Supplementary figures and tables:

Table S1. The total number of reads after trimming, number and percentage of reads that mapped for the *in vitro* 24 h unstimulated naïve (day 0, collected before immunization) and immune (day 38, collected 17 days after the second immunization with attAHSV4) PBMC, the naïve (day 0) and immune (day 38) PBMC stimulated with virAHSV4 for 24 h transcriptome data sets. As well as the *in vivo* naïve PBMC (day 0) collected before immunization, PBMC (day 1) collected 24 h after the first immunization with attAHSV4 and PBMC (day 22) collected 24 h after the second immunization with attAHSV4 transcriptome data sets.

Transcriptome data sets	Total number of reads after trimming	Number of reads mapped	% reads that mapped
***In vitro,* 24 h stimulation:**			
Day 0 unstimulated naïve PBMC	23,82 x 10^6	2,71 x 10^6	11,42
Day 0 virAHSV4 stimulated naïve PBMC	24,34 x 10^6	2,68 x 10^6	11,06
Day 38 unstimulated immune PBMC	3,77 x 10^6	3,05 x 10^5	8,09
Day 38 virAHSV4 stimulated immune PBMC	26,59 x 10^6	2,55 x 10^6	9,63
***In vivo,* vaccination:**			
Day 0 naïve horses	22,53 x 10^6	2,01 x 10^6	8,94
Day 1 attAHSV4 immunized horses	21,55 x 10^6	2,16 x 10^6	10,03
Day 22 attAHSV4 immunized horses	28,67 x 10^6	2,65 x 10^6	9,26

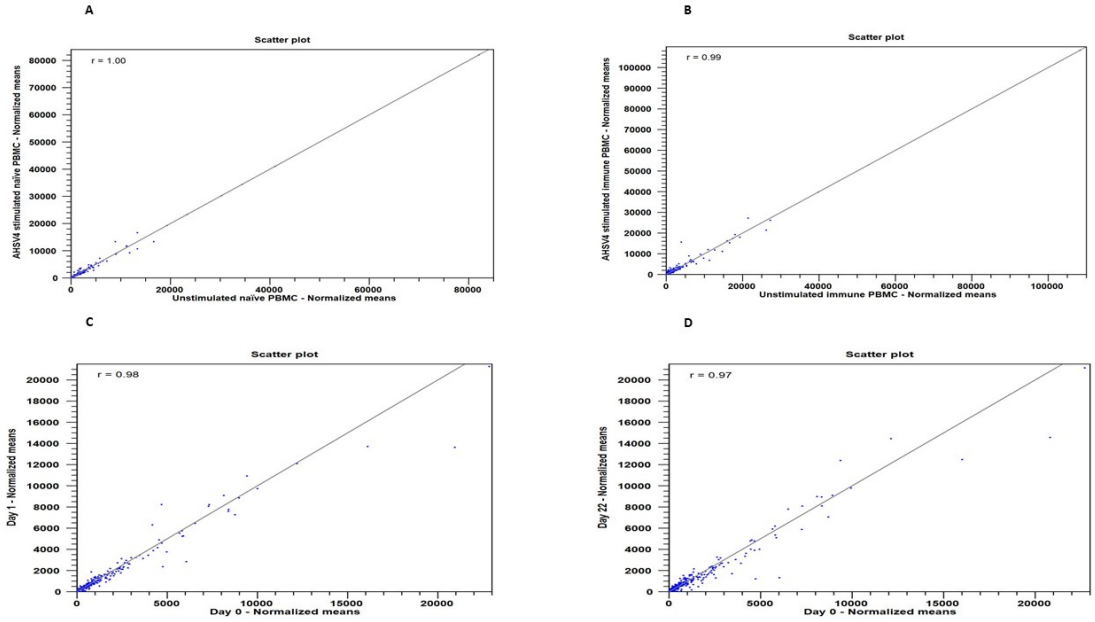


Fig. S1. Transcriptome data analysis: scatter plots. Scatter plot of (A) *in vitro* naïve PBMC (day 0) stimulated with the virAHSV4 for 24 h of group means using normalised expression values normalised to unstimulated naïve PBMC (day 0). Of (B) *in vitro* immune PBMC (day 38) stimulated with the virAHSV4 for 24 h of group means using normalised expression values normalised to unstimulated immune PBMC (day 38). Of (C) *in vivo* PBMC (day 1) collected 24 h after the first immunization with the attAHSV4 of group means using normalised expression values normalised to the before immunization naïve PBMC (day 0). Of (D) *in vivo* PBMC (day 22) collected 24 h after the second immunization with the attAHSV4 of group means using normalised expression values normalised to the before immunization naïve PBMC (day 0).

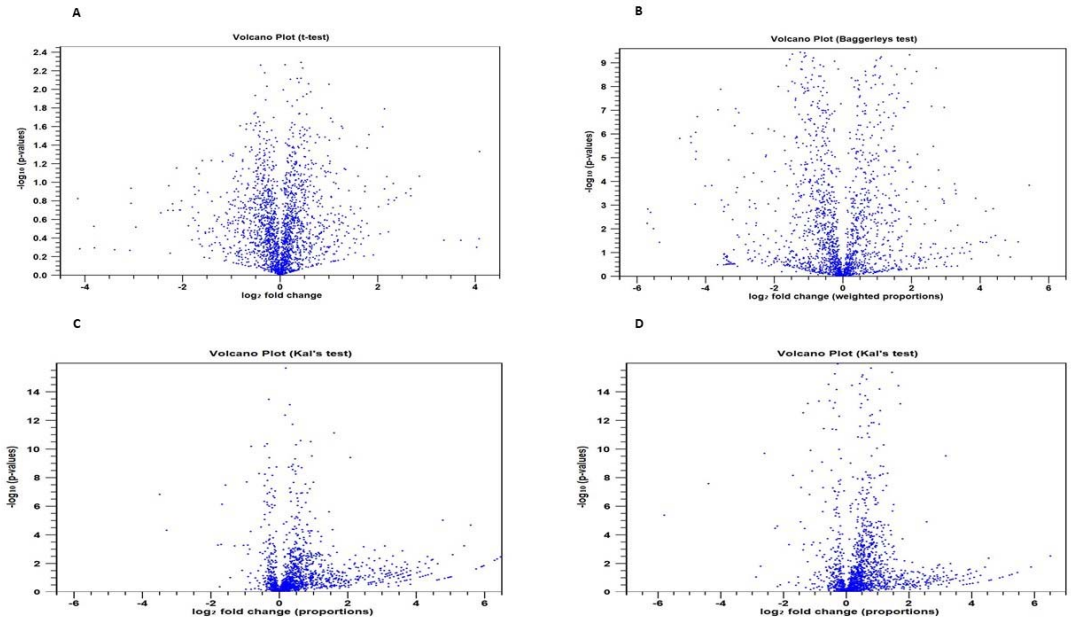


Fig. S2. Transcriptome data analysis: volcano plots. Volcano plot for the expression difference in mRNA of (A) *in vitro* naïve PBMC (day 0) stimulated with the virAHSV4 for 24 h compared to unstimulated naïve PBMC (day 0) and (B) *in vitro* immune PBMC (day 38) stimulated with the virAHSV4 for 24 h compared to unstimulated immune PBMC (day 38). Of (C) *in vivo* PBMC (day 1) collected 24 h after the first immunization with the attAHSV4 and (D) *in vivo* immune PBMC (day 22) collected 24 h after the second immunization with the attAHSV4 compared to the before immunization naïve PBMC (day 0), plotted on the x-axis and Baggerley's FDR-adjusted significance is plotted on the y-axis (–log10 scale).

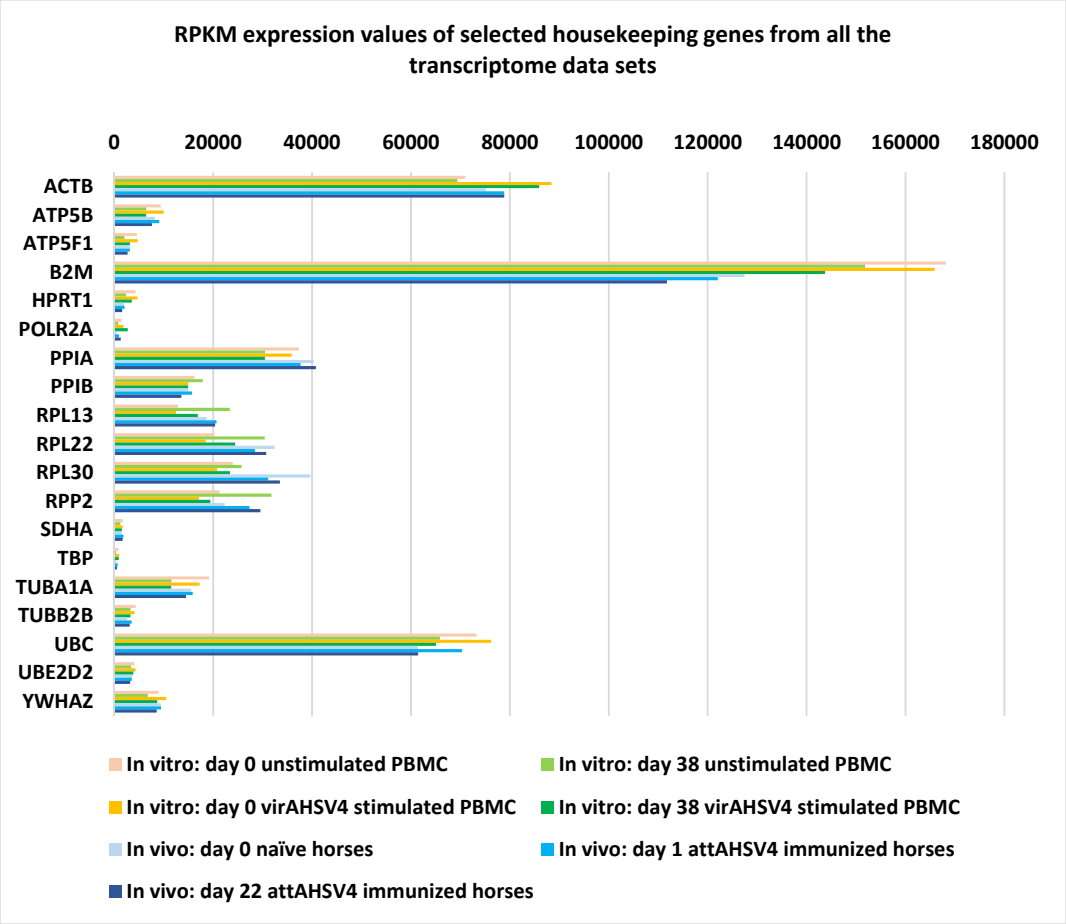


Fig. S3. The RPKM expression values of the selected housekeeping genes (https://www.sigmaaldrich.com/) from the *in vitro* 24 h unstimulated naïve (day 0, collected before immunization) and immune (day 38, collected 17 days after the second immunization with attAHSV4) PBMC, the naïve (day 0) and immune (day 38) PBMC stimulated with virAHSV4 for 24 h, the *in vivo* naïve PBMC (day 0) collected before immunization, PBMC (day 1) collected 24 h after the first immunization with attAHSV4 and PBMC (day 22) collected 24 h after the second immunization with attAHSV4 transcriptome data sets.

Table S2. The total up-regulated (black, positive) and down-regulated (red, negative) differentially expressed genes during the virAHSV4 primary and secondary immune responses associated with the immune system (KEGG Pathways, Reactome Pathways and Biological Process). The false discovery rates (FDR) are shown in table.

