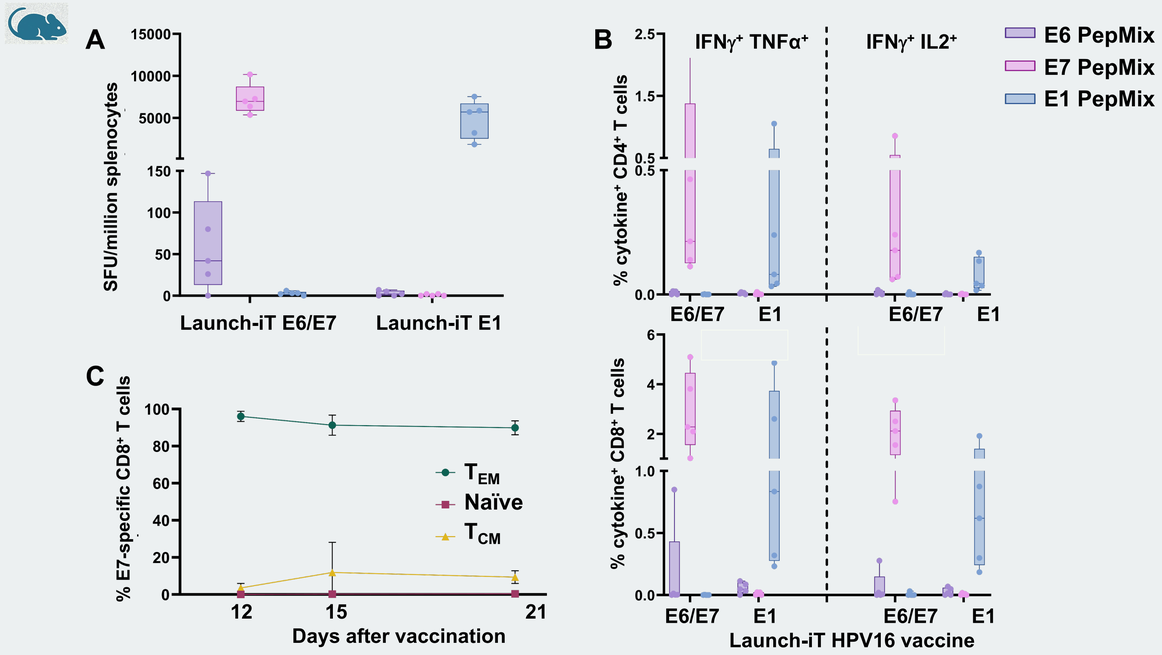
- Two weeks after vaccination, *Ifnar*$^{-/-}$ mice were challenged with C3.43 tumor cells, which expresses physiologically relevant levels of the HPV16 E6 and E7 antigens. This model served as an *in vivo* surrogate to evaluate the efficacy of vaccine-induced immune cells in clearing HPV16-infected cells by monitoring tumor growth compared to mice that were either not vaccinated or vaccinated with a control Launch-iT containing an insert encoding an antigen not related to HPV.



Results

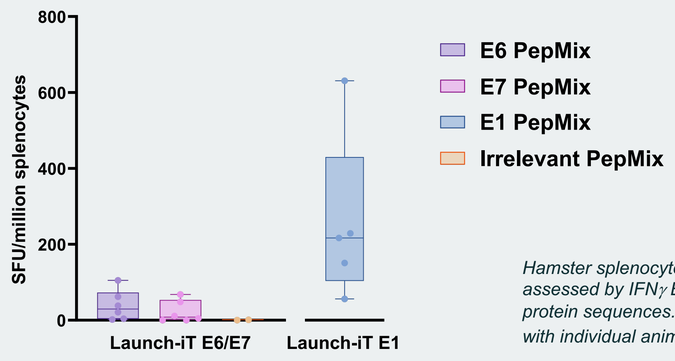
Immunogenicity

HPV-specific T cell responses raised in *ifnar*$^{-/-}$ mice through Launch-iT HPV16 vaccination were polyfunctional and primarily displayed an effector memory T cell (T_{EM}) phenotype – which has been linked to anti-tumor activity[6] – with increase of central memory (T_{CM}) cells over time, indicating the induction of durable memory over time[7].



