Background Human endogenous retroviruses and, in particular the betaretrovirus HERV-K, are upregulated at the protein level in a wide range of cancers. Spontaneous immunity to HERV-K has been observed in autoimmune diseases and cancers. Recently, Ng et al., studying non-small-cell lung cancer (NSCLC) linked the presence of HERV-K transcripts and HERV-K immunity to the formation of tertiary lymphoid structures, antibody-dependent cellular cytotoxicity and clinical responses to checkpoint inhibitor therapy. Other NSCLC expressed gamma-retroviral HERVs were not found to be spontaneously immunogenic.1

Methods HERV-K TM protein was produced in X5 insect cells. Consensus HML-2 sequences of HERV-K Gag and Env were encoded in human adenovirus type 19a/64, 5 and 5/F35. HERV-W antigen containing vectors were encoded in human Ad19a/64 vectors. In some vectors a point mutation was introduced into a putative immune suppressor domain (ISD mutation) in the HERV-K envelope (HERV-K-ISDmut). Viral vectors were used for cell transductions and animal immunizations. Readouts were tumor biopsy sequencing, qPCR, Flow cytometry, transmission electron microscopy, cell based ELISA assays and tumor challenges.

Results We report the presence of HERV-K expression in most late-stage cancers. Transduction with HERV-K Gag and Env, resulted in accumulation and release of high levels of virus-like-particles. HERV-K particles exhibited dense and regularly spaced protrusions consistent with a pronounced envelope incorporation we had not observed previously with HIV and murine retroviral particles.2 3 To explore this further we made chimeric antigens co-encoding HERV-K Gag and either HERV-W or HERV-H envelope (figure 1). Each of HERV-W/H env and HERV-K Gag construct succeeded in increased B cell responses in vivo when compared to HERV-W env vectors without the Gag. By using a chimeric HERV-W envelopes with a HERV-K transmembrane domain and cytoplasmic tail we saw further increased incorporation of envelope spikes into VLPs and markedly enhanced antibody responses.

In keeping with an unusually dense incorporation of antigen into VLPs, HERV-K-ISDmut immunization broke tolerance toward HERV-K envelope in transgenic mice and induced robust humoral and cellular responses in non-human primates. HERV-K-ISDmut further exerted therapeutic efficacy against weak expressing HERV-K+ murine syngeneic cancer cell lines.

Conclusions HERV-K, a widely expressed cancer associated endogenous retrovirus, forms highly effective retroviral particles that can be used as scaffolds to incorporate distantly related gamma-retroviral sequences and increase their immunogenicity. These findings may explain HERV-K B cell immunogenicity in lung cancer1 and we provide a therapeutic platform for enhancing or de novo inducing immunity to cancer associated endogenous retroviruses.

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Ethics Approval The animal studies were reviewed and approved by the National Animal Experiments Inspectorate (Dyreforsøgsstilsynet, license no. 2019-15-0201-00203). Clinical study to collect late stage tumor samples was conducted in accordance with the Declaration of Helsinki and approved by an institutional review board and the Regional Ethics Committee (Danish Ethical Committee, file number: 1300530 and H-16046103 respectively). All patients provided signed informed consent.

Consent Abstract does not contain sensitive or identifiable material.
Abstract 1147-F Figure 1  Envelope chimeras with HERV-K derived transmembrane domain and cytoplasmic tail (K-Gag<sub>TMCT</sub> W-Env) increase VLP incorporation and immune responses against cell surface WT Env as compared to non-chimeric envelope (K-Gag W-Env) and Envelope expressed with non-VLP forming Gag (W-Gag W-Env)

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