STRING v11 analysis	virAHSV4							
	Primary immune response				Secondary immune response			
	Up	FDR	Down	FDR	Up	FDR	Down	FDR
KEGG Pathways (total genes in pathway)								
RIG-I-like receptor signaling pathway (70)	21	8,26E-16	-12	1,51E-07	27	1,29E-14	-11	2,08E-05
Toll-like receptor signaling pathway (102)	24	6,07E-16	-16	3,45E-09	42	8,65E-23	-21	1,03E-10
NOD-like receptor signaling pathway (166)	48	4,08E-34	-21	3,33E-10	64	7,26E-33	-37	8,36E-19
Reactome Pathways (total genes in pathway)								
Toll Like Receptor 3 (TLR3) Cascade (95)	20	1,21E-11	-13	3,05E-06	37	1,10E-18	-17	6,82E-08
Interferon alpha/beta signaling (66)	8	7,90E-04	-9	1,20E-04	11	1,50E-03	-12	7,37E-06
Innate Immune System (1012)	105	3,04E-39	-93	2,20E-34	213	1,01E-70	-155	3,51E-62
Adaptive Immune System (733)	86	4,39E-35	-65	1,76E-22	178	4,02E-66	-136	1,97E-62
Biological process (total genes in pathway)								
Myeloid leukocyte activation (574) [a]	40	1,44E-09	-45	1,29E-13	84	1,18E-17	-74	6,23E-24
Lymphocyte activation (358) [b]	35	5,07E-12	-29	3,92E-09	74	6,02E-23	-38	4,79E-10
T cell activation (225)	26	1,92E-10	-18	8,63E-06	55	7,01E-20	-26	1,07E-07
B cell activation (145)	11	1,80E-03	-8	2,97E-02	27	6,72E-08	-10	1,20E-02

[a] Myeloid leukocytes include monocytes, macrophages, dendritic cells and granulocytes.

[b] Lymphocytes include conventional T cells, B cells, unconventional T cells and NK cells.

Table S3. The total up-regulated (black, positive) and down-regulated (red, negative) differentially expressed genes during the attAHSV4 primary and secondary immune responses associated with the immune system (KEGG Pathways, Reactome Pathways and Biological Process). The false discovery rates (FDR) are shown in table.

STRING v11 analysis	attAHSV4							
	Primary immune response				Secondary immune response			
	Up	FDR	Down	FDR	Up	FDR	Down	FDR
KEGG Pathways (total genes in pathway)								
RIG-I-like receptor signaling pathway (70)	25	8,68E-12	-10	2,69E-06	26	1,20E-12	-9	7,76E-05
Toll-like receptor signaling pathway (102)	33	4,12E-14	-22	1,21E-15	33	2,15E-14	-24	9,27E-16
NOD-like receptor signaling pathway (166)	57	2,70E-24	-28	3,50E-17	66	1,52E-31	-35	3,73E-21
Reactome Pathways (total genes in pathway)								
Toll Like Receptor 3 (TLR3) Cascade (95)	28	2,15E-11	-16	1,48E-10	29	1,31E-11	-19	1,10E-11
Interferon alpha/beta signaling (66)	20	7,24E-08	-		20	5,53E-08	-	
Innate Immune System (1012)	186	1,22E-43	-87	2,69E-35	199	3,37E-52	-124	3,72E-55
Adaptive Immune System (733)	139	5,05E-33	-82	1,78E-40	146	7,29E-38	-91	1,32E-39
Biological process (total genes in pathway)								
Myeloid leukocyte activation (574) [a]	81	6,79E-13	-39	5,72E-12	89	8,74E-17	-58	1,36E-20
Lymphocyte activation (358) [b]	76	1,58E-20	-23	7,19E-07	93	2,27E-31	-27	2,79E-07
T cell activation (225)	57	2,17E-18	-14	2,80E-04	67	2,71E-25	-19	5,90E-06
B cell activation (145)	27	1,06E-06	-8	1,55E-02	35	3,24E-11	-8	3,96E-02

[a] Myeloid leukocytes include monocytes, macrophages, dendritic cells and granulocytes.

[b] Lymphocytes include conventional T cells, B cells, unconventional T cells and NK cells.

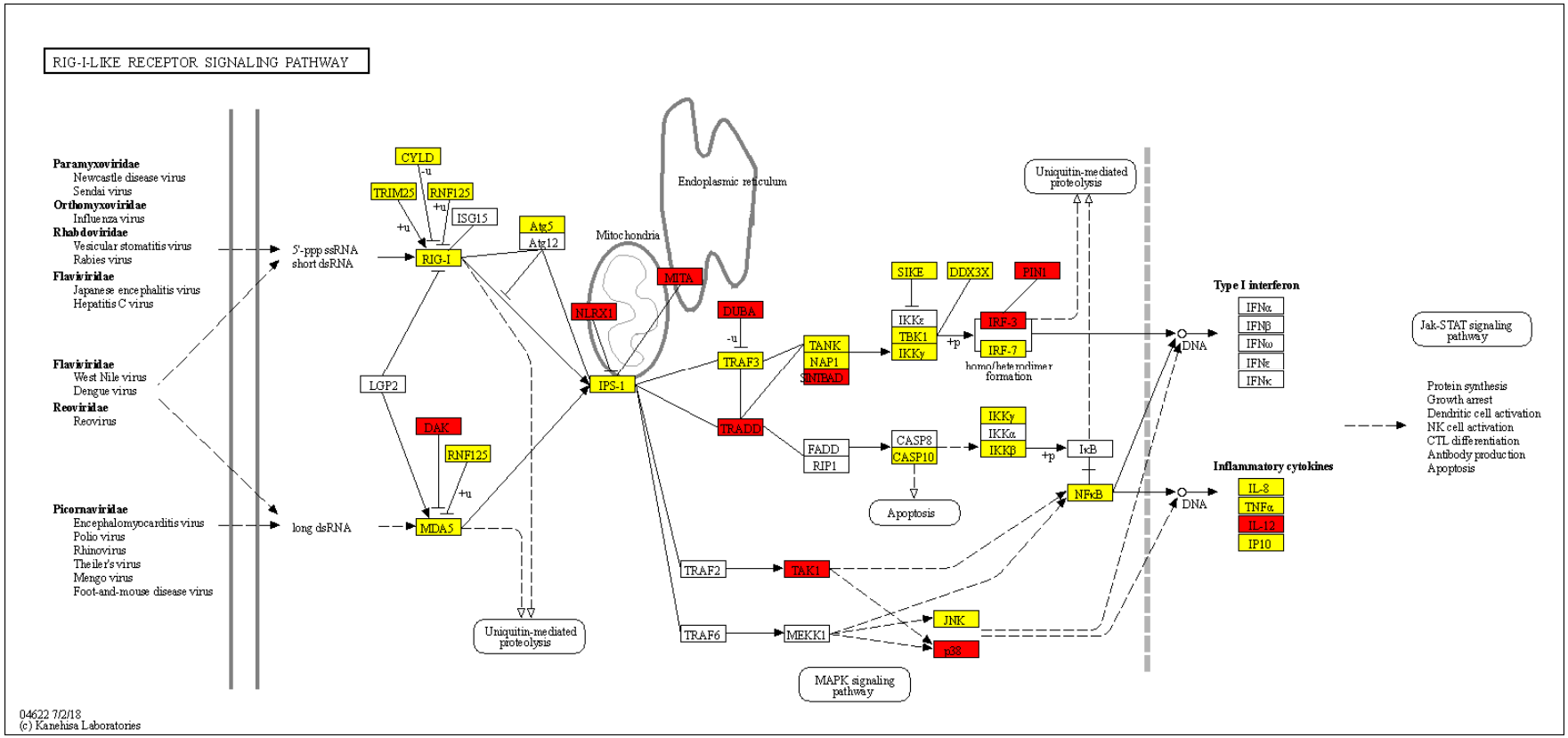


Fig. S4A. The RLR pathway during the *in vitro* virAHSV4 primary immune response (http://www.genome.jp/kegg/pathway.html). The yellow genes are up-regulated and the red genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

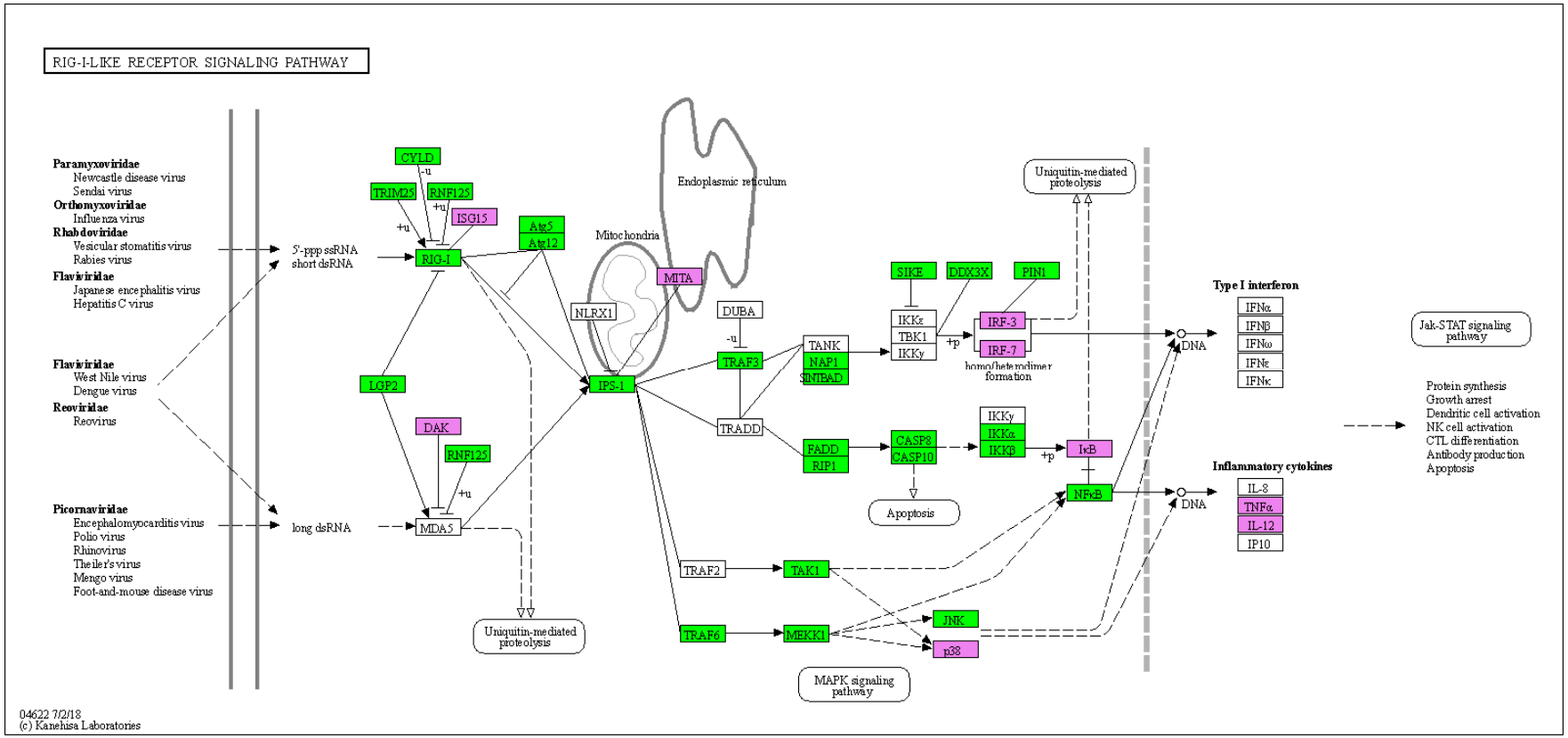


Fig. S4B. The RLR pathway during the *in vitro* virAHSV4 secondary immune response (http://www.genome.jp/kegg/pathway.html). The green genes are up-regulated and the purple genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

