Supplementary Material

Predicting RTS,S-vaccine-mediated protection from transcriptomes in a malaria-challenge clinical trial

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1 N-PLS-DA METHODOLOGICAL DETAILS

The transcriptome data set was represented as a multiway data set (subject $\times$ probe set [gene] $\times$ time). In the N-PLS-DA, the data were transformed into a series of components (similar to principal component analysis [PCA] (Jackson, 1991; Jolliffe, 2002)) where the first component encapsulates the most variation in the total data set that correlates with controlled human malaria infection (CHMI) outcome, and the subsequent components encapsulate progressively less variation. Together, these factors describe variations in the data set which were encapsulated in predictive mathematical models. Hence the kinetics of the changes induced by the vaccination were captured explicitly in each of the mathematical models.

Each mathematical model was generated through the iterative selection of probe sets and the selection of the minimal number of components required from the transformed data set to achieve optimal model performance. Model performance was evaluated by a double cross validation (DCV) approach. DCV resulted in 10 collections (ensembles) of 10 models of correlation, yielding a total of 100 individual models, with performance statistics. The difference in model performance was identified using the DQ$^2$ statistic. This statistic is based on a least-squares method for analyzing the difference between prediction and CHMI outcome (Westerhuis et al., 2008) and was more discriminatory than using the fraction of correctly classified outcomes. The consideration of two or three components was typically sufficient for optimal prediction performance. Each model typically consisted of data from 2-40 probe sets and optimal performance was typically observed after several rounds of probe set selection. Predictive performance was validated using label permutation. The worst, average and best model performance measures in a given ensemble of models were always higher than the most frequent performance measure generated by label.

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2 SUPPLEMENTARY TABLE 1

Genes/probe sets selected by the data-driven modeling

| Gene            | Probe set ID    | Frequency of use in models | Cluster |
|-----------------|-----------------|----------------------------|---------|
| ACTG1           | 224585_x_at     | 1                          | D       |
| ATL2            | 222700_at       | 2                          | A       |
| ATP5I           | 209492_x_at     | 4                          | D       |
| ATP6V0C<sup>a,b</sup> | 36994_at     | 20                         | D       |
| ATP6V0C<sup>a</sup>   | 200954_at       | 1                          | D       |
| AURKAIP1        | 225555_x_at     | 8                          | D       |
| B3GALT6         | 1553959_a_at    | 1                          | D       |
| BAG1            | 202387_at       | 29                         | B       |
| BAG5            | 202984_s_at     | 3                          | D       |
| C11orf73        | 219979_s_at     | 1                          | C       |
| C14orf64        | 1559097_at      | 3                          | A       |
| CCDC59          | 222792_s_at     | 2                          | D       |
| CCT6P1          | 227301_at       | 1                          | A       |
| CD302           | 203799_at       | 1                          | C       |
| CNPY4           | 227313_at       | 2                          | A       |
| COMMD1          | 226024_at       | 1                          | D       |
| CSNK1G2         | 202573_at       | 10                         | D       |
| DENND4C         | 205684_s_at     | 1                          | A       |
| DPP3            | 232510_s_at     | 1                          | D       |
| DVL1            | 203230_at       | 1                          | C       |
| EDEM2           | 78047_s_at      | 5                          | D       |
| EIF4E2          | 213571_s_at     | 11                         | B       |
| EMC10           | 224727_at       | 21                         | B       |
| EXOSC6          | 227696_at       | 3                          | A       |
| FAM21A/B /C     | 212370_x_at     | 4                          | B       |
| FAM21A/B /C /D  | 214946_x_at     | 1                          | B       |
| FAM53C          | 218023_s_at     | 1                          | B       |
| FBXO9           | 212991_at       | 30                         | A       |
| GADD45B         | 207574_s_at     | 9                          | B       |
| GLIPR1          | 226142_at       | 1                          | D       |
| GTF2E2          | 202680_at       | 97                         | B       |
| GTF2F1          | 202355_s_at     | 45                         | D       |
| HECTD1          | 224481_s_at     | 2                          | A       |
## Supplementary Material

