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## Targeting endogenous retroviruses using a novel adenoviral vaccine technology

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## TARGETING ENDOGENOUS RETROVIRUSES USING A NOVEL ADENOVIRAL VACCINE TECHNOLOGY

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Human Endogenous Retroviruses (HERVs) are promising cancer vaccine targets as they are reactivated in cancers while being silent in healthy tissues. Around 8-9% of our genome is made up of HERVs and reactivation of HERVs, especially HERV-K, have been implicated in tumorigenesis via oncogenic signaling and immune evasion. As one of the means for cancer immune evasion, HERVs utilize an Immune Suppressive Domain (ISD) located in their envelope protein (Env). Here, our cancer vaccine strategy was to evaluate if adenoviral vaccines encoding a virus-like particle immunogen design including Gag for particle formation and an ISD mutated Env protein (ISDmut) as a surface target, could induce potent and efficacious immune responses. For this purpose, we used the adenoviral vectors hAd19a and hAd5.

In initial proof-of-concept studies, targeting the mouse version of ERVs (murine leukemia virus, MelARV), our ISDmut MelARV vaccine induced significantly higher CD8+T cell responses compared to the WT vaccine in mice. Therapeutic vaccination in combination with checkpoint inhibitors eradicated large colorectal tumors in 80% of the mice and protected against heterologous re-challenge. In a heterologous prime-boost vaccination in mice the immune response could be further increased, reaching 7-8% specific T cells targeting MelARV. For HERV-K, a more stringent transgenic mouse model was used which is tolerant for HERV-K. Here, two immunizations were able to rise HERV-K specific T cells. Finally, in non-human primates where simian ERV ENV shares 90 % of similarities with HERV-K Env, our vaccine induced strong antibody responses that bind human cancer cell lines.

Overall, our results indicate that an adenoviral prime-boost regimen encoding a virus-like particle forming antigen with a mutated ISD should allow broad cancer targeting.