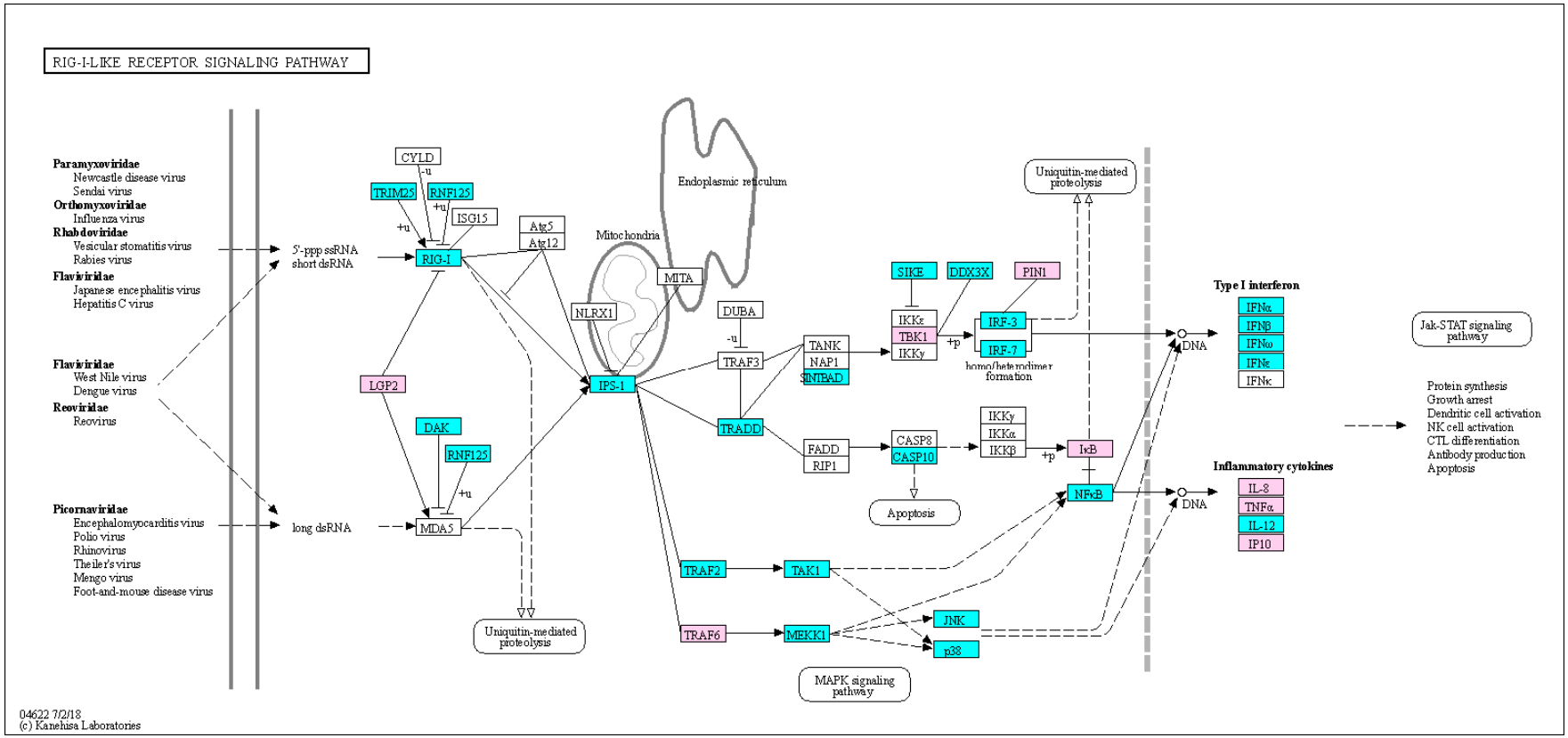


Fig. S4C. The RLR pathway during the *in vivo* attAHSV4 primary immune response (http://www.genome.jp/kegg/pathway.html). The blue genes are up-regulated and the pink genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

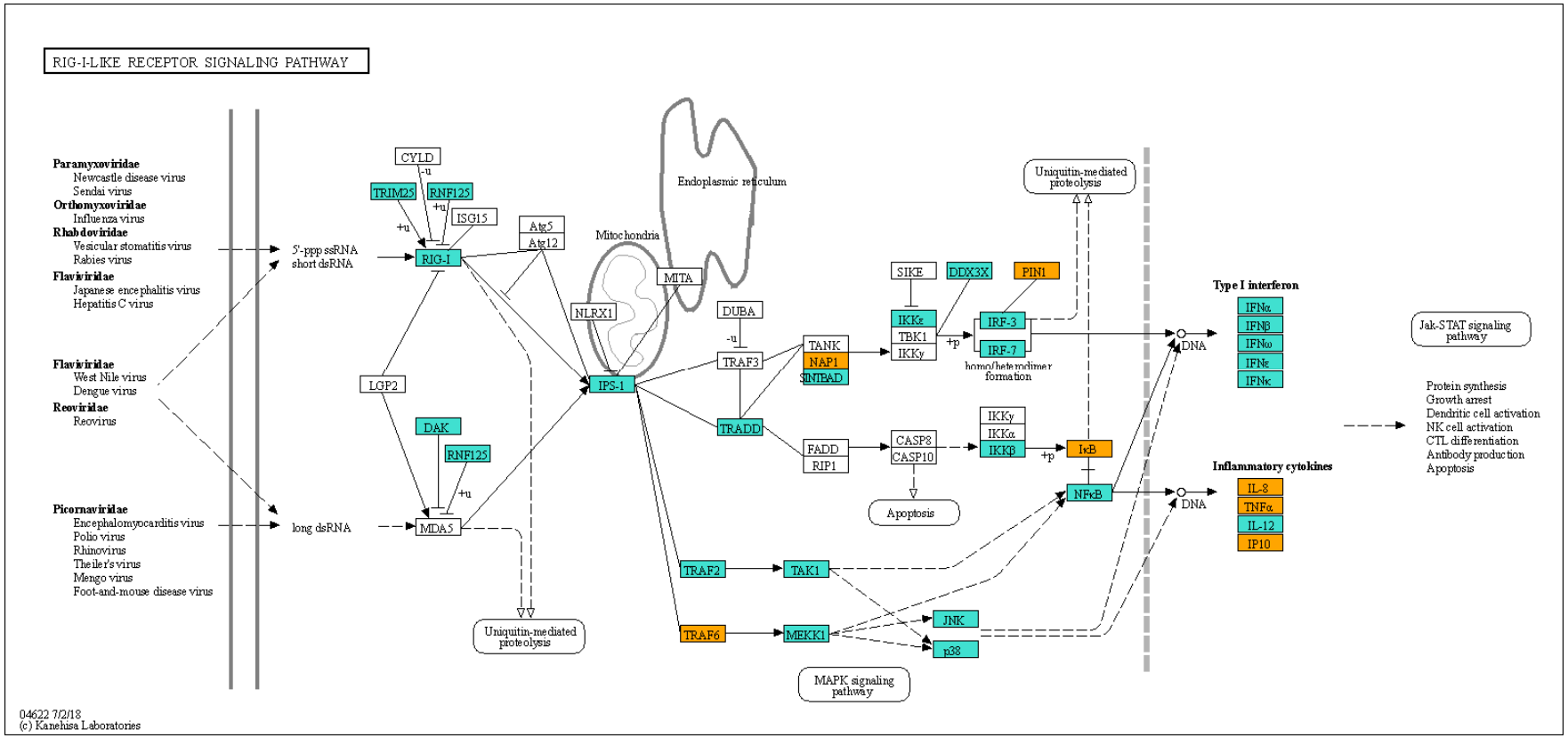


Fig. S4D. The RLR pathway during the *in vivo* attAHSV4 secondary immune response (http://www.genome.jp/kegg/pathway.html). The turquoise genes are up-regulated and the orange genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

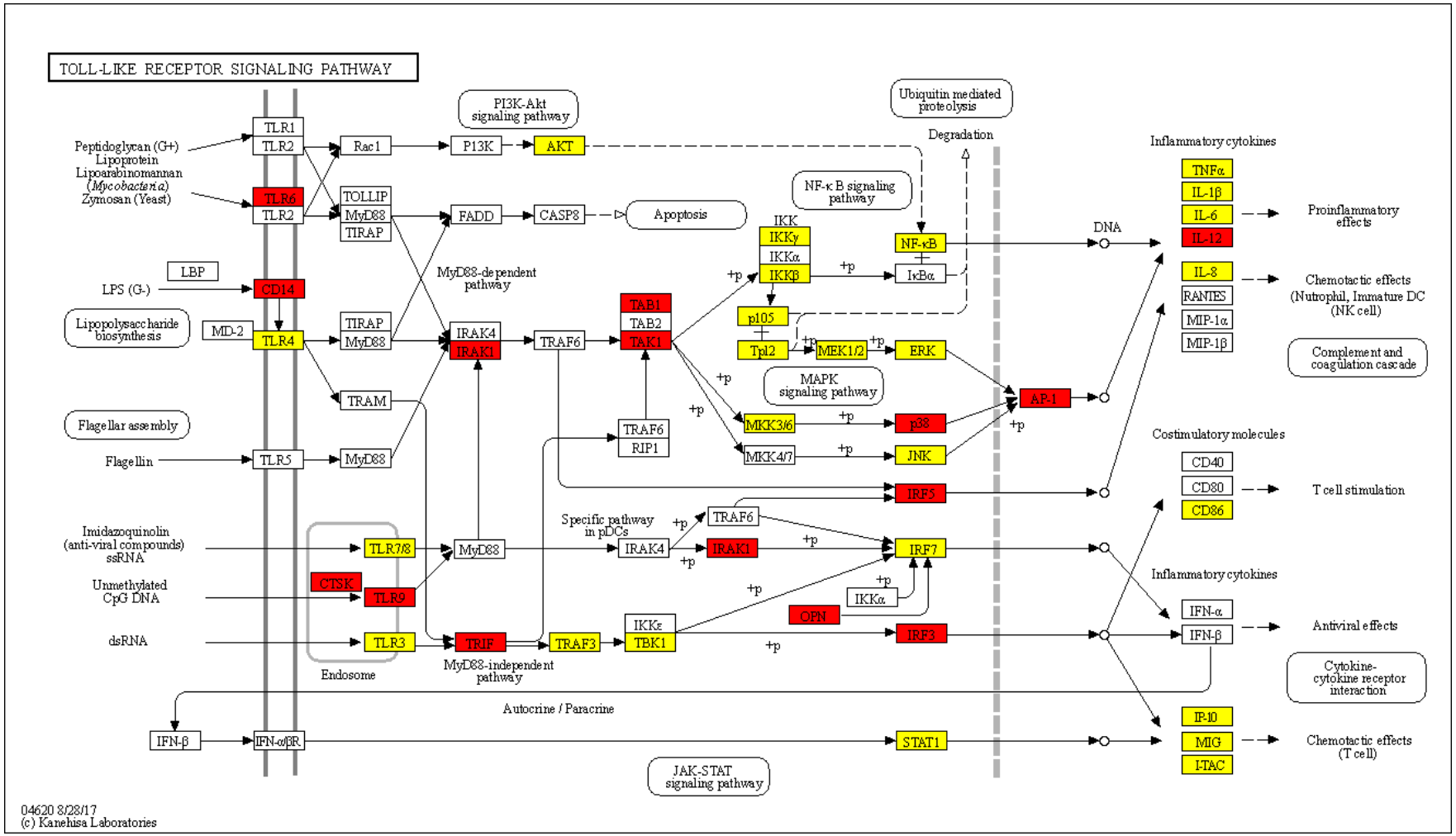


Fig. S5A. The TLR pathway during the *in vitro* virAHSV4 primary immune response (http://www.genome.jp/kegg/pathway.html). The yellow genes are up-regulated and the red genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