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| Gene       | Probe set ID       | Frequency of use in models | Cluster |
|------------|--------------------|-----------------------------|---------|
| HLA-A<sup>a,b</sup> | 215313_x_at      | 71                          | B       |
| HLA-A<sup>a</sup>    | 213932_x_at      | 1                           | B       |
| HLA-B       | 209140_x_at      | 2                           | B       |
| HLA-C       | 208812_x_at      | 1                           | B       |
| HLA-DMB     | 203932_at        | 1                           | B       |
| HSP90B1     | 200598_s_at      | 2                           | B       |
| ICAM2       | 213620_s_at      | 1                           | D       |
| IDH3G       | 202471_s_at      | 6                           | B       |
| IL23A       | 217328_at        | 4                           | A       |
| IPW         | 241834_at        | 1                           | A       |
| IRF7        | 208436_s_at      | 1                           | B       |
| KLHL6       | 1560396_at       | 1                           | B       |
| LMLN        | 244881_at        | 3                           | A       |
| LRPAP1      | 201186_at        | 11                          | D       |
| LLRRC14     | 32062_at         | 1                           | D       |
| LSMEM1      | 239203_at        | 2                           | C       |
| LYRM2       | 227712_at        | 6                           | D       |
| MRFAP1      | 226091_s_at      | 1                           | C       |
| MT1F        | 217165_x_at      | 2                           | B       |
| MT2A        | 212185_x_at      | 1                           | B       |
| MYBBP1A     | 219098_at        | 1                           | D       |
| MYD88       | 209124_at        | 32                          | B       |
| NAP1L5      | 228062_at        | 1                           | A       |
| NAPRT1      | 226707_at        | 1                           | B       |
| NCAPH2      | 40640_at         | 13                          | B       |
| NCBP2-AS2   | 225657_at        | 9                           | D       |
| NCF1C       | 214084_x_at      | 1                           | B       |
| NOB1        | 223018_at        | 57                          | D       |
| NSD1        | 219084_at        | 2                           | B       |
| NUCKS1      | 229353_s_at      | 1                           | D       |
| NUDT14      | 231914_at        | 2                           | D       |
| OR2A9P      | 222290_at        | 10                          | A       |
| ORC2        | 204853_at        | 11                          | A       |
| PDCD4       | 212593_s_at      | 1                           | A       |
| PDZK1       | 205380_at        | 1                           | A       |
| PLA2G12A    | 242323_at        | 2                           | A       |
| PLIN2       | 209122_at        | 1                           | D       |
| Gene            | Probe set ID   | Frequency of use in models | Cluster |
|-----------------|----------------|----------------------------|---------|
| PMF1            | 202337_at      | 2                          | D       |
| PML             | 211012_s_at    | 8                          | B       |
| POLE4           | 1553587_a_at   | 1                          | B       |
| PTPN6           | 206687_s_at    | 1                          | B       |
| PUS7L           | 229751_s_at    | 3                          | A       |
| RAD23A          | 201046_s_at    | 1                          | D       |
| RAPH1           | 225189_s_at    | 1                          | A       |
| RBBP6           | 227635_at      | 5                          | B       |
| RHBD2F2         | 219202_at      | 1                          | B       |
| RIC8A           | 221647_s_at    | 2                          | D       |
| RMND5A          | 212482_at      | 4                          | A       |
| RNASEH2C        | 226453_at      | 2                          | B       |
| RNF31           | 231635_x_at    | 58                         | B       |
| RPF2            | 225866_at      | 1                          | D       |
| RPL23           | 200888_s_at    | 7                          | C       |
| RPS6KA3         | 203843_at      | 2                          | D       |
| RRAS            | 212647_at      | 3                          | D       |
| SCO2            | 205241_at      | 8                          | B       |
| SELPLG          | 209879_at      | 1                          | D       |
| SFXN3           | 217226_s_at    | 1                          | D       |
| SHARPIN         | 220973_s_at    | 5                          | D       |
| SP110<sup>a,b</sup> | 223980_s_at  | 3                          | B       |
| SP110<sup>a</sup> | 209762_x_at   | 2                          | B       |
| SRSF1           | 211784_s_at    | 1                          | C       |
| STK10           | 40420_at       | 1                          | D       |
| STUB1           | 217934_x_at    | 8                          | D       |
| SWT1            | 223548_at      | 1                          | A       |
| TAF1            | 227205_at      | 1                          | A       |
| TAF10           | 200055_at      | 1                          | D       |
| TAX1BP1         | 200977_s_at    | 1                          | B       |
| TBCB<sup>a,b</sup> | 211759_x_at  | 17                         | D       |
| TBCB<sup>a</sup> | 216194_s_at   | 1                          | D       |
| TNIP2           | 48531_at       | 1                          | B       |
| TRAPPc5         | 225870_s_at    | 1                          | D       |
| TRIM26          | 202702_at      | 4                          | B       |
| TRIM52          | 1568594_s_at   | 1                          | A       |
| TSTA3           | 36936_at       | 1                          | D       |
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| Gene     | Probe set ID | Frequency of use in models | Cluster |
|----------|--------------|----------------------------|---------|
| TTC33    | 231479_at    | 1                          | A       |
| UBB      | 200633_at    | 2                          | D       |
| UCP2\textsuperscript{a,b} | 208997_s_at | 8                          | D       |
| UCP2\textsuperscript{a}   | 208998_at    | 8                          | D       |
| USP40    | 225089_at    | 1                          | A       |
| WAS      | 38964_r_at   | 2                          | B       |
| WWP2     | 204022_at    | 6                          | B       |
| ZFP36    | 201531_at    | 1                          | B       |
| ZNF117   | 235408_x_at  | 9                          | C       |

