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AI-Powered Antigen Discovery for Herpesvirus Vaccine Development

EVAXION

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Introduction

Herpesviruses like CMV remain a major clinical challenge due to their ability to establish lifelong latency and evade immune detection, causing severe disease in in immunocompromised individuals. Despite decades of research, no approved CMV vaccine exists, highlighting the need for innovative strategies.

AI-driven vaccine design enables multi-antigen formulations targeting both latent and lytic phase of infection and induction of both humoral and cellular responses.

At Evaxion, we use our AI-Immunology™ platform to identify novel CMV vaccine targets, i.e., cross-protective B-cell antigens and T-cell epitopes, which are currently undergoing preclinical evaluation.

By harnessing AI's predictive power, we aim to overcome traditional vaccine limitations and accelerate the development of both preventive and therapeutic solutions for CMV.

Conclusions

AI-driven strategies represent a paradigm shift in vaccine development. In the context of CMV, key challenges such as complex infection cycles, immune evasion and strain diversity are being addressed by our AI-Immunology™ platform by combining novel B-cell antigens with AI-predicted T-cell epitopes.

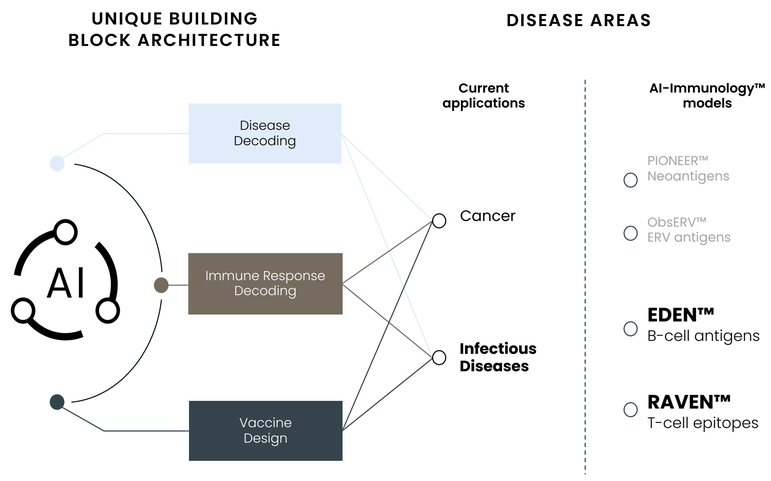
Using Evaxion's AI-Immunology™ platform, we have identified novel CMV vaccine targets that are currently being evaluated in preclinical models with early promising results. The vaccine targets include a combination of novel and well-described B-cell antigens and T-cell epitopes targeting different phases of the infection. Evaluation of additional antigen targets are ongoing with expected pre-clinical read-out later this year.

The platform's modular design and predictive power can be applied to other complex pathogens, with the goal of accelerating vaccine discovery and improving immune protection across diverse populations.

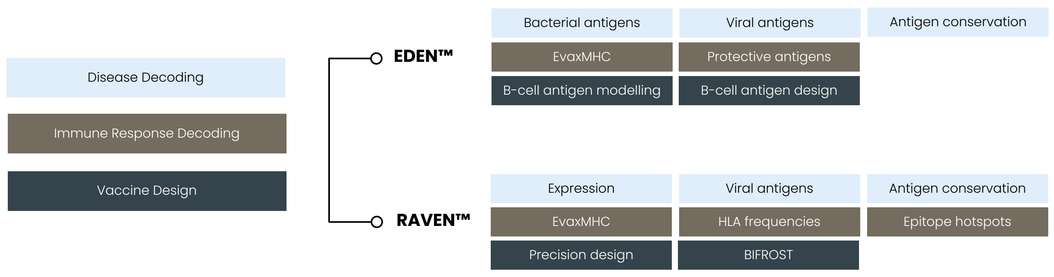
AI-Immunology™ platform

AI-Immunology™ platform enables accelerated and unbiased antigen discovery by integrating proprietary datasets, large protein language models, and advanced machine learning to decode disease biology, immune responses, and vaccine design.