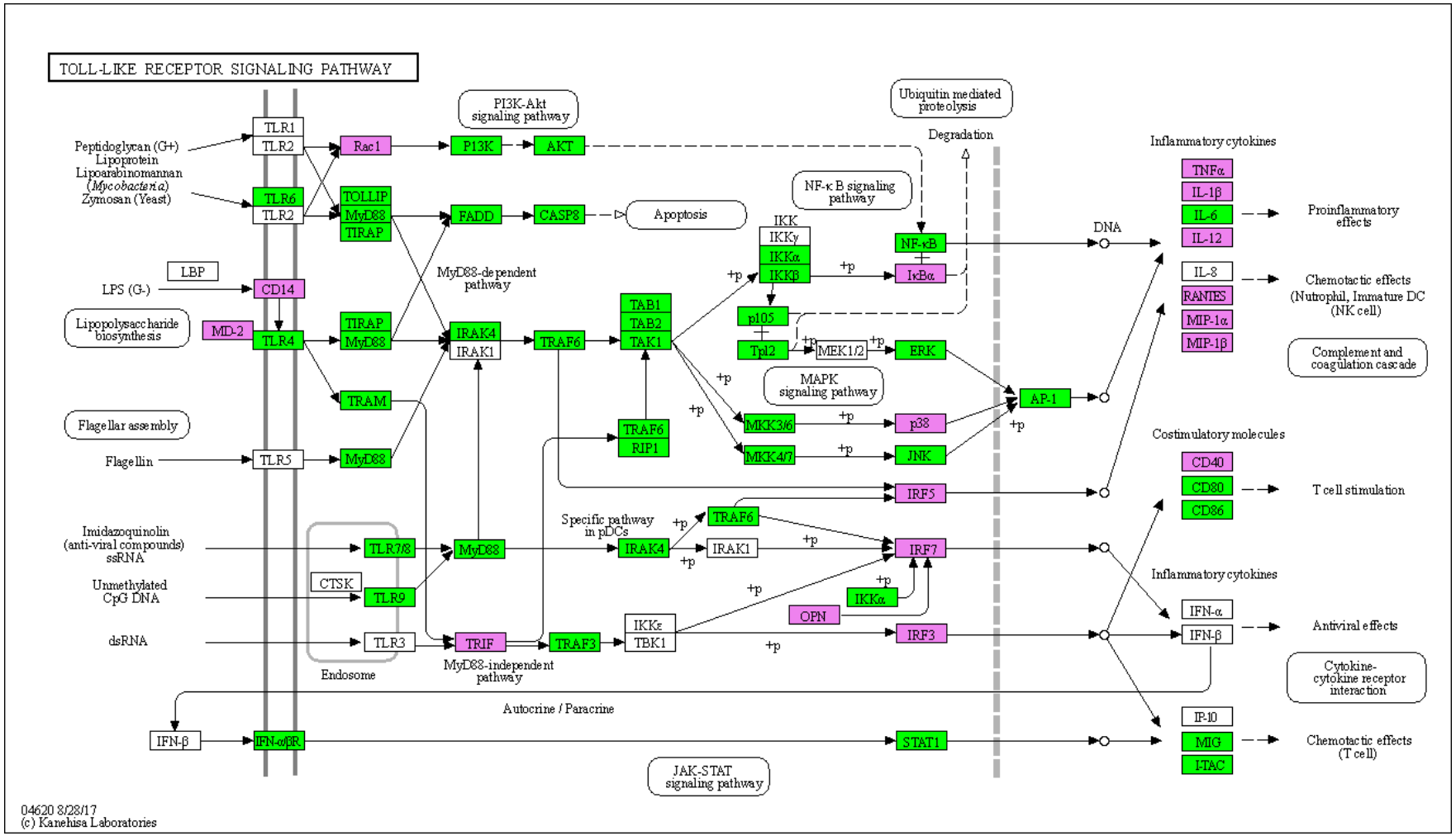


Fig. S5B. The TLR pathway during the *in vitro* virAHSV4 secondary immune response (http://www.genome.jp/kegg/pathway.html). The green genes are up-regulated and the purple genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

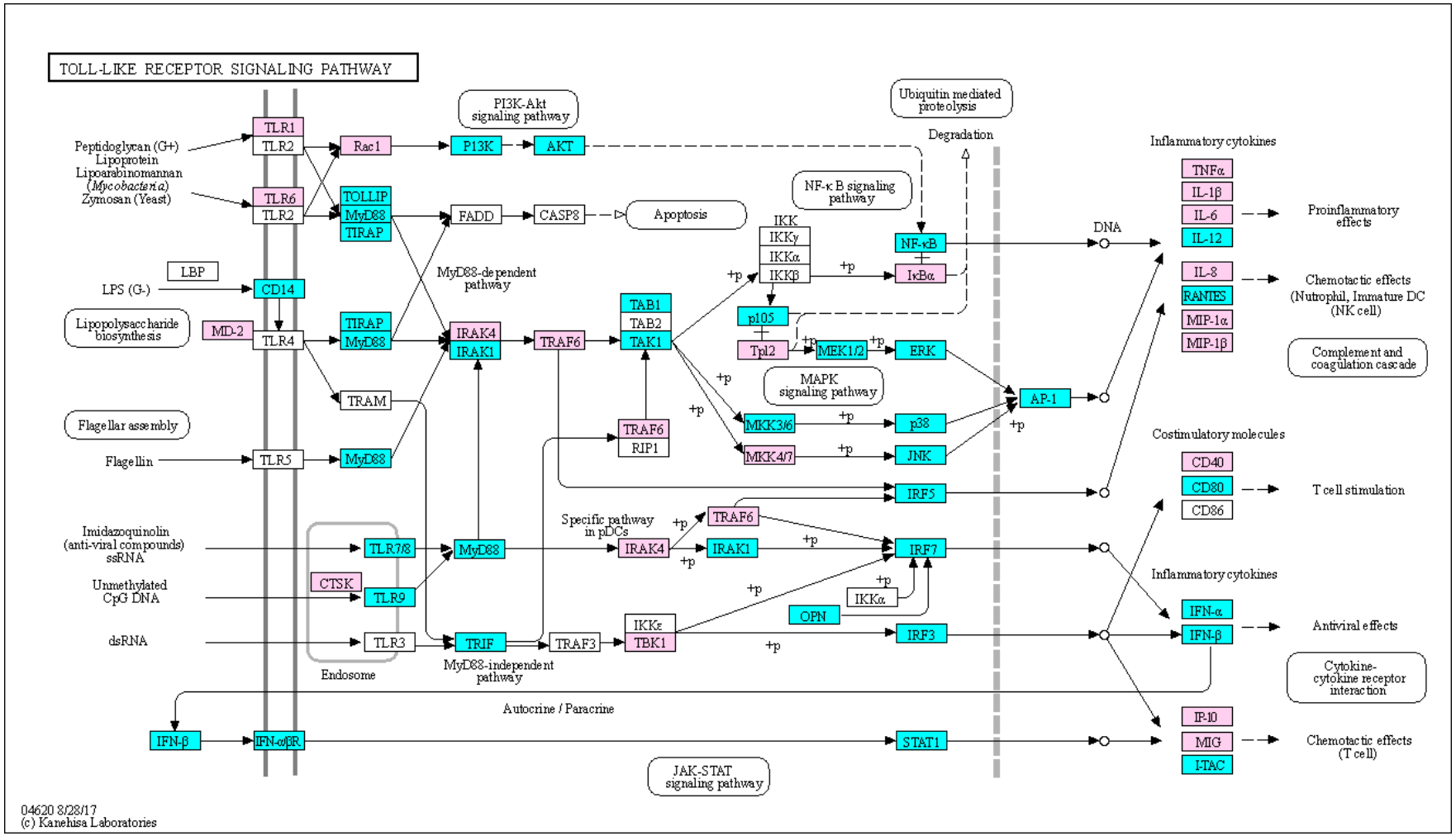


Fig. S5C. The TLR pathway during the *in vivo* attAHSV4 primary immune response (http://www.genome.jp/kegg/pathway.html). The blue genes are up-regulated and the pink genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

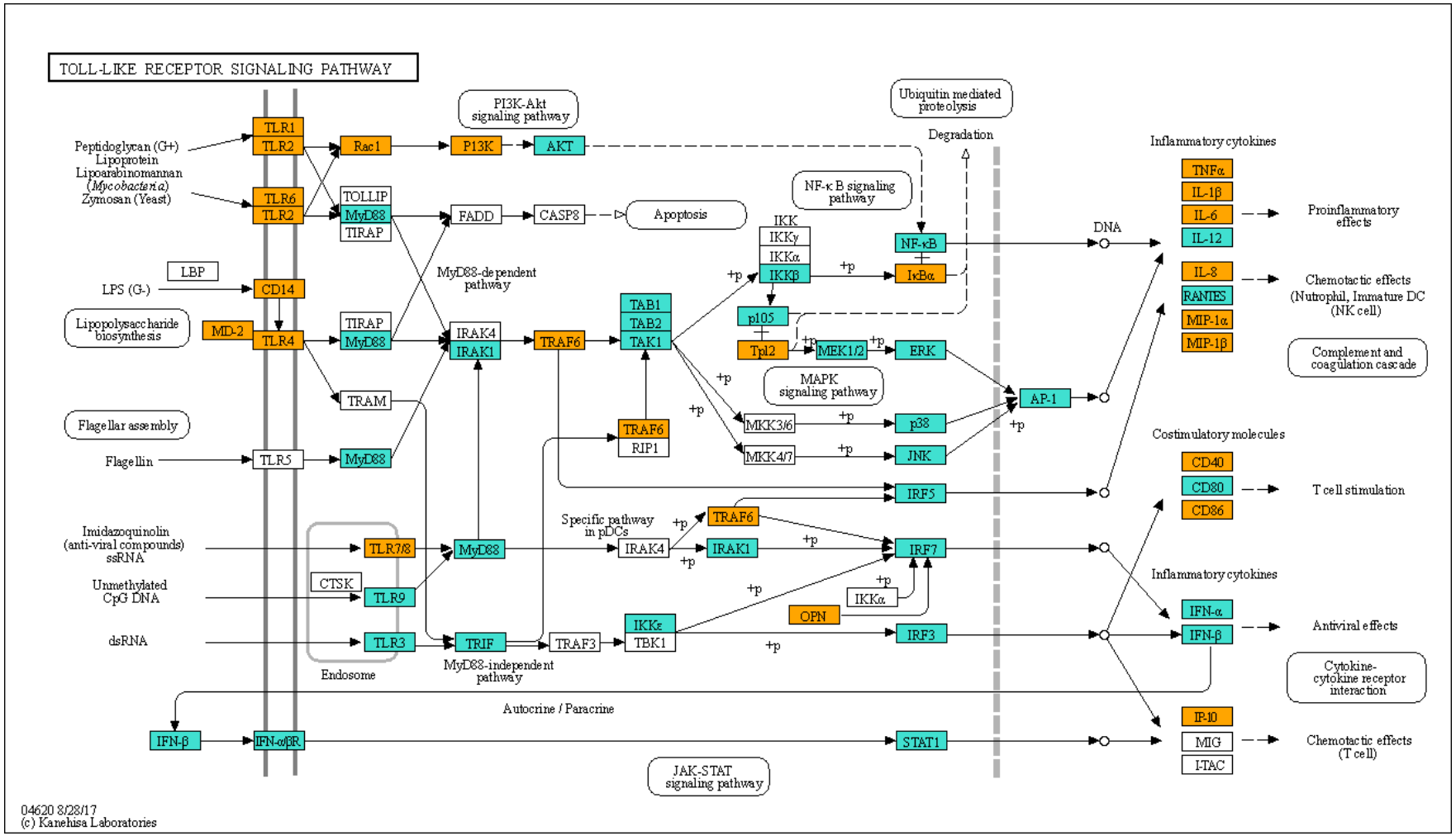


Fig. S5D. The TLR pathway during the *in vivo* attAHSV4 secondary immune response (http://www.genome.jp/kegg/pathway.html). The turquoise genes are up-regulated and the orange genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