\textsuperscript{a}For genes with more than one probe set, the data from the probe set that was most frequently represented in the models were considered as the representative data for that gene in the manuscript.
3 SUPPLEMENTARY TABLE 2

References to support the characterization of the immune-related genes selected by the data-driven modeling.

| Gene       | Cluster | Freq. | NF-κB | IFN-γ | Ubiq. | References                                                                 |
|------------|---------|-------|-------|-------|-------|----------------------------------------------------------------------------|
| FBXO9      | A       | 30    | +     | +     |       | (Cenciarelli et al., 1999; Winston et al., 1999; Yang et al., 2009)          |
| IL23A      | A       | 4     | +     | +     |       | (Carmody et al., 2007; Teng et al., 2010; Qian et al., 2011; Sheikh et al., 2011) |
| CNPY4      | A       | 2     |       |       |       | (Konno et al., 2006; Hart and Tapping, 2012)                                |
| PDCD4      | A       | 1     | +     | +     |       | (Hilliard et al., 2006; Yamanaka et al., 2009; Sheedy et al., 2010; Cohen and Prince, 2013) |
| HLA-A      | B       | 71    | +     | +     |       | (Hakem et al., 1991; Girdlestone et al., 1993; Min et al., 1996; Boehm et al., 1997; Girdlestone, 2000; Johnson, 2003; Shen et al., 2009; Othman et al., 2012; Norman et al., 2013; Sleiman et al., 2014) |
| RNF31      | B       | 58    | +     |       | +     | (Gerlach et al., 2011; Ikeda et al., 2011; Tokunaga et al., 2011; Stieglitz et al., 2013; Schaeffer et al., 2014) |
| MYD88      | B       | 32    | +     |       |       | (Adachi et al., 1998; Burns et al., 1998; Cohen, 2014)                      |
| BAG1       | B       | 29    | +     |       |       | (Tsukahara and Maru, 2010; Kettern et al., 2011)                           |
| NCAPH2     | B       | 13    |       |       |       | (Gosling et al., 2007; Gosling et al., 2008)                               |
| GADD45B    | B       | 9     | +     |       |       | (Takekawa and Saito, 1998; Papa et al., 2004; Liu et al., 2005; Thyss et al., 2005) |
| PML        | B       | 8     | +     | +     | +     | (Wu et al., 2003; Carracedo et al., 2011; Guo et al., 2014)                 |
| SCO2       | B       | 8     | +     |       |       | (Mauro et al., 2011)                                                      |
| WWP2       | B       | 6     | +     |       | +     | (Chen et al., 2009; Yang et al., 2013)                                     |
| SP110      | B       | 3     | +     |       |       | (Pan et al., 2005; Tosh et al., 2006; Abhimanyu et al., 2011; Cai et al., 2013; Fox et al., 2014) |
| HLA-B      | B       | 2     | +     |       |       | (Chamberlain et al., 1991; Hakem et al., 1991; Min et al., 1996; Boehm et al., 1997) |
| HSP90B1    | B       | 2     | +     |       | +     | (Randow and Seed, 2001; Yang et al., 2007; Liu et al., 2010; Staron et al., 2010) |
| MT1F       | B       | 2     | +     |       |       | (Vandeghinste et al., 2000; Huang et al., 2009)                            |
| RNASEH2C   | B       | 2     |       |       |       | (Rice et al., 2013; Crow et al., 2015)                                     |
| Gene       | Cluster | Freq. | NF-κB | IFN-γ | Ubq | References                                                                 |
|------------|---------|-------|-------|-------|-----|----------------------------------------------------------------------------|