For infectious diseases, AI-Immunology™ uses models EDEN™ and RAVEN™ to identify protective B-cell antigens and T-cell epitopes, respectively.



The EDEN™ and RAVEN™ models are composed of several modules. Both models are supported by EvaxMHC, a state-of-the-art peptide–MHC interaction predictor trained on thousands of MHC alleles. Together, they enable the design of vaccines with broad population coverage and strong immunogenicity against fast-evolving and complex pathogens.



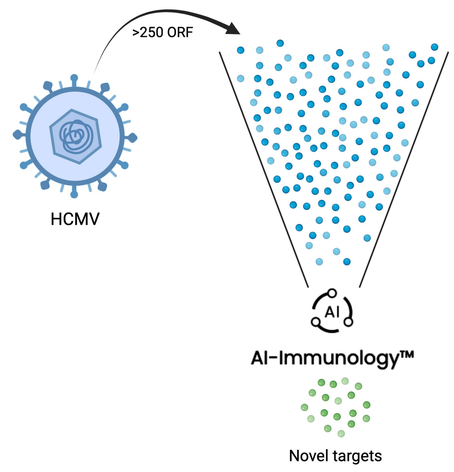
Strategy for AI-Immunology™ driven CMV vaccine design

CMV vaccine development is challenged by the virus ability to establish latency, evade the host immune system, and its high genetic variability across strains.

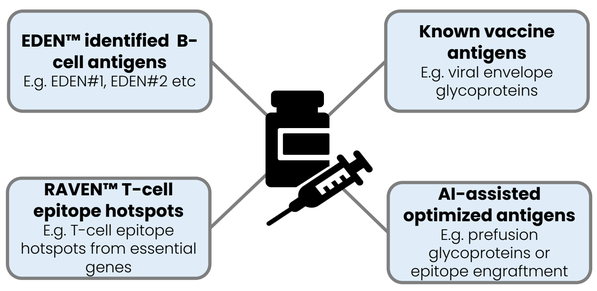
Despite strong humoral responses induced by vaccines targeting viral glycoproteins such as gB and the pentameric complex, these approaches alone have not achieved sufficient viral control in completed clinical trials.

With over 250 canonical ORFs, and possibly more than 750, less than 4% of the HCMV proteome has been explored for vaccine purposes in clinical trials.

The AI-Immunology™ platform allows for unbiased identification of novel antigens to include in a next-generation multicomponent vaccine.



Next generation CMV vaccine



Multicomponent vaccine: Targeting CMV effectively requires more antigens than current candidates than currently being explored in clinical trials.

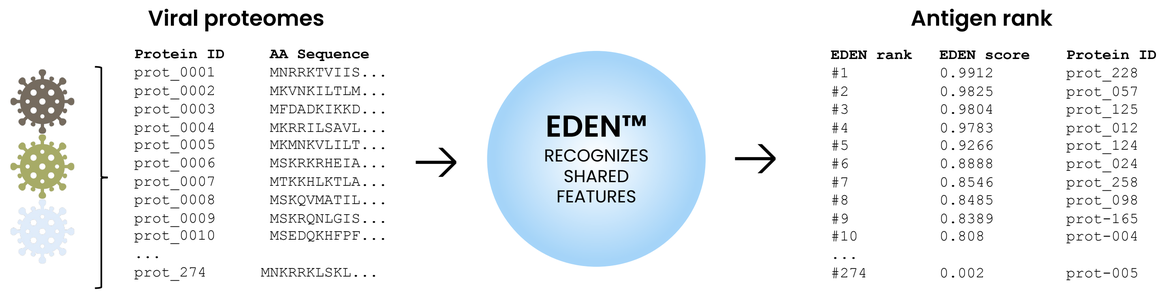
Dual immune activation: Strong antibody and broad T-cell responses are essential to target CMV's complexity and ability to evade immune attack.

Broad protection: Including conserved antigens and antigens with multifunctional roles helps address strain diversity, broad tropism and immune escape.

