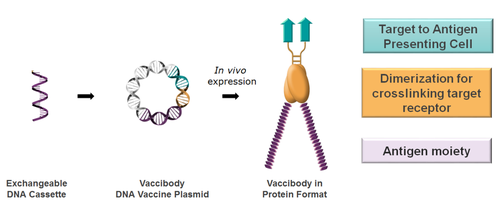
Vaccibody DNA vaccine platform VB10.NEO induces strong neoantigen specific CD8+ T cell responses critical to cure established tumors in pre-clinical models

Elisabeth Stubsrud*, Stine Granum*, Helene Zell-Flagstad, Audun Bersaas, Lise M. Skullerud, Monika Sekelja, Karoline Schjetne, Agnete B. Fredriksen. * Authors contributed equally
Vaccibody AS, Oslo, Norway

RATIONALE FOR THE STUDY

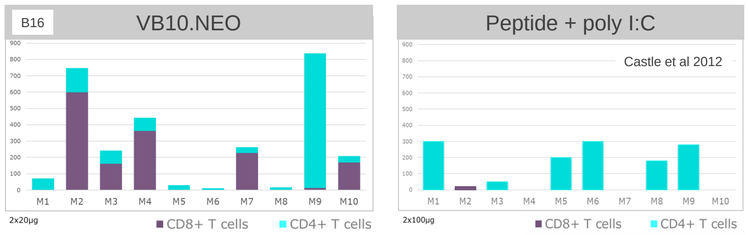


Recent advances in the field of cancer immuno-therapy have identified CD8+ T cell responses against tumor-specific neoantigens as a key driver of tumor regression and pro-longed survival.

VB10.NEO is a potent DNA plasmid vaccine with intrinsic adjuvant effect designed for efficient delivery of personalized tumor-specific neoantigens. VB10.NEO plasmid is translated *in vivo* and the secreted protein will covalently bind to endocytic receptors on APC by a targeting unit expressing CCL3 (MIP-1a) allowing efficient uptake, presentation and cross-presentation of the neoantigens. In addition, CCL3 will attract immune cells by chemotaxis and induce maturation of APC locally.

UNIQUE ACTIVATION OF CD8+ T CELLS

T cell responses against predicted CD8+ T cell epitopes previously reported as non-immunogenic or activating only weak T cell responses using either synthetic long peptides + poly I:C, RNA vaccines or non-targeted DNA vaccines (Castle et al. 2012, Yadav et al. 2014, Aurisicchio et al., 2019) activated strong CD8+ T cell responses when delivered in the Vaccibody format, demonstrating a unique and strong ability to prime CD8+ T cells using the VB10.NEO vaccine platform. The response was also accompanied by CD4+ T cell responses.

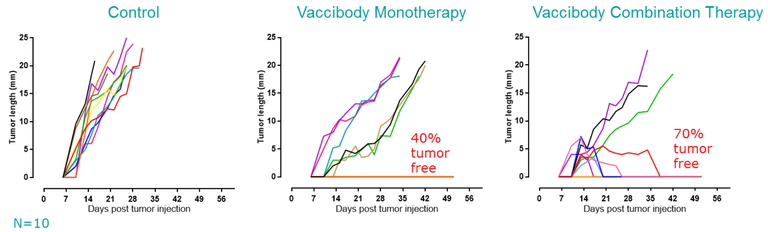


C57Bl/6 mice were vaccinated i.m with electroporation with 20 mg VB10.NEO holding previously published neoepitopes from B16 melanoma model (top panel, Castle et al 2012) or MC38 colon carcinoma (bottom panel, Yadav et al 2014). After vaccination, splenocytes were harvested, pooled and restimulated with the corresponding neoepitopes and analysed by IFN-γ ELISpot. Responses were compared with responses published in the corresponding publications (right panels).

PROTECTIVE TUMOR RESPONSES

In a therapeutic tumor setting, VB10.NEO vaccinated mice (monotherapy) induced tumor protective responses.

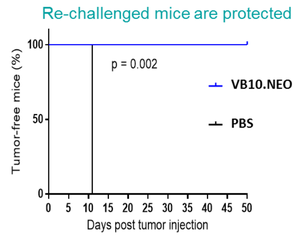
The effect was augmented when combining VB10.NEO with anti-PD-1 where complete regression of large established tumors was observed.