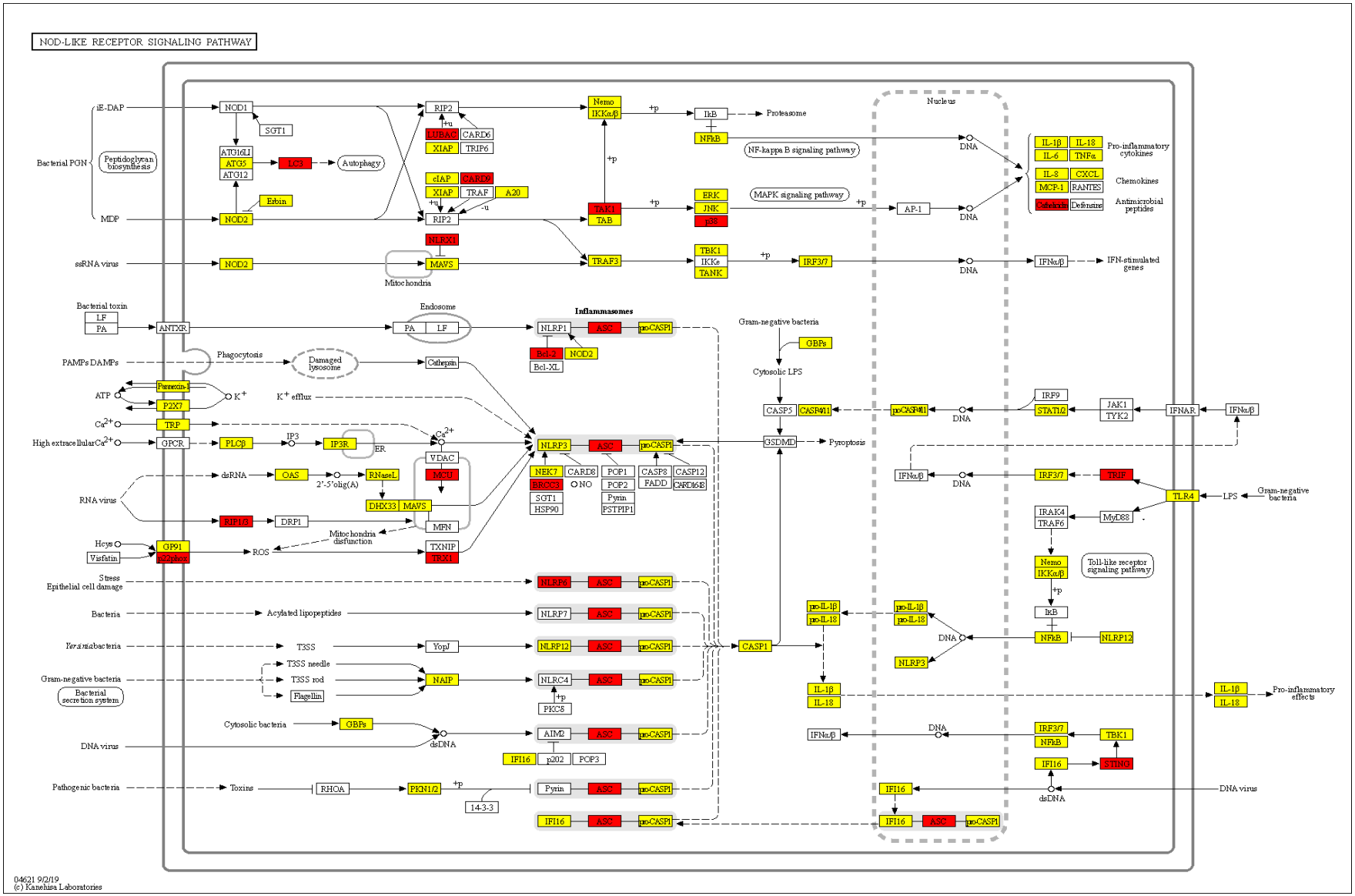


Fig. S6A. The NLR pathway during the *in vitro* virAHSV4 primary immune response (http://www.genome.jp/kegg/pathway.html). The yellow genes are up-regulated and the red genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

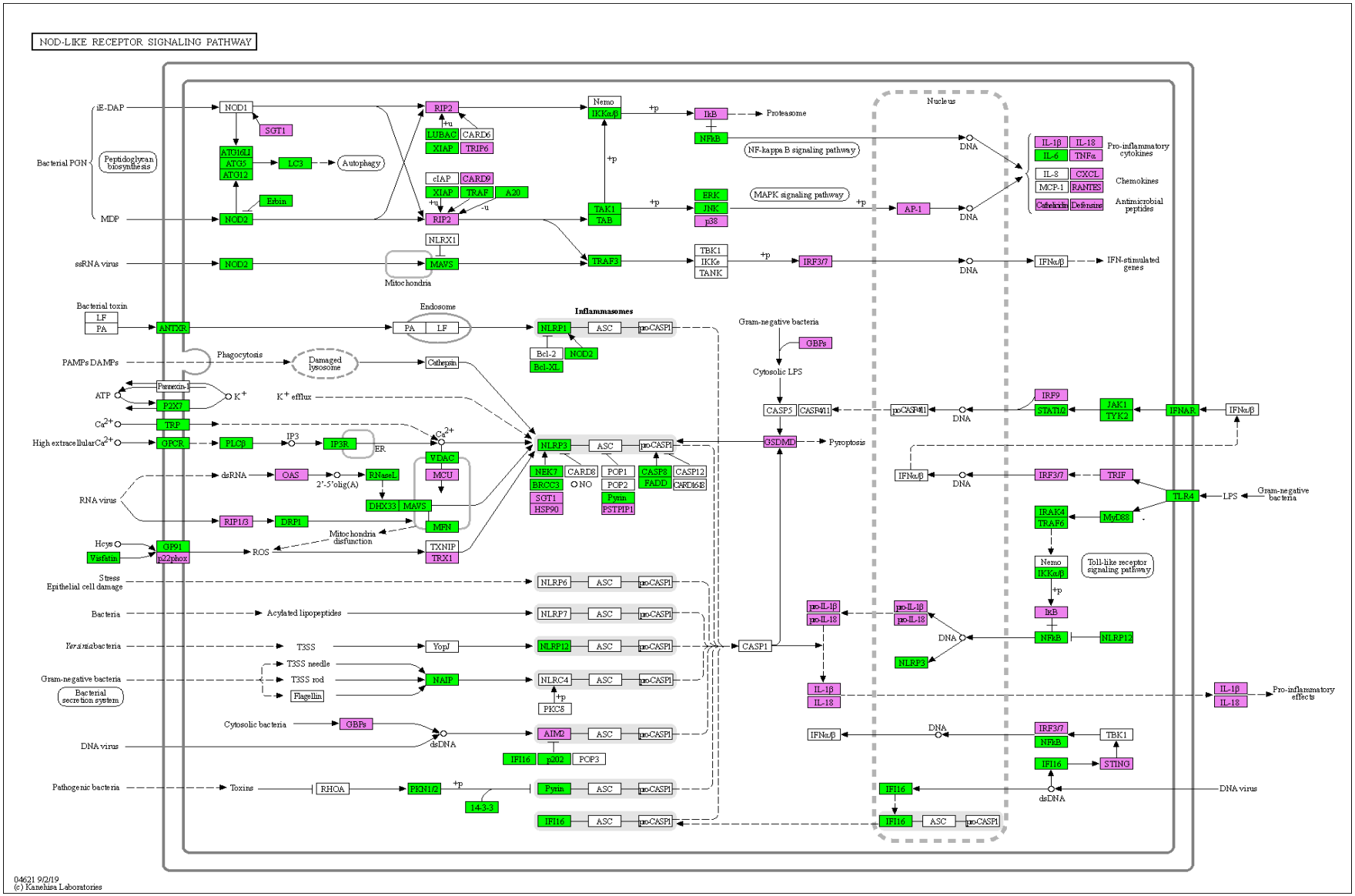


Fig. S6B. The NLR pathway during the *in vitro* virAHSV4 secondary immune response (http://www.genome.jp/kegg/pathway.html). The green genes are up-regulated and the purple genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

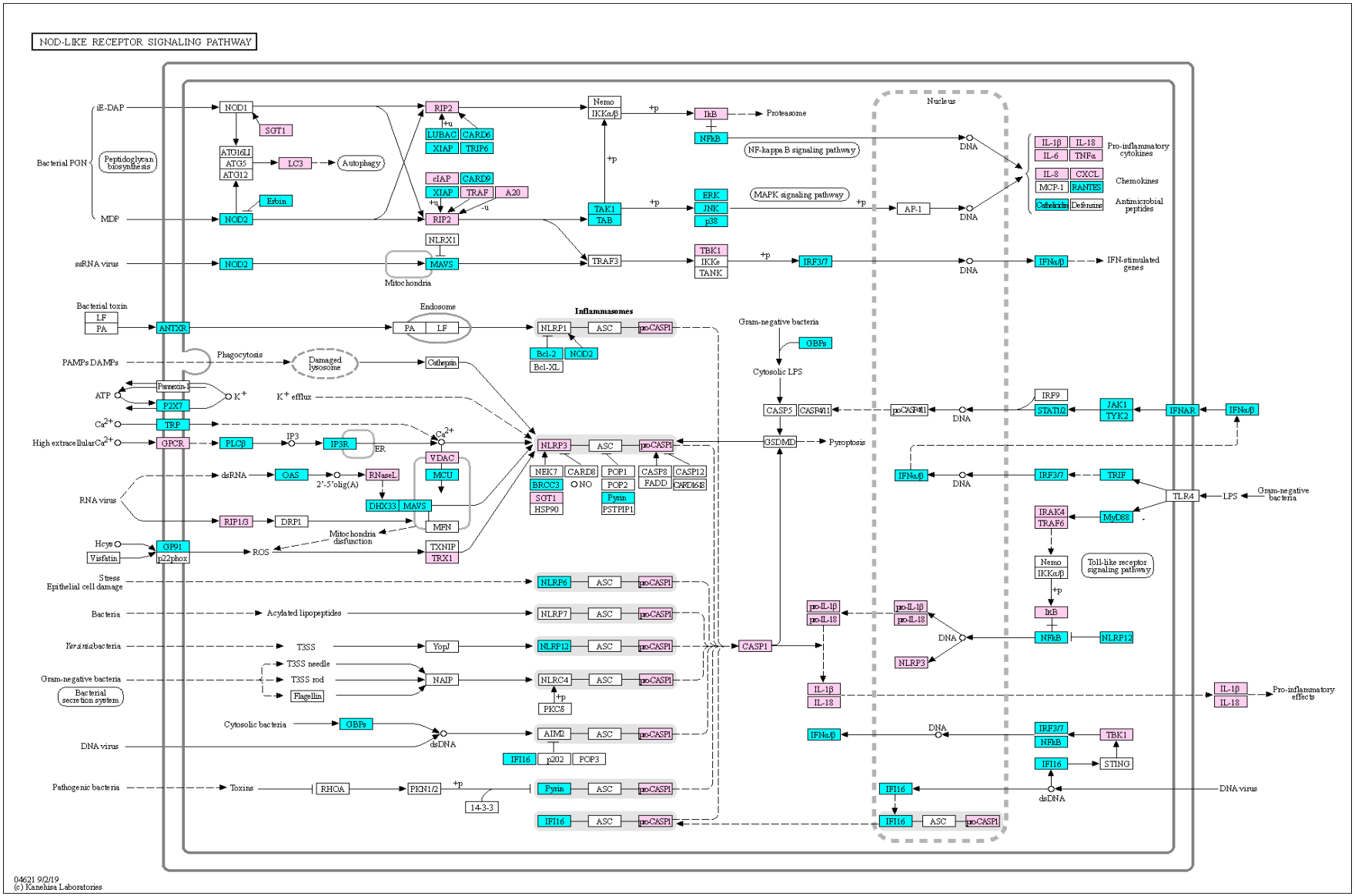


Fig. S6C. The NLR pathway during the *in vivo* attAHSV4 primary immune response (http://www.genome.jp/kegg/pathway.html). The blue genes are up-regulated and the pink genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