AI-guided antigen re-engineering: Structural optimization of selected promising targets are made to enhance neutralising antibody responses or T-cell responses.

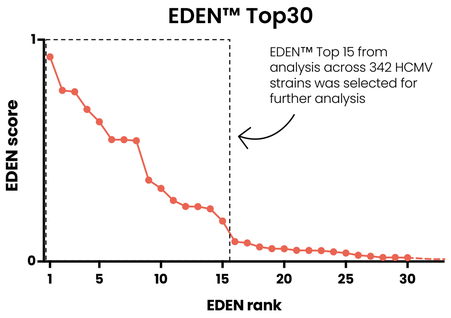
EDEN™ identifies protective antigens

EDEN™ is trained to recognize shared protective features within the amino acid sequence of proteins. The input data is proteomic data, and the output is a ranked list of protective proteins. The highest-ranking proteins are then tested for immunogenicity and protection in *in vivo* and *in vitro* models.



Cross-protective antigens across 343 CMV strains were identified using EDEN™. The EDEN™ 15 candidates were subject to further literature and sequence analysis, narrowing down the list to 10 antigens for design and expression. Five were excluded due to variability, too small size, redundancy, or homology to human proteins.

EDEN™ Top30



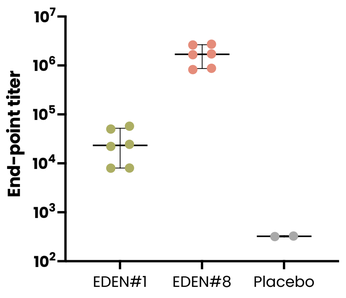
EDEN™ antigens selected for preclinical testing

Target	Putative function	Conservation*
EDEN#1	Latency, immune evasion	high
EDEN#3	Assembly	high
EDEN#4	Replication	high
EDEN#5	Capside maturation	high
EDEN#6	Endocytosis, cell-to-cell spread	medium
EDEN#8	Cell-to-cell spread	high
EDEN#9	Immune evasion	medium
EDEN#10	Latency, re-activation	medium
EDEN#11	Chaperone	medium
EDEN#15	Transactivator	high

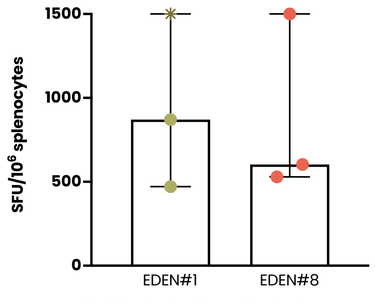
* High conservation: mean homology >98%
Medium conservation: mean homology >95%

Two EDEN™ antigens (EDEN#1 and EDEN#8) were successfully produced in S2 cells. Mice (BALB/c) received 3 doses of 10 µg (i.m.) of each antigen formulated with AddaVax and poly(I:C). Both antigens induced strong antigen-specific IgG and T-cell responses. Virus neutralisation studies are ongoing with promising early results.

IgG titer



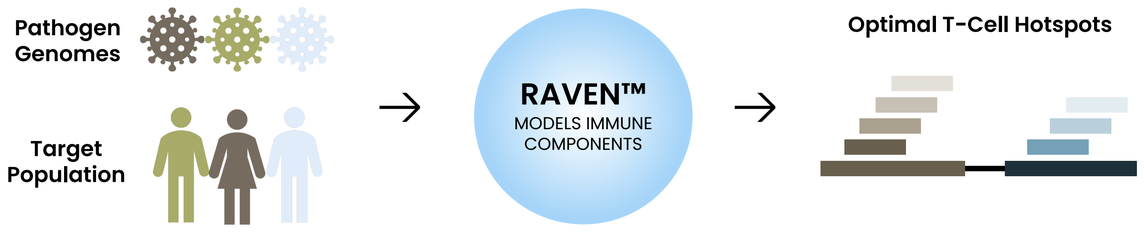
IFNγ ELISPOT



Point indicated by a star, had a response too high for measurement.