| WAS        | B       | 2     | +     | +     |     | (Orange et al., 2002; Borg et al., 2004; Gismondi et al., 2004; Huang et al., 2005; Krzewski et al., 2006; Serrano-Pertierra et al., 2012; Ham et al., 2013; Catucci et al., 2014; Sarkar et al., 2014; 2015) |
| HLA-C      | B       | 1     | +\(^a\) | +     |     | (Boehm et al., 1997; Boss, 1997; Johnson, 2003; Shen et al., 2009; Othman et al., 2012) |
| HLA-DMB    | B       | 1     | +\(^a\) | +     |     | (Steimle et al., 1994; Boehm et al., 1997; Boss, 1997; Westerheide et al., 1997) |
| IRF7       | B       | 1     | +     | +     |     | (Kawai et al., 2004; Ogawa et al., 2005; Chau et al., 2008; Beattie et al., 2011) |
| KLHL6      | B       | 1     |       |       |     | (Gupta-Rossi et al., 2003; Kroll et al., 2005) |
| MT2A       | B       | 1     | +     | +     |     | (Giacconi et al., 2007; Jin et al., 2010; Toh et al., 2010; Pan et al., 2013) |
| PTPN6      | B       | 1     | +     |       |     | (Tsui et al., 2006; Orr et al., 2010; Lee et al., 2011; Orr and Lanier, 2011; Wang et al., 2012a) |
| RHBD1F2    | B       | 1     |       |       |     | (Adrain et al., 2012; Mellwain et al., 2012; Issuree et al., 2013) |
| TAX1BP1    | B       | 1     | +     | +     |     | (Shembade et al., 2007; Shembade et al., 2010; Shembade et al., 2011; Verstrepen et al., 2011; Nakano et al., 2013) |
| TNIP2      | B       | 1     | +     |       |     | (Papoutsopoulou et al., 2006; Leotoing et al., 2011; Callahan et al., 2013) |
| ZFP36      | B       | 1     | +     | +     |     | (Liang et al., 2009; Schichl et al., 2009; Bros et al., 2010; Kang et al., 2011; Kaplan et al., 2011; Qian et al., 2011; Schott et al., 2014) |
| CD302      | C       | 1     |       |       |     | (Kato et al., 2007) |
| STUB1      | D       | 8     | +     | +     |     | (Kettern et al., 2011; Yang et al., 2011; Chen et al., 2013) |
| UCP2       | D       | 8     | +     | +     |     | (Bai et al., 2005; Haschemi et al., 2011) |
| SHARPIN    | D       | 5     | +     | +     |     | (Gerlach et al., 2011; Ikeda et al., 2011; Tokunaga et al., 2011; Sieber et al., 2012; Wang et al., 2012b; Pouwels et al., 2013) |
| RRAS       | D       | 3     | +     |       |     | (Li et al., 2001; Shang et al., 2011; Singh et al., 2011) |
| RPS6KA3    | D       | 2     | +     |       |     | (Lin et al., 2008; Kakugawa et al., 2009; Peng et al., 2010; Takada, 2015; Takada et al., 2016) |
| COMMD1     | D       | 1     | +     | +     |     | (Maine et al., 2007; Starokadomskyy et al., 2013; Bartuzi et al., 2014; O'Hara et al., 2014) |
| DPP3       | D       | 1     |       |       |     | (Gamrekelashvili et al., 2013) |
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| Gene   | Cluster | Freq. | NF-κB | IFN-γ | Ubiq | References |
|--------|---------|-------|-------|-------|------|------------|
| ICAM2  | D       | 1     |       |       |      | (Somersalo et al., 1995; Helander et al., 1996; Lehmann et al., 2003; Banerjee et al., 2007; Porter and Hall, 2009; Boscacci et al., 2010) |
| MYBBP1A| D       | 1     | +     |       |      | (Owen et al., 2007; Cai et al., 2013) |
| PLIN2  | D       | 1     |       |       |      | (Bougnères et al., 2009) |
| RAD23A | D       | 1     |       | +     |      | (Andersson et al., 2005; Fang et al., 2013) |
| STK10  | D       | 1     | +     |       |      | (Endo et al., 2000; Tao et al., 2002; Fukumura et al., 2013) |