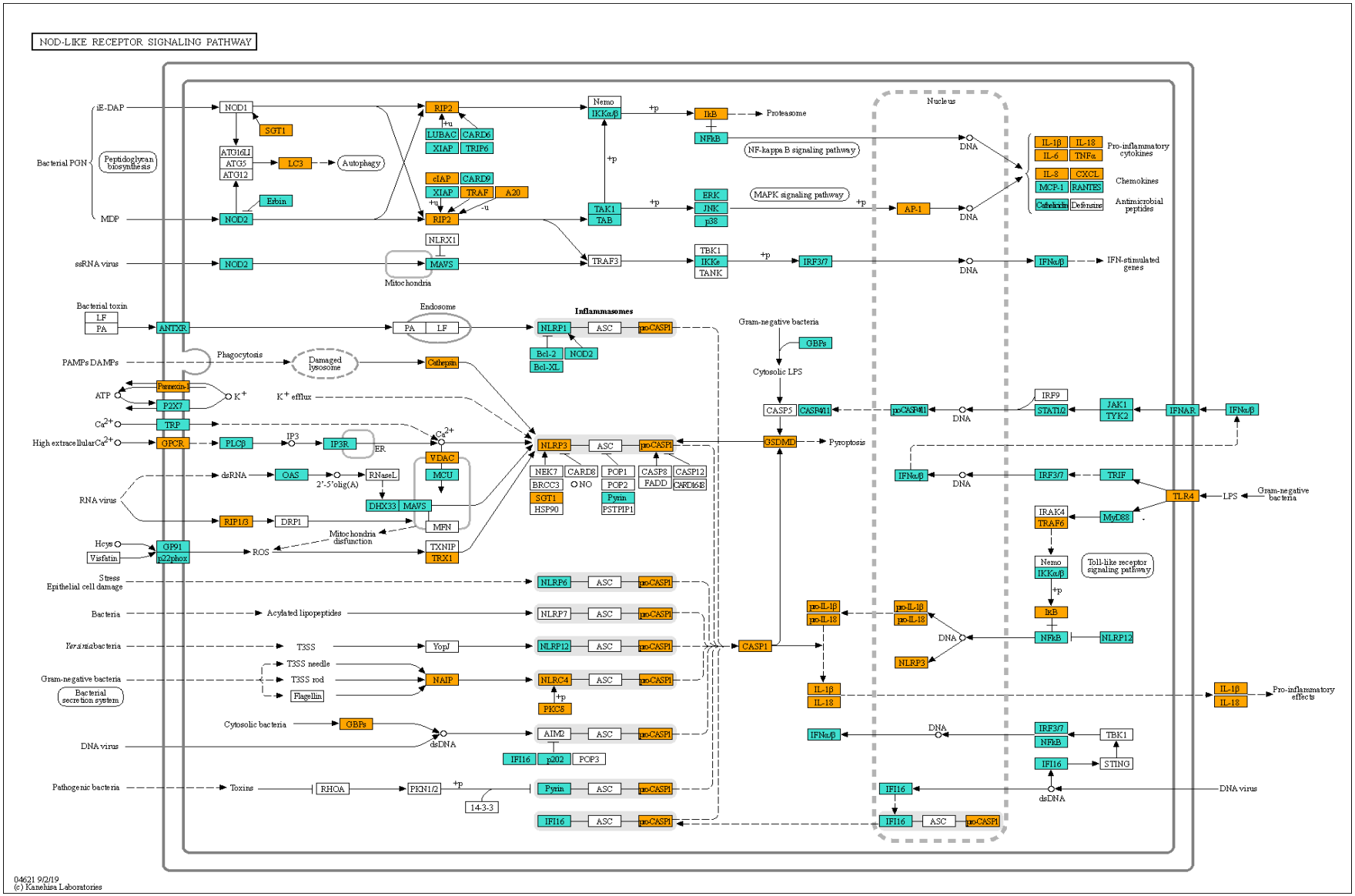


Fig. S6D. The NLR pathway during the *in vivo* attAHSV4 secondary immune response (http://www.genome.jp/kegg/pathway.html). The turquoise genes are up-regulated and the orange genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

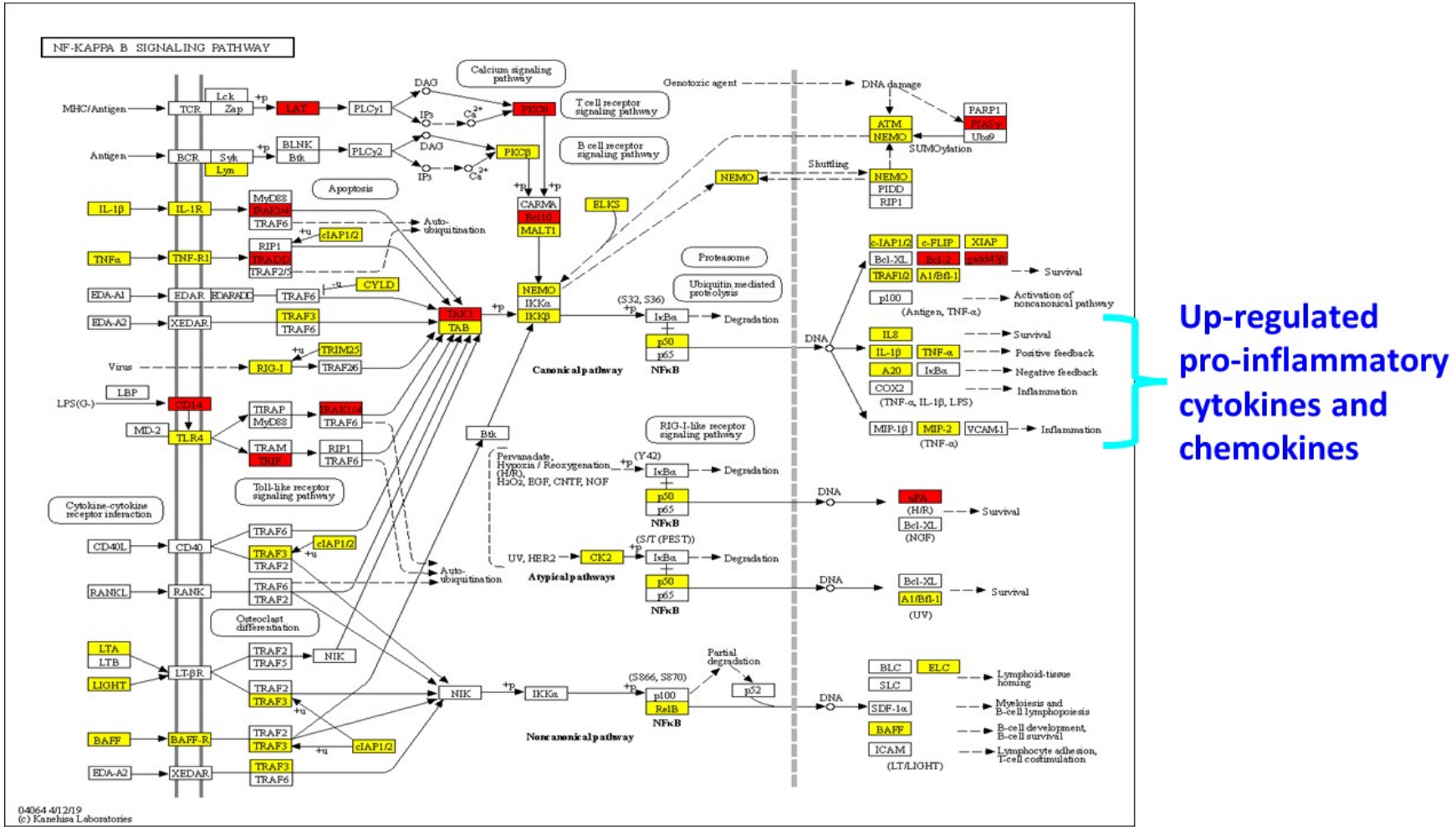


Fig. S7A. The NF-κB signalling pathway during the *in vitro* virAHSV4 primary immune response (http://www.genome.jp/kegg/pathway.html). The yellow genes are up-regulated and the red genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

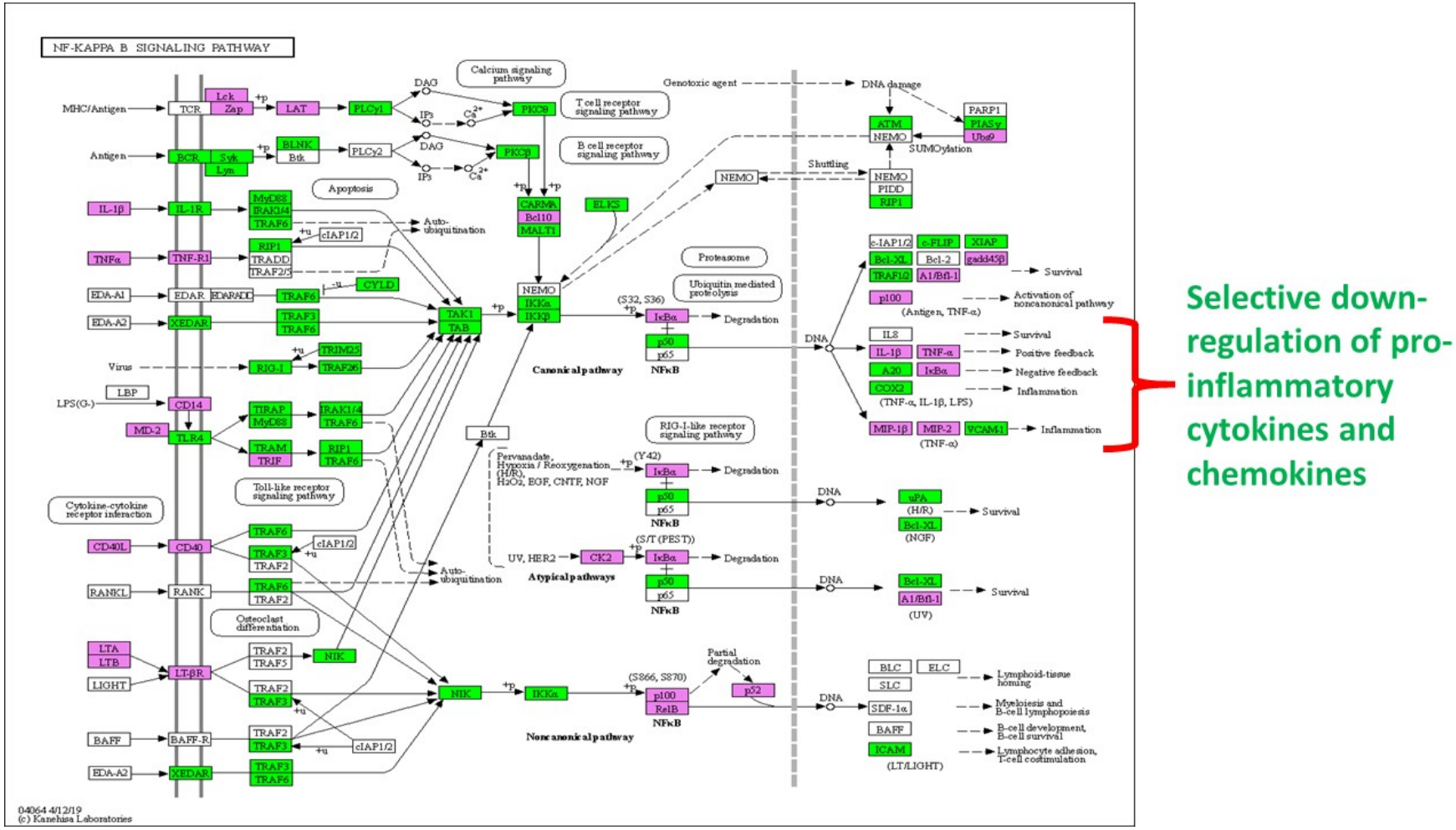
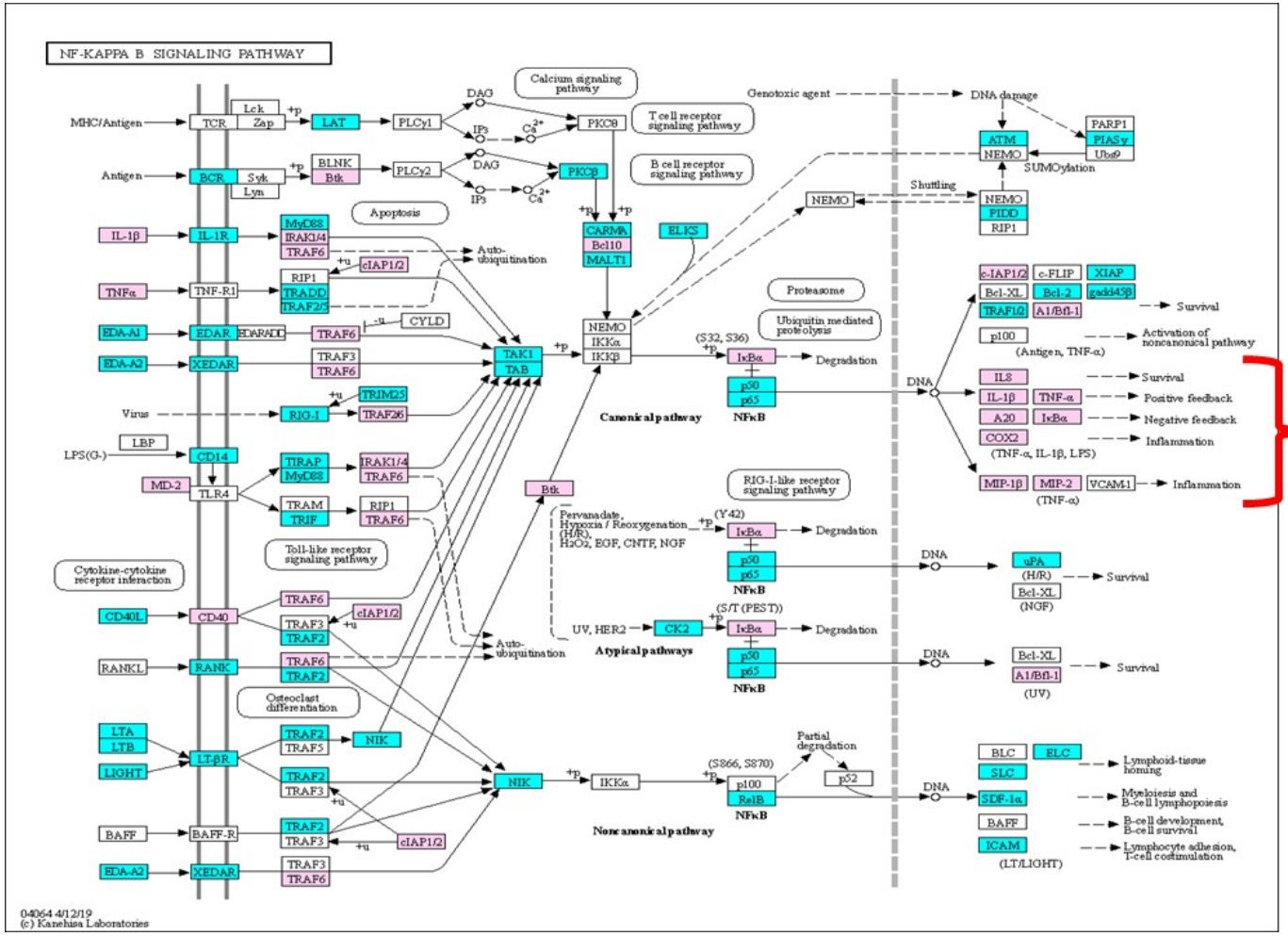