Panels A and B: Two weeks post-vaccination, mouse splenocytes were collected and T-cell responses were assessed by using peptide mixes spanning full protein sequences by IFN-g ELISPOT (Panel A, SFU: spot forming unit) and by intracellular cytokine staining, to assess polyfunctionality (Panel B, IFNγ+TNFα+ and IFNγ+IL2+ CD8+ T cells [upper part] and CD4+ T cells [lower part]). Responses were corrected for background, with individual animal data shown as points. Panel C: blood samples were collected at multiple timepoints after Launch-iT HPV16 E6/E7 vaccination and HPV16 E7-specific (MHC multimer+) CD8+ T cells were co-stained with CD62L and CD44 to identify effector memory (T_{EM}, CD44+/CD62L-), naïve (CD44-/CD62L+) and central memory (T_{CM}, CD44+/CD62L+) T-cell subsets.

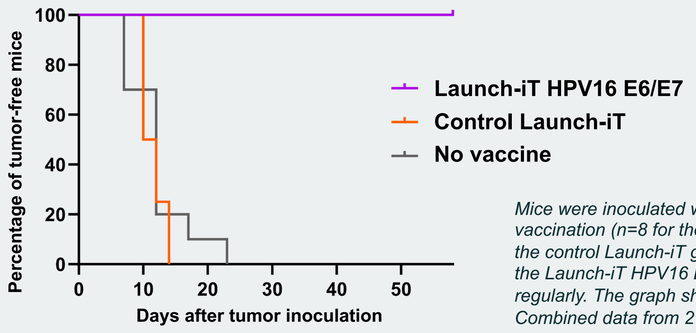
Launch-iT HPV16 was shown to generate E6, E7 and E1-specific immune responses in the immunocompetent hamster model as well.



Hamster splenocytes were collected and T-cell responses were assessed by IFNγ ELISPOT using peptide mixes spanning full protein sequences. Background-corrected responses are shown, with individual animal responses indicated by points.

Efficacy

Immune responses induced by Launch-iT HPV16 E6/E7 provided protection against C3.43 tumor cell challenges in all tested mice (n=18). In contrast, tumor growth was observed in all mice that received a control Launch-iT vaccine containing an insert encoding a HPV-unrelated antigen (n=8) or no vaccine at all (n=10).



Mice were inoculated with C3.43 tumor cells either 17 days post-vaccination (n=8 for the Launch-iT HPV16 E6/E7 group and n=8 for the control Launch-iT group) or 14 days post-vaccination (n=10 for the Launch-iT HPV16 E6/E7 group). Tumor growth was monitored regularly. The graph shows percentages of tumor-free mice. Combined data from 2 independent experiments are shown.

Data from ongoing studies also indicate efficacy when Launch-iT HPV16 E6/E7 vaccination is administered post-exposure to TC-1 tumor cells expressing the HPV16 E6 and E7 antigens.

Conclusions

- Launch-iT HPV16 candidates induced robust T cell responses against early HPV16 antigens in both a YF17D virus-permissive mouse model and an immunocompetent hamster model. The HPV-specific immune responses in mice showed a polyfunctional profile, with HPV16-specific CD8+ T cells mainly exhibiting an effector memory phenotype, while central memory T cells increased over time.
- Mice vaccinated with Launch-iT HPV16 E6/E7 candidates were fully protected from tumor formation after challenge with C3.43 cells, and data from ongoing studies also show effectiveness of Launch-iT HPV16 is given after exposure to TC-1 tumor cells.
- Overall, these findings support the continued development of Launch-iT as an immunotherapy to eliminate persistent HPV infections, prevent progression, and clear cervical precancerous lesions.

Contact information

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