A034 · Learned Immune Architectures of Durable Antibody Responses Across Vaccines

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Vaccination is one of the most effective public health interventions. However, vaccine efficacy varies widely among individuals, as immunity arises from complex interplay between genetic, pathogen, and immunological factors. To date, most systems vaccinology studies have remained pathogen-specific, precluding the discovery of potential shared immune architectures underlying durable antibody responses. To address this gap, we leveraged transcriptomic data from 1,032 participants receiving influenza, hepatitis B, or yellow fever vaccines to develop an interpretable machine learning framework for comparative analysis across diverse vaccine platforms. Pathogen-specific models using Blood Transcriptional Module-based feature aggregation accurately predicted high antibody responders and consistently outperformed gene-level models. Distinct predictive immune architectures identified across vaccines were further resolved for dominant hierarchical immune programs using surrogate decision trees. This approach identified the dominant decision boundaries underlying each vaccine model, highlighting leukocyte migration and Th2 differentiation in Hepatitis B, CD4+ T cells, M2 macrophages, and c-MYC signaling in Influenza, and B-cell receptor signaling with B-cell developmental pathways in Yellow Fever. Cross-pathogen concordance analyses further identified four shared transcriptional modules, suggesting partially conserved immune architectures across diverse vaccines. Interestingly, one concordant module converged on mitochondrial immunometabolic pathways and was consistently elevated in high responders, which suggests a shared role for cellular energy metabolism in supporting durable antibody responses. Together, these findings provide new insights into the immune mechanisms underlying durable vaccine responses and establish an interpretable machine learning framework that enables the discovery of shared and vaccine-specific immune architectures and may inform the rational design of next-generation vaccines.

Learned Immune Architectures of Durable Antibody Responses Across Vaccines

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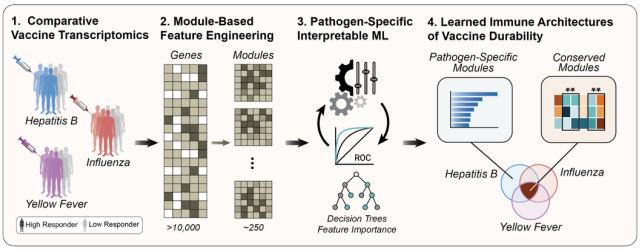
Background: Vaccination is one of the most effective public health interventions, yet the magnitude and durability of vaccine-induced immunity vary substantially among individuals. This heterogeneity reflects a complex interplay among host genetics, prior infections, environmental exposures, and vaccine-specific factors. Systems vaccinology has enabled the identification of molecular signatures associated with vaccine immunogenicity; however, most studies examine vaccines independently. This pathogen-specific focus limits our ability to discover potential shared immune architectures underlying durable antibody responses.



Methods: To address this gap, we leveraged harmonized transcriptomic and antibody-response data from 1,032 participants receiving influenza, hepatitis B, or yellow fever vaccines across studies within the Immune Signatures Data Resource. Analyses were conducted separately within each pathogen to prevent cross-pathogen information leakage and account for differences in vaccine platform, pathogen biology, and study design. Baseline and early post-vaccination gene-expression measurements were adjusted for age before post-vaccination fold changes were calculated. Gene-level fold changes were then aggregated into biologically interpretable Blood Transcriptional Modules (BTMs) using gene set variation analysis. Participants were classified as high or low antibody responders based on their antibody response titers.

We evaluated multiple supervised machine-learning approaches, including support vector machines, elastic-net regression, random forest, and boosting-based models. Models were trained using an 80/20 training–test split with repeated 10-fold cross-validation. Gene-level and BTM-level models were compared to determine whether pathway-based feature aggregation improved predictive performance, and predictive BTMs were identified using bootstrapped permutation feature importance. Surrogate decision trees were subsequently fitted to the final models to identify dominant hierarchical decision boundaries and provide an interpretable representation of how high and low responders were distinguished. Finally, cross-pathogen concordance analysis was performed to identify transcriptional modules shared across vaccines.

Results: BTM-based models consistently outperformed gene-level models, demonstrating that pathway-level aggregation improved both predictive performance and biological interpretability. Final models predicted high durable antibody responders with area under the receiver operating characteristic curve values of 0.82 for yellow fever, 0.75 for hepatitis B, and 0.69 for influenza. Distinct predictive immune architectures identified across vaccines were further resolved for dominant hierarchical immune programs using surrogate decision trees. This approach identified the dominant decision boundaries underlying each vaccine model, highlighting leukocyte migration and Th2 differentiation in Hepatitis B, CD4+ T cells, M2 macrophages, and c-MYC signaling in Influenza, and B-cell receptor signaling with B-cell developmental pathways in Yellow Fever. Surrogate decision trees showed that immune programs formed distinct hierarchical pathways predictive of antibody responses within each vaccine, providing an interpretable view of the dominant decision boundaries underlying otherwise complex ensemble predictions. Cross-pathogen concordance analyses further identified four shared transcriptional modules, suggesting partially conserved immune architectures across diverse vaccines. Interestingly, one concordant module converged on mitochondrial immunometabolic pathways and was consistently elevated in high responders, which suggests a shared role for cellular energy metabolism in supporting durable antibody responses.

Discussion: Together, these findings indicate that durable vaccine responses arise from partially conserved immunological processes that are expressed through vaccine-specific transcriptional architectures. Pathway-level feature aggregation improved prediction relative to gene-level modeling, while surrogate decision trees revealed how combinations of immune programs defined distinct routes to durable immunity. This comparative and interpretable systems-vaccinology framework provide a foundation for identifying reproducible immune mechanisms across vaccines and may help guide biomarker development, vaccine optimization, and the rational design of next-generation vaccines.