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VSV EBOVAC — VSV-ZEBOV VACCINE SAFETY AND IMMUNOGENICITY

Safety Analysis of Adults and Pediatric Responses to VSV-EBOV — VSV-EBO PLUS

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Transcriptomic analysis of the immune response to the rVSV-ZEBOV Ebola vaccine

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Facts & Figures	VSV-EBOVAC	VSV-EBOPLUS
Start date	01/03/2015	01/04/2016
End date	28/02/2019	31/03/2021
Contributions		
IMI funding	3 887 260 €	8 553 750 €
EFPIA in kind	0 €	4 828 910 €
Other	898 750 €	2 048 000 €
Total Cost	4 786 010 €	15 430 660 €
Project website	www.vsv-ebovac.eu	http://www.vsv-eboplus.eu/

Challenge

rVSV-ZEBOV is a live-attenuated recombinant vesicular stomatitis virus (VSV) vaccine expressing the Zaire Ebolavirus glycoprotein and is the only Ebola vaccine with demonstrated clinical efficacy. In order to investigate the immune response after the vaccine and find a gene signature to predict the vaccine response, we studied the whole blood transcriptome from 51 volunteers injected either with 10^7 or $5x10^7$ PFU of rVSV-ZEBOV and 13 placebo.

Approach & Methodology

RNA was extracted from whole blood samples collected at different time points after vaccination and analyzed by targeted transcriptome sequencing of 20,812 human genes. The gene expression levels were compared to identify the differentially expressed genes (DEGs) at each time point and then analyzed to understand their biological role by functional analysis. Differential expression analysis was performed using the edgeR package comparing the baseline expression, i.e. the day of vaccination, and the other time points. The enrichment of blood transcription modules, derived from system biological studies of 5 human vaccines, was evaluated using the R package tmod with an input table containing the DEGs ordered by FDR.

Results

At day 1 after vaccination 5,469 differentially expressed genes (DEGs) were detected, this number decreased over time: at day 35 only 10 DEGs were detected.

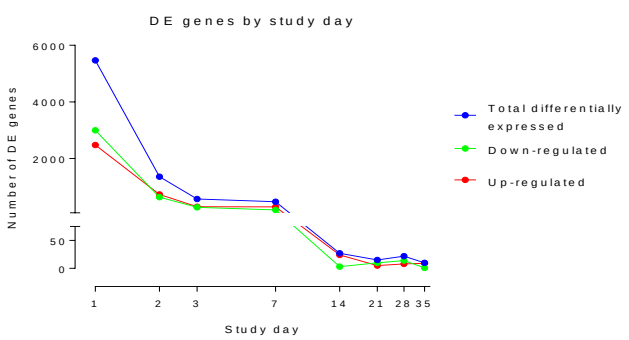

Figure 1. Number of DE genes over time from vaccination. Significant DE genes were defined by an adjusted *P*-value < 0.05 obtained with the Benjamini and Hochberg's correction method. Samples up to day 14 were analyzed using the function `glmTreat` with a threshold on fold change (fc > 1.2 and fc < 0.83).

From day 1 to day 14 after vaccination a total of 135 blood transcription modules resulted affected, with a core of 22 modules, mainly related to innate immunity pathways activation, enriched from day 1 to day 14 which were (Figure 2).

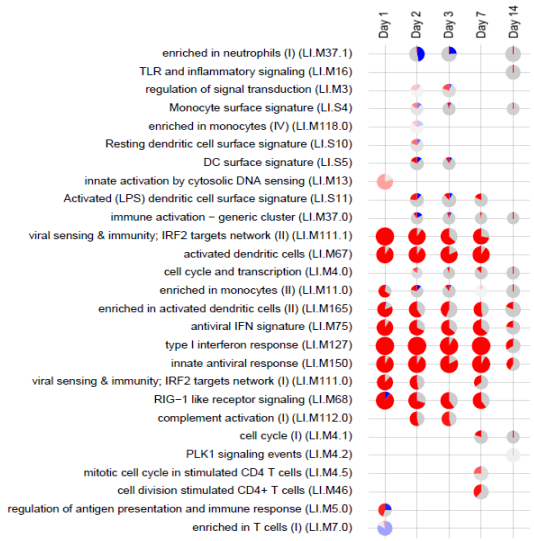

Figure 2. Gene set enrichment analysis from day 1 to day 14. Pie plots of enriched modules from day 1 to day 14 with adjusted P-value $<10^{-5}$. Each module is represented as a circle where the size is proportional to the AUC value (number of genes in the module and ranking), while the colour intensity represents the adjusted *P*-value and the colors indicate the proportion of up-regulated (red), down-regulated (blue) and unaffected (grey) genes.

Normalized gene expression was then correlated with specific anti-ZEBOV glycoprotein IgG titers detected at one year after vaccination. We identified 15 strongly correlated genes at day 14 after vaccination (Spearman's ρ>0.5, p<0.001, Figure 4). This correlation increased when gene expression of all 15 genes was converted into a score (Figure 5). A score threshold was calculated that could separate the samples in two main groups based on the antibody titer (Figure 5).

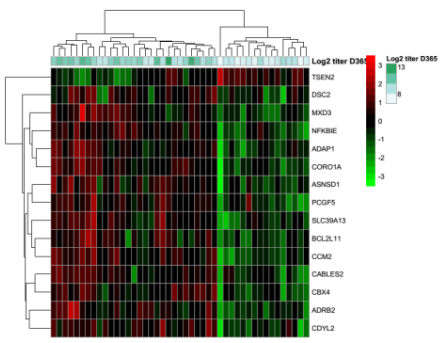

Figure 4. Heat map showing the expression levels of 15 genes at day 14 correlating with the anti-glycoprotein IgG titers at day 365. Genes are presented as scaled and normalized by average and SD.

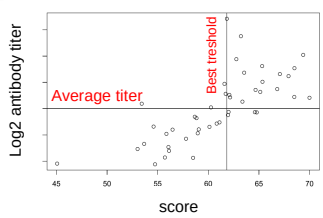

Figure 5. Correlation between score and antibody titer. Each dot represents a sample. Score was calculated as Σ expression of positively correlated genes – Σ expression of negatively correlated genes. Spearman's Rho=0.8, p-value=$2,2*10^{-16}$

Value of IMI collaboration

The IMI-supported VSV-EBOVAC and VSV-EBOPLUS projects allowed the acquisition of unique sets of samples, which have been analysed by different partners with cutting-edge technologies, generating highly multidimensional data.

Impact & take home message

Vaccination with rVSV-ZEBOV induced a strong and durable modulation of genes associated with innate response. An algorithm strongly correlating with antibody titers one year after vaccination was developed based on the expression levels of 15 genes.

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This work has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking under the VSV-EBOVAC [grant no 115842] and VSV-EBOPLUS [grant no 116068] projects.