Fig. S7B. The NF-κB signalling pathway during the *in vitro* virAHSV4 secondary immune response (http://www.genome.jp/kegg/pathway.html). The green genes are up-regulated and the purple genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.



Selective down-regulation of pro-inflammatory cytokines and chemokines

Fig. S7C. The NF-κB signalling pathway during the *in vivo* attAHSV4 primary immune response (http://www.genome.jp/kegg/pathway.html). The blue genes are up-regulated and the pink genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

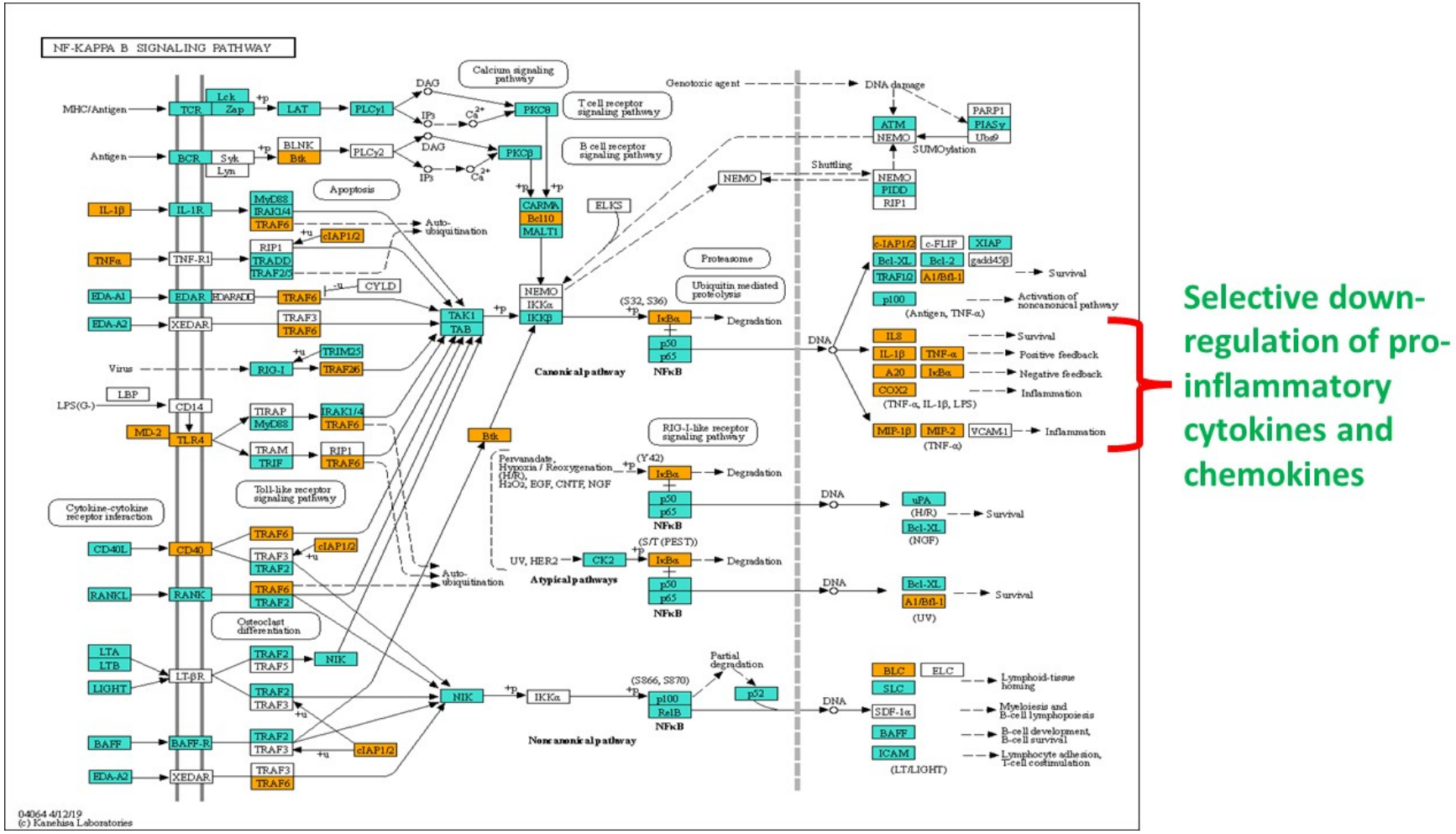


Fig. S7D. The NF-κB signalling pathway during the *in vivo* attAHSV4 secondary immune response (http://www.genome.jp/kegg/pathway.html). The turquoise genes are up-regulated and the orange genes are down-regulated. Only the significantly up-regulated and down-regulated genes are shown in colours in the figure.

Table S4. The up-regulated (black, positive) and down-regulated (red, negative) interferon-stimulated genes (ISGs) identified by the Interferome database v2.01 (www.interferome.org) with a fold change (normalized values) of ≥ 1.2 and *P*-values ≤ 0.05 (significant) during the virAHSV4 (vAHSV4) primary (prim) and secondary (sec) immune responses and attAHSV4 (aAHSV4) the primary (prim) and secondary (sec) immune responses. The functions of the ISGs are shown in table.

ISGs	vAHSV4		aAHSV4		Gene functions (www.string-db.org/, www.uniprot.org/ and www.genecards.org/)
	prim	sec	prim	sec	
ACP2	-1,2				Hydrolyzes orthophosphoric monoesters to alcohol and phosphate
ADAR	1,3	3,6	1,4	1,5	Catalyzes the hydrolytic deamination of A to I in dsRNA (A-to-I RNA editing)
AIM2		-1,5			Cytosolic dsDNA sensor and inflammasome formation
ANAPC5	1,2				Component of APC/C involved in ubiquitination and interaction with transcription coactivators
ARAP3		1,5	2,1	2,3	Modulates actin cytoskeleton remodeling
ARRB1		15,6	1,8	1,6	Mediates both receptor desensitization and resensitization processes
C2		1,4	1,4		Component of the classical complement pathway
CACNA1C			1,8	2,2	Mediates influx of calcium ions into cells upon membrane polarization
CANX		1,4	1,2		Assists with folding and assembly of newly synthesized glycoproteins in the ER
CASP1	1,2		-1,3	-2,2	Inflammatory caspase
CASP10	1,4	9,1	1,2	1,4	Apoptotic initiator caspase
CD117				1,2	Surface receptor for KITLG/SCF
CD14	-1,2	-1,7	1,5		Coreceptor for LPS
CD274	1,8	2,3	1,3	1,8	Binds to PD1 to promote Treg functions or inhibit effector T cell responses
CD38	1,5	1,5	1,7	1,7	Synthesizes cADPR and NAADP (second messengers)
CD68	-1,3			-1,5	Involved in phagocytic activities of tissue macrophages
CD74	1,3	-1,2			Plays a role in MHC class II antigen processing
CD80		1,6	1,4	1,4	Binds to CD28 to induce naïve or effector T cell proliferation and cytokine production
CD9		-1,3	1,3	1,5	Involved in platelet activation and aggregation
CFB		1,6			Component of the alternative complement pathway
CFL2	-1,3	1,3	1,2		Involved with actin polymerization and depolymerization
CHMP5		1,2			Component of ESCRT-III involved in MVBs formation and sorting
CISH		-2,1	1,7	6,7	Negative regulator of cytokine signalling via JAK/STAT5. Inhibits STAT5 trans-activation
CLDN23			2,1	2,9	Involved in tight junction-specific obliteration of the intercellular space
COLEC12	-1,6		2,2	1,4	Mediates the recognition, internalization and degradation of oxLDL
CRLF2	1,3	-2,2	1,7	1,6	Receptor for TSLP
CTSC		-1,3		1,2	Functions as both an exopeptidase and endopeptidase. Activates serine proteases
CTSL	1,4	-1,5	2,5	2,3	Important for degradation of proteins in lysosomes

Table S4 continued. The up-regulated (black, positive) and down-regulated (red, negative) ISGs identified by the Interferome database v2.01 (www.interferome.org) with a fold change (normalized values) of ≥ 1.2 and *P*-values ≤ 0.05 (significant) during the virAHSV4 (vAHSV4) primary (prim) and secondary (sec) immune responses and attAHSV4 (aAHSV4) the primary (prim) and secondary (sec) immune responses. The functions of the ISGs are shown in table.