*Association suggested from Ingenuity Pathway Analysis in Figure 6*

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### SUPPLEMENTARY TABLE 3

Genes/probe sets used in the IFN-driven modeling

| Gene        | Probe set ID  | Frequency of use in models | Cluster |
|-------------|---------------|----------------------------|---------|
| BAK1        | 203728_at     | 14                         | H       |
| BAX<sup>a,b</sup> | 208478_s_at   | 14                         | H       |
| BAX<sup>a</sup>  | 211833_s_at   | 2                          | H       |
| BCL2<sup>a,b</sup> | 207004_at     | 52                         | G       |
| BCL2<sup>a</sup>  | 203685_at     | 8                          | E       |
| BCL2<sup>a</sup>  | 203684_s_at   | 1                          | E       |
| CCL8        | 214038_at     | 11                         | E       |
| CXCL10      | 204533_at     | 10                         | H       |
| DDX58<sup>a,b</sup> | 242961_x_at  | 24                         | E       |
| DDX58<sup>a</sup> | 218943_s_at   | 13                         | F       |
| DDX58<sup>a</sup> | 222793_at     | 5                          | H       |
| EIF2AK2<sup>a,b</sup> | 213294_at    | 3                          | H       |
| EIF2AK2<sup>a</sup> | 204211_x_at   | 2                          | H       |
| GBP1<sup>a,b</sup> | 202269_x_at   | 20                         | H       |
| GBP1<sup>a</sup>  | 231577_s_at   | 9                          | H       |
| GBP1<sup>a</sup>  | 202270_at     | 5                          | H       |
| IFI16<sup>a,b</sup> | 208965_s_at   | 12                         | F       |
| IFI16<sup>a</sup>  | 206332_s_at   | 2                          | H       |
| IFI16<sup>a</sup>  | 208966_x_at   | 2                          | H       |
| IFI35        | 209417_s_at   | 3                          | H       |
| IFI44<sup>a,b</sup> | 214059_at     | 7                          | H       |
| IFI44<sup>a,c</sup> | 214453_s_at   | 0                          |         |
| IFIH1<sup>a,b</sup> | 219209_at     | 15                         | H       |
| IFIH1<sup>a</sup>  | 1555464_at    | 2                          | H       |
| IFIT1<sup>c</sup>  | 203153_at     | 0                          |         |
| IFIT2        | 226757_at     | 6                          | H       |
| IFIT3<sup>a,b</sup> | 204747_at     | 4                          | H       |
| IFIT3<sup>a</sup>  | 229450_at     | 2                          | H       |
| IFITM1<sup>a,b</sup> | 201601_x_at   | 1                          | F       |
| IFITM1<sup>a,c</sup> | 214022_s_at   | 0                          |         |
| IFITM2       | 201315_x_at   | 3                          | F       |
| IFITM3       | 212203_x_at   | 1                          | F       |
| IFNGR1<sup>a,b</sup> | 242903_at     | 6                          | E       |
| IFNGR1<sup>a</sup>  | 202727_s_at   | 2                          | E       |
| IFNGR1<sup>a,c</sup> | 211676_s_at   | 0                          |         |
| IFNGR2       | 201642_at     | 2                          | H       |
| Gene      | Probe set ID | Frequency of use in models | Cluster |
|-----------|--------------|----------------------------|---------|
| IRF1<sup>a,b</sup> | 238725_at | 27 | F |
| IRF1<sup>a</sup> | 202531_at | 13 | F |
| IRF7 | 208436_s_at | 36 | F |
| IRF9 | 203882_at | 9 | F |
| ISG15 | 205483_s_at | 30 | H |
| ISG20<sup>a,b</sup> | 33304_at | 1 | F |
| ISG20<sup>b,c</sup> | 204698_at | 0 | |
| JAK1<sup>a,b</sup> | 240613_at | 67 | G |
| JAK1<sup>a</sup> | 201648_at | 45 | G |
| JAK1<sup>a</sup> | 1552611_a_at | 44 | G |
| JAK1<sup>a</sup> | 239695_at | 13 | E |
| JAK1<sup>a</sup> | 1552610_a_at | 3 | G |
| JAK2<sup>a,b</sup> | 205842_s_at | 16 | H |
| JAK2<sup>a</sup> | 205841_at | 11 | H |
| JAK2<sup>a</sup> | 1562031_at | 5 | H |
| MT1E | 212859_x_at | 10 | F |
| MT1G | 204745_x_at | 7 | F |
| MT2A | 212185_x_at | 66 | F |
| MX1 | 202086_at | 13 | F |
| MX2 | 204994_at | 2 | H |
| OAS1<sup>a,b</sup> | 205552_s_at | 8 | H |
| OAS1<sup>a,c</sup> | 202869_at | 0 | |
| OAS2<sup>a,b</sup> | 228607_at | 12 | F |
| OAS2<sup>a</sup> | 204972_at | 2 | H |
| OAS2<sup>a</sup> | 206553_at | 1 | H |
| OAS3 | 218400_at | 3 | H |
| OASL<sup>a,b</sup> | 210797_s_at | 12 | H |
| OASL<sup>a</sup> | 205660_at | 2 | H |
| PIAS1<sup>a,b</sup> | 217864_s_at | 24 | G |
| PIAS1<sup>a</sup> | 217862_at | 6 | E |
| PIAS1<sup>a</sup> | 217863_at | 1 | E |
| PML | 235508_at | 8 | F |
| PSMB8 | 209040_s_at | 11 | H |
| PTPN2<sup>a,b</sup> | 241623_at | 11 | E |
| PTPN2<sup>a</sup> | 241622_at | 5 | E |
| PTPN2<sup>a</sup> | 241983_at | 5 | E |
| PTPN2<sup>b,c</sup> | 213136_at | 0 | |
| PTPN2<sup>b,c</sup> | 213137_s_at | 0 | |
| RELA<sup>a,b</sup> | 201783_s_at | 42 | H |
| RELA<sup>a</sup> | 230202_at | 5 | H |
### Supplementary Material: Van den Berg et al. Predicting RTS,S-vaccine-mediated protection from transcriptomes in a malaria-challenge clinical trial