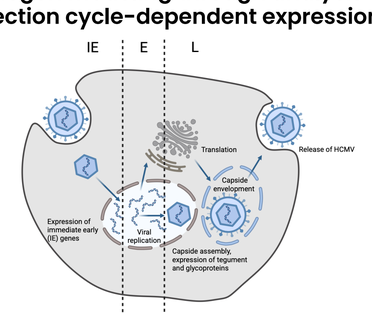
RAVEN™ identifies epitopes for cytotoxic- and helper T-cell response

RAVEN™ identifies immunogenic T-cell epitopes by integrating viral genomic and proteomic data with MHC profiles. It ranks epitopes based on their potential to induce strong CD4+ and CD8+ T-cell responses, optimised for population coverage. Epitope-rich regions (T-cell hotspots) are prioritised for vaccine design.

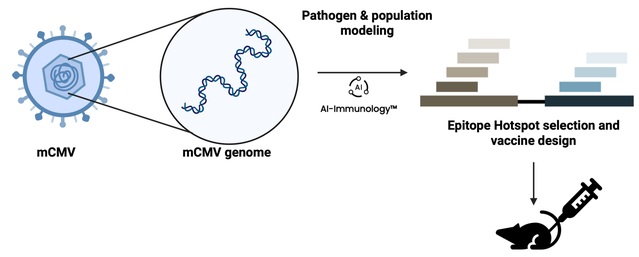


Key open reading frames (ORFs) were identified and selected based on infection cycle-dependent expression, expression level and function (e.g. immune evasion, replication). T-cell epitope-rich hotspots were predicted within selected ORFs. To support preclinical validation, pathogen and population modeling were performed using MCMV in mouse immunogenicity and infection models.

Pathogen modeling through analysis of infection cycle-dependent expression

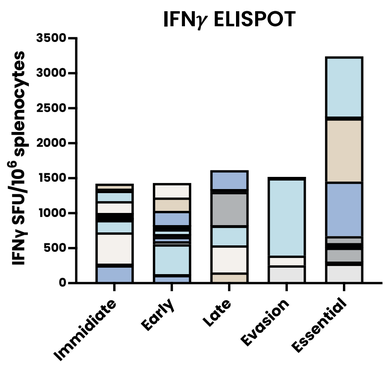


Design of MCMV T-cell vaccine for preclinical testing in mouse models

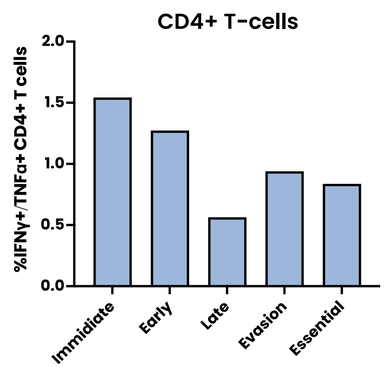


Immunogenicity of RAVEN™ T-cell vaccine designs was confirmed through re-activation of splenocytes from animals vaccinated with two doses of the T-cell vaccine, showing induction of both CD4+ and CD8+ T-cell responses. Protection studies *in vitro* and in mouse challenge models are ongoing.

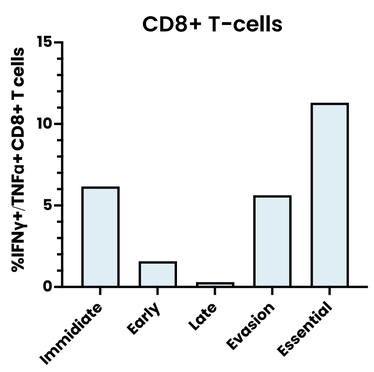
IFNγ ELISPOT



CD4+ T-cells



CD8+ T-cells



Acknowledgment

ExpreS2ion Biotechnologies produced the two tested EDEN™ antigens using their proprietary ExpreS2 protein expression system. We also thank the valuable input and advice to this project given by the Scientific Advisory Board, including Stanley Plotkin, Mark Schleiss and Laura Gibson. Their guidance has helped sharpen our antigen prioritisation strategy and reinforced our focus on multi-component vaccine design. We appreciate their continued support as we move toward candidate nomination.

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