ISGs	vAHSV4		aAHSV4		Gene functions (www.string-db.org/, www.uniprot.org/ and www.genecards.org/)
	prim	sec	prim	sec	
CXCL1	1,2	-1,6	-3,3	-8,8	Chemotactic for neutrophils
CXCL2	2,4	-1,4	-2,4	-2,6	Chemotactic for neutrophils
CXCL3		-1,5	-2,4	-6,4	Chemotactic for neutrophils
CXCL8	2,1		-1,4	-3,8	Chemotactic for neutrophils. Neutrophil activation
CXCL9	3,5	3,1	-1,4		Chemotactic for activated T cells and NK cells
CXCL10	2,1		-3,8	-6,6	Chemotactic for T cells, monocytes and NK cells
CXCL11	3,1	23,5	2,1		Chemotactic for activated T cells and NK cells
CXCL13			1,7	1,5	Chemotactic for B cells
CCL2	1,2			2,3	Chemotactic for monocytes and basophils
CCL7		-1,3	8,9	6,7	Chemotactic for monocytes and eosinophils
CCL8	1,7	1,4	-2,4	-5,2	Chemotactic for monocytes, lymphocytes, basophils and eosinophils
CCL13				-1,2	Chemotactic for monocytes, lymphocytes, basophils and eosinophils
CCL19	4,7		1,7		Lymphocyte homing to secondary lymphoid organs
CCL20	9,8	-3,9	-8,7	-15,9	Chemotactic for lymphocytes, dendritic cells and neutrophils
CCL22		3,4	14,2	10,5	Chemotactic for activated T cells, monocytes, dendritic cells and NK cells
CCL24		-1,2	5,1	5,4	Chemotactic for resting T cells and eosinophils
CCR1		2,2	2,9	1,9	Receptor for CCL3, CCL5, CCL7 and CCL23
CCR2	1,3	2,1	1,3		Receptor for CCL2, CCL7 and CCL13
DAB2		1,4	1,2		Adapter protein required for clathrin-mediated endocytosis of selected cargo proteins
DAPP1		2,5			Regulates B cell antigen receptor signaling downstream of PI3K
DDX58	1,2	1,3	1,3	1,3	Cytosolic dsRNA sensor (RIG-I)
DHX58		1,5	-1,2		Negative or positive regulator of RIG-I and MDA5
DUSP5		-1,2	-1,4	-3,3	Negative regulator of MAPKs (particular ERK1)
EDN1			1,9	3,1	A potent vasoconstrictor
EHD4	1,4	1,5	1,7	1,5	Involved in early endocytic membrane fusion and membrane trafficking of recycling endosomes
EIF2AK2	1,8	6,3			Phosphorylates eIF2α to inhibit global mRNA translation and allow preferential translation of selected genes
FAS		1,6		1,2	Receptor for FASL (TNFSF6)
FASL		2,7			Binds to FAS to induce the extrinsic apoptosis pathway

Table S4 continued. The up-regulated (black, positive) and down-regulated (red, negative) ISGs identified by the Interferome database v2.01 (www.interferome.org) with a fold change (normalized values) of ≥ 1.2 and *P*-values ≤ 0.05 (significant) during the virAHSV4 (vAHSV4) primary (prim) and secondary (sec) immune responses and attAHSV4 (aAHSV4) the primary (prim) and secondary (sec) immune responses. The functions of the ISGs are shown in table.

ISGs	vAHSV4		aAHSV4		Gene functions (www.string-db.org/, www.uniprot.org/ and www.genecards.org/)
	prim	sec	prim	sec	
FBXO6		2,6	2,3	1,7	Involved in ERAD and the DNA damage response
FCAR	-1,6	2,1		1,3	Receptor for the Fc region of IgA
FCER1A	1,6	1,2		-1,4	The high affinity receptor for the Fc region of IgE
FOS	-1,4	1,9	2,2	1,2	Involved in cell proliferation, differentiation, signal transduction and apoptosis
GADD45B	-1,3	-1,7		-1,8	Mediates the activation of MAPKs (p38 and JNK pathways) in response to stress
GBP1	2,5		1,3		Promotes oxidative killing, deliver antimicrobial peptides to autophagolysosomes and exhibits antiviral activity
GBP2	2	-1,4		-1,3	Promotes oxidative killing, deliver antimicrobial peptides to autophagolysosomes and exhibits antiviral activity
GBP4	1,8		1,3	1,2	Antimicrobial activity
GBP5	2,2		1,2		Promotes NLRP3 inflammasome assembly
GNB4	1,5	2,3	2,1	1,5	Involved in various transmembrane signalling systems
GSN			1,3		Functions in both assembly and disassembly of actin filaments
GUCY1A3		6,1	1,7		Alpha subunit of the guanylate cyclase enzyme, which is activated by nitric oxide
HIST2H2AC	-1,6	-4,2	1,7	1,6	Part of nucleosome that compact DNA into chromatin which limits its accessibility to the cellular machineries
HSPB1	-1,3	-2,6		-1,3	Promotes the correct folding of proteins
IFI16	1,4	3,4	1,2	1,3	Cytosolic dsDNA sensor
IFIH1	1,5				Cytosolic dsRNA sensor (MDA5)
IRF7	1,5	-1,9	1,3	1,2	Transcription factor of type I and type III IFNs
IRF9		-1,5			Transcription factor downstream of type I and type III IFN signalling pathways
IL1R1	1,7	2,1	1,4	1,3	Receptor for IL-1α and IL-1β
IL2RA	-1,2	1,4	1,9	2,1	Component of the IL-2R complex used by IL-2
IL12RB2		2,1	1,7	1,8	Component of the IL-12R complex used by IL-12
IL15RA	2,1	-1,6	1,2		Component of the IL-15R complex used by IL-15
ITGA2		3,8	1,5	1,7	Receptor for collagens and other related proteins
ISG15		-3,1			Antiviral functions mediated via ISGylation to target proteins or as an unconjugated protein
JAK2	1,5	2,1		-1,2	Mediates cytokine signalling by associating with type I or type II receptors
LAMP3	1,2	2,6	1,3	1,4	Present in lysosomes of mature dendritic cells
LGMN			1,2	1,2	Involved in protein processing for MHC class II antigen presentation in the lysosomal/endosomal system
LMNB1	1,4	1,6			Component of the nuclear lamina

Table S4 continued. The up-regulated (black, positive) and down-regulated (red, negative) ISGs identified by the Interferome database v2.01 (www.interferome.org) with a fold change (normalized values) of ≥ 1.2 and *P*-values ≤ 0.05 (significant) during the virAHSV4 (vAHSV4) primary (prim) and secondary (sec) immune responses and attAHSV4 (aAHSV4) the primary (prim) and secondary (sec) immune responses. The functions of the ISGs are shown in table.

ISGs	vAHSV4		aAHSV4		Gene functions (www.string-db.org/, www.uniprot.org/ and www.genecards.org/)
	prim	sec	prim	sec	
MB21D1		-2,1	-1,4	-1,9	Cytosolic dsDNA sensor (CGAS)
MCL1		1,4	1,5	1,7	Isoform 1 inhibits apoptosis and other isoforms promote apoptosis
MEFV		2,3	1,7	1,8	Autophagy receptor for the degradation of some inflammasome components (e.g. CASP1, NLRP1 and NLRP3)
MMP9		-1,2	1,4		Involved in local proteolysis of the extracellular matrix and in leukocyte migration
MRC1	1,4	1,8	1,3		Mediates the endocytosis of glycoproteins by macrophages
MSR1				-1,5	Mediates the endocytosis of many macromolecules
MYC	-1,2	-1,5	-3,4	-1,8	Transcription factor of growth-related genes
MYD88		1,3	1,4	1,3	Adapter protein in the TLR and IL-1R signalling pathways
OAS1		-1,5		1,4	Antiviral, activates RNase L to subsequently cleave cellular and viral RNA
OAS2	1,6		1,7	1,3	Antiviral, activates RNase L to subsequently cleave cellular and viral RNA
OAS3	1,4	2,7	1,8	1,7	Antiviral, activates RNase L to subsequently cleave cellular and viral RNA
PDCD1LG2		-1,2	-1,2	-1,4	Binds to PD1 to promote Treg functions or inhibit effector T cell responses
PMAIP1	-1,4	2,2			Promotes the activation of caspases and apoptosis
PML		1,9	1,4	1,6	Involved in tumor suppression, apoptosis, DNA damage response and viral defense mechanisms
PRF1		-1,3	1,6	1,3	Form pores on the plasma membrane of target cells. Involved in the perforin/granzyme apoptosis pathway
PRKD2			1,2	1,3	Converts transient DAG signals into prolonged physiological effects downstream of PKC
PRLR			1,7	1,9	Receptor for prolactin
PSMB8		-2,2	-3,8	-1,2	Immunoproteasome subunit involved in antigen processing to generate class I binding peptides
PSMB9	1,3	-1,6	-1,3	-1,3	Immunoproteasome subunit involved in antigen processing to generate class I binding peptides
PTGS1			1,3	2,4	Converts arachidonate to prostaglandin H2 (PGH2)
RASGRP3	1,3	2,2	1,4	1,5	Guanine nucleotide exchange factor for RAS and RAP1
RBCK1				1,2	Part of the LUBAC complex that is involved in the activation of NF-κB downstream of NOD1 and NOD2
RGL1		2,4	-1,6	-1,2	Guanine nucleotide exchange factor
RIPK2		-1,2	-1,2	-1,2	Adapter protein in the NOD1 and NOD2 signalling pathways
SCIN		3,2	1,6	1,5	Regulatory role in exocytosis
SERPINE1	1,5	3,1			Negative regulator of fibrinolysis (breakdown of blood clots) by binding to tPA and uPA
SERPING1	3,3		1,9	1,8	Negative regulator of the classical complement pathway by binding to C1r or C1s
SIGLEC1	1,3	1,7	1,8	1,3	Mediates clathrin dependent endocytosis

Table S4 continued. The up-regulated (black, positive) and down-regulated (red, negative) ISGs identified by the Interferome database v2.01 (www.interferome.org) with a fold change (normalized values) of ≥ 1.2 and *P*-values ≤ 0.05 (significant) during the virAHSV4 (vAHSV4) primary (prim) and secondary (sec) immune responses and attAHSV4 (aAHSV4) the primary (prim) and secondary (sec) immune responses. The functions of the ISGs are shown in table.

ISGs	vAHSV4		aAHSV4		Gene functions (www.string-db.org/, www.uniprot.org/ and www.genecards.org/)
	prim	sec	prim	sec	
SLC11A1	-1,3	-1,3	1,3	1,5	Involved in iron metabolism and host resistance to some pathogens
SMAD6		-3,6	-1,6	-1,4	Mediates TGF-β and BMP anti-inflammatory activities
SOCS1	-1,3	3,7		1,5	Negative regulator of cytokine signalling via JAK/STAT3. Binds to JAKs that inhibits their kinase activity
SOCS3	1,2	-1,4	2,7		Negative regulator of cytokine signalling via JAK2. Binds to JAK2 that inhibits its kinase activity
SORT1		4,6	1,4	1,6	Functions as a sorting receptor in the Golgi compartment and as a clearance receptor on the cell surface
STAT1	1,9	1,3	1,3	1,3	Mediates IFN (all types) and many other cytokine signalling
STAT2	1,7	1,6	1,2	1,2	Mediates type I and type III IFN signalling
TAP1	1,2	-1,2			Involved in the transport of antigens from the cytoplasm to the ER for association with MHC class I molecules
TAP2		-1,5			Involved in the transport of antigens from the cytoplasm to the ER for association with MHC class I molecules
TBXAS1	-1,5			-2,3	Catalyzes the conversion of prostglandin H2 to thromboxane A2
TFPI			2,7	2,4	Has an antithrombotic function and also associate with lipoproteins in plasma
THBD	1,4	1,5	11,4	6,3	Receptor that binds thrombin and activates downstream targets that reduce the amount of thrombin generated
TLR3	1,5			1,3	dsRNA sensor inside intracellular compartments (e.g. endosomes)
TLR4	1,7	1,9		-1,4	Expressed on the cell surface and senses many PAMPs and DAMPs
TLR7	1,5	2,7	1,2	-1,2	ssRNA sensor inside intracellular compartments (e.g. endosomes)
TNFSF10	1,5	1,6	1,4	1,3	Binds to TNFRSF10B (TRAILR) to induce the extrinsic apoptosis pathway
TNFSF13B	1,8			1,6	Involved in B cell activation, proliferation and differentiation
TNFSF18		4,8	2,3		Modulates T cell survival in peripheral tissues
TRIM25	1,5	8,1	1,7	1,8	Antiviral by mediating the K63-linked polyubiquitination of the CARD-like region of RIG-I, required for inducing signal transduction
UBE2S	-1,2	-3,5			Enhances the proteasomal degradation of APC/C substrates and mitotic exit
UBE2L6	-1,4	1,4	1,2		Catalyzes the attachment of ubiquitin or ISG15 to proteins
UBQLNL			2,9	2,7	Ubiquitin-like proteins (ubiquilin) associate with both proteasomes and ubiquitin ligases
VSIG4		6,2	-1,2	-2,1	Phagocytic receptor and negative regulator of T cell proliferation and IL-2 production
ZBP1		-2,1			Cytosolic dsDNA sensor