| Gene   | Probe set ID | Frequency of use in models | Cluster |
|--------|--------------|----------------------------|---------|
| RTP4   | 219684_at    | 15                         | H       |
| SOCS1<sup>a,b</sup> | 210001_s_at  | 34                         | H       |
| SOCS1<sup>a</sup> | 213337_s_at  | 8                          | H       |
| STAT1<sup>a,b</sup> | 200887_s_at  | 44                         | F       |
| STAT1<sup>a</sup> | 209969_s_at  | 15                         | F       |
| TAP1   | 202307_s_at  | 79                         | F       |

<sup>a</sup>For genes with more than one probe set, the data from the <sup>b</sup>probe set that was most frequently represented in the models were considered as the representative data for that gene in the manuscript.

<sup>c</sup>Genes/probe sets that were not selected by the modeling process.
Flow diagram describing how the N-PLS-DA was conducted.
Unlike the principal transcriptome data set, the validation transcriptome data set was generated using the validation transcriptome data set. The evaluation of IFN-pathway gene expression for a potential microarray-batch effect using the validation-transcriptome data set.

The evaluation of IFN-pathway gene expression for a potential microarray-batch effect using the validation-transcriptome data set.

Unlike the principal transcriptome data set, the validation transcriptome data set was generated from a single kit of microarrays. The heatmap describes IFN pathway gene expression in protected (PR), non-protected (NP) and non-protected with delayed onset of parasitemia (DL) groups before (prePIII) and 1, 3 and 14 days after the third vaccine injection (1dPIII, 3dPII and 14dPIII, respectively). Mean RNA expression relative to prePI is described in accordance with the colored scale. Certain genes are represented by more than one probe set.
Evaluation of the expression of Clusters A to D probe sets for a potential microarray-batch effect using the validation transcriptome data set.

Unlike the principal transcriptome data set, the validation transcriptome data set was generated from a single kit of microarrays (Vahey et al., 2010). Mean RNA-expression levels relative to pre-dose 1 (prePI), at pre-dose 3 [prePIII] and 1, 3 and 14 days after dose 3 [1dPIII, 3dPIII, and 14dPIII, respectively]), with respect to protection status of subjects (protected [PR], non-protected [NP] and non-protected with delayed parasitemia [DL]) for each of the four clusters (A–D) of probe sets among the 116 probe sets (110 genes) identified by the data-driven model. The error bars indicate the standard error of the mean (SEM). Also, simulated modeling suggested that such a batch effect (which may have confounded the effect of identifying protection status at 14dPIII) would have been mitigated by the N-PLS-DA because data from several time points were included (not shown).