CT26 colon carcinoma cells (5 x 10^4) were implanted s.c at day 0, prior to i.m. vaccination + electroporation with 50 µg VB10.NEO construct holding 20 neoepitopes from CT26 tumor cells at day 0, 3, 7, 10, 14. 200 µg anti-PD-1 was injected i.p. q7d starting at day 7. Each line represents individual mice (N=10).

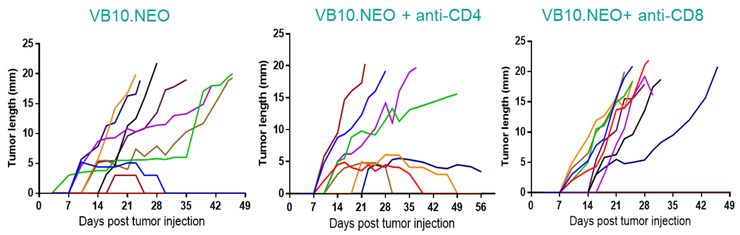
In mice re-challenged with a second dose of CT26 tumor cells, all mice were fully protected.

This finding demonstrates that VB10.NEO elicits strong and long-lasting tumor protective memory immune responses.



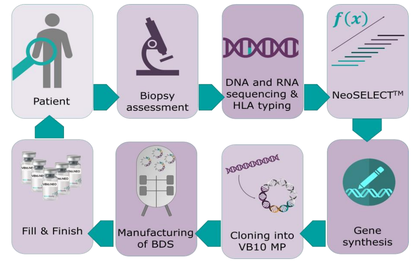
CD8+ T CELLS CRITICAL FOR PROTECTION

A critical role of CD8+ T cells for the observed tumor protection was confirmed when depleting CD8+ T cells in a therapeutic tumor model.



CT26 colon carcinoma cells (5 x 10^4) were implanted s.c at day 0, prior to i.m. vaccination + electroporation with 50 µg VB10.NEO construct holding 20 neoepitopes from CT26 tumor cells at day 0, 3, 7, 10, 14. Anti-CD4 or anti-CD8 mAb was injected i.p. q7d starting at day 7. Each line represents individual mice (N=10).

NEOEPITOPE CANCER VACCINE



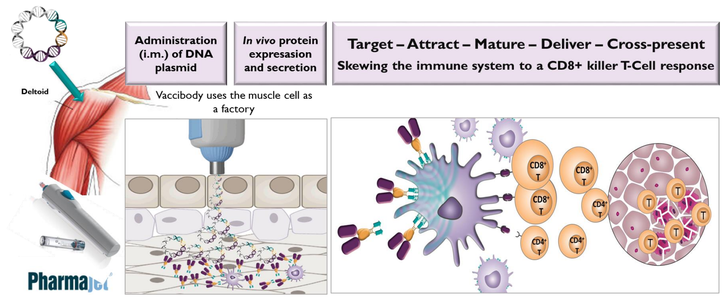
VB10.NEO plasmid DNA constructs are robust and flexible holding up to at least 40 neoepitopes.

VB10.NEO targeted approach induce strong neoantigen-specific T cell responses with an effective homo-logous boost.

VB10.NEO is safe, easily delivered i.m. and uses a standardized robust and rapid manufacturing process.

Vaccibody has developed its own proprietary NeoSELECT™ platform to select patients unique tumor mutations which can efficiently be inserted into individualized VB10.NEO constructs.

Mechanism of Action – Intrinsic Adjuvant for Direct Targeting



CONCLUSIONS

- VB10.NEO is a robust vaccine delivery platform holding up to 40 neoepitopes and efficiently targets neoantigens to APC by binding to the endocytic chemokine receptors via its natural ligand MIP-1α (CCL3).
- VB10.NEO immunotherapy induce strong CD8+ T cell responses critical for anti-tumor effect which demonstrate the unique characteristic of the Vaccibody platform to potentiate activation of CD8+ T cells.
- VB10.NEO alone and in combination with anti-PD-1 synergize the potent immune responses resulting in durable complete tumor regression mediated by critical CD8+ T cell responses and induction of long-lasting memory immune responses.
- VB10.NEO is an ideal platform for bringing individualized neoantigen cancer vaccines to the market due to a rapid and cost-effective DNA plasmid manufacturing process.
- These pre-clinical data support the scientific rational for the current ongoing clinical trial investigating VB10.NEO in combination with checkpoint inhibitors in patients with advanced solid tumors (NCT03548467) presented in Poster #CT217.

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Abstract #5033

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