# VacDesignR®: a computational tool to optimize viral-based individualized neoantigen therapeutic vaccine production

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## Background

Modified Vaccinia virus Ankara (MVA) is an attenuated vaccinia virus with a double-stranded DNA genome used to develop individualized neoantigen therapeutic vaccines (INTV), such as TG4050. TG4050 is currently evaluated in a Phase 1/2 clinical trial in Head and Neck cancers* (NCT04183166). During production, MVA are prone to homologous recombinant events; this genetic engineering advantage remains an issue if unwanted homologous regions are incorporated. Overexpression of hydrophobic peptides and peptides containing transmembrane (TM) domains, might impair the viability of cells and therefore the yield of virus produced. The successful incorporation of a high variety of peptides requires the control of these specific features by computational methods.

## Method

VacDesignR® is a software selecting and assembling up to 30 predicted immunogenic peptides (IPs) to be cloned in the MVA genome. The 3 main generation steps are the peptides selection, the inter-cassette repartition and the intra-cassette ordering. The IPs are filtered for homologous regions and sorted based on TM and Hydropathy (H) scores, defining 3 “production difficulties” classes: Low, Medium or High. IPs from the 3 classes are then dispatched to each cassette. This inter-cassette balanced repartition is performed 30,000 times to generate random batches and calculate H mean score. The intra-cassette repartition applies pre-defined slot positions. >2000 combinations are performed for each cassette. Only the fusions with the lowest H and TM scores are kept for final plasmid production.

## Results

Evaluated during the conception of MVA-based individualized neoantigen vectors, the production of recombinant viruses succeeded in <30% rate without optimization and >80% rate with VacDesignR®, which allows the use of this vector as INTV.

## Conclusions

VacDesignR® is an efficient and effective computational tool to optimize plasmid design avoiding unwanted homologous recombination and production issues by keeping the TM and H scores low. Future versions including AI-based components are currently evaluated to improve performance.

*Le Tourneau, ASCO 2025