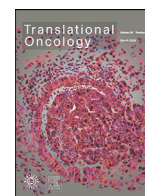


Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Letters to the Editor

Comment on: Endogenous retroviruses expressed in human tumours cannot be used as targets for anti-tumour vaccines



In my short communication “Endogenous retroviruses expressed in human tumours cannot be used as targets for anti-tumour vaccines” [1], I indicated possible risk factors when human endogenous retroviruses (HERVs), which are highly expressed in some human tumours and in the placenta, will be used as targets for tumour vaccination and immunotherapy. The main risk factors are expression of HERVs on human embryonic stem cells (ESC), and on immune and other cells. Expression on human ESC is well-documented [2], expression on immune and other cells is documented at least after infections (for review see [3]). Interaction of the vaccine or therapy with these normal cells may be harmful.

In the accompanying comment, Holst and co-workers deny these risk factors [4], partially not recognising the virological background. For example, in one of their studies in a mouse model [5], they immunised against the melanoma associated retrovirus (MelARV) using an adenoviral vector and prevented colorectal tumor growth and progression in mice. However, MelARV is not an endogenous retrovirus, it is a recombinant virus not present in the murine genome. It is also not surprising that immunisation against proteins of HERV-K, artificially expressed on the surface of mouse tumour cells, successfully reduced tumour growth in the mouse [6]. The HERV- proteins are not expressed on mouse ESC and mouse immune cells.

In the human system, the authors claim that “existing HERV-K-specific T cell responses induced in human breast and ovarian cancers points towards a favorable safety profile” [4]. However, in these studies cytotoxic T cells killing HERV-K-expressing tumour cells were induced only *in vitro*, but not *in vivo*, in the patient [7,8]. These HERV-K-specific cytotoxic cells did not kill normal cells, but there were no investigations whether human ESC were among these normal cells.

Further, the authors compare HERV antigens with fetal antigens. They argue, that clinical vaccine trials in phase 3 for the fetal antigen melanoma-associated antigen A3 (MAGE-A3) and a specific CAR(chimeric antigen receptor)-T cell therapy targeting the New York esophageal squamous cell cancer-1 (NY-ESO-1) were performed without specific safety signals. The truth is, that the study using MAGE-A3 had been stopped [9]. Whereas the cancer testis antigen MAGE-A3 is indeed expressed on human ESCs [10], I was unable to find such data for NY-ESO-1.

The authors claim that I ignore the fact that immune responses against antigens expressed on dendritic cells are a natural part of tumor immune responses, but I don't do this and this has nothing to do

with a potential harmful effect of vaccination against HERVs as tumour treatment.

In conclusion, there is no evidence for an effective and safe application of HERVs as targets for tumour vaccination and I repeat my sentence, that “anti-retroviral vaccines should not be used without further safety investigations in this field” [1].

CRedit authors statement

Joachim Denner: Conceptualisation, writing

Declaration of Competing Interest

The author declares an absence of competing or financial interests.

Funding

No funding was received for this publication.

Joachim Denner*

Institute of Virology, Free University Berlin, Robert von Ostertag-Strasse 7-13, 14163 Berlin, Germany

*Corresponding author.

E-mail address: Joachim.Denner@fu-berlin.de

References

- [1] J. Denner, Endogenous retroviruses expressed in human tumours cannot be used as targets for anti-tumour vaccines, *Transl Oncol* 14 (1) (2021) 2020–2021.
- [2] N.V. Fuchs, S. Loewer, G.Q. Daley, et al., Human endogenous retrovirus K (HML-2) RNA and protein expression is a marker for human embryonic and induced pluripotent stem cells, *Retrovirology* 10 (1) (2013) 115.
- [3] V. Gröger, A. Emmer, M.S. Staeger, H. Cynis, Endogenous Retroviruses in Nervous System Disorders, *Pharmaceuticals* 14 (2021) 70.
- [4] A.-V. Bermejo, T.K. Nielsen, P. Holst, Comment on: Endogenous retroviruses expressed in human tumours cannot be used as targets for anti-tumour vaccines, *Transl. Oncol.* (2021).
- [5] L. Neukirch, T.K. Nielsen, H. Laursen, J. Daradoumis, C. Thirion, P.J. Holst, Adenovirus based viruslike-vaccines targeting endogenous retroviruses can eliminate growing colorectal cancers in mice, *Oncotarget* 10 (14) (2019) 1458–1472.
- [6] B. Kraus, K. Fischer, S.M. Büchner, et al., Vaccination directed against the human endogenous retrovirus-K envelope protein inhibits tumor growth in a murine model system, *PLoS One* 8 (8) (2013) e72756.
- [7] K. Rycaj, J.B. Plummer, B. Yin, et al., Cytotoxicity of human endogenous retrovirus K-specific T cells toward autologous ovarian cancer cells, *Clin Cancer Res* 21 (2) (2015) 471–483.

DOI of original article: [10.1016/j.tranon.2021.101040](https://doi.org/10.1016/j.tranon.2021.101040)

<https://doi.org/10.1016/j.tranon.2021.101041>

Received 4 February 2021; Accepted 5 February 2021

1936-5233/© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

- [8] F. Wang-Johanning, L. Radvanyi, K. Rycaj, et al., Human endogenous retrovirus K triggers an antigen-specific immune response in breast cancer patients, *Cancer Res* 68 (14) (2008) 5869–5877.
- [9] J.F. Vansteenkiste, B.C. Cho, T. Vanakesa, et al., Efficacy of the MAGE-A3 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive nonsmall-cell lung cancer (MAGRIT): a randomised, double-blind, placebo-controlled, phase 3 trial, *Lancet Oncol* 17 (6) (2016) 822–835.
- [10] N. Lifantseva, A. Koltsova, T. Krylova, T. Yakovleva, G. Poljanskaya, O. Gordeeva, Expression patterns of cancer-testis antigens in human embryonic stem cells and their cell derivatives indicate lineage tracks, *Stem Cells Int* 2011 (2011) 795239.