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# Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

## Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

| n/a | Confirmed | |
|---|---|---|
| ☐ | ☒ | The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ | The statistical test(s) used AND whether they are one- or two-sided<br>*Only common tests should be described solely by name; describe more complex techniques in the Methods section.* |
| ☐ | ☒ | A description of all covariates tested |
| ☐ | ☒ | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ | A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ | For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted<br>*Give P values as exact values whenever suitable.* |
| ☒ | ☐ | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☐ | ☒ | Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated |

*Our web collection on statistics for biologists contains articles on many of the points above.*

## Software and code

Policy information about availability of computer code

| | |
|---|---|
| Data collection | Clinical data was collected and stored in commercially available REDCap (https://www.project-redcap.org) and exported for analyses in Microsoft Excel. Transcriptomic data was recorded in Microsoft Excel and processed by the Partek Genomics Suite Analysis software (Version 7). CE-TOFMS analysis was carried out using an Agilent CE capillary electrophoresis system equipped with an Agilent 6210 time-of-flight mass spectrometer, Agilent 1100 isocratic HPLC pump, Agilent G1603A CE-MS adapter kit, and Agilent G1607A CE-ESI-MS sprayer kit (Agilent Technologies, Waldbronn, Germany). The systems were controlled by Agilent G2201AA ChemStation software version B.03.01 for CE (Agilent Technologies) and connected by a fused silica capillary (50 µm i.d. × 80 cm total length) with commercial electrophoresis buffer (H3301-1001 and H3302-1021 for cation and anion analyses, respectively, HMT) as the electrolyte. |
| Data analysis | For transcriptomic analysis, Partek Genomics Suite Analysis software (Version 7) and Microsoft Excel (version 16.16.8) was used for processing the microarray data. Pathway analysis was performed using the Enrichr tool, Reactome 2016 database. GSEA blood transcription modules (BTM) framework described by Li et al., 2014 was used to analyze the immune cell subsets involved. For CE-MS/MS analysis, signal peaks were annotated according to the HMT metabolite database based on their m/z values with the MTs. Areas of the annotated peaks were then normalized based on internal standard levels and sample volumes in order to obtain relative levels of each metabolite. Partial least square discriminant analysis was performed by HMT's proprietary software, PeakStat (ver 3.18, HMT) and SampleStat (ver 3.14, HMT), respectively. Pathway analysis is performed by MetaboAnalyst 4.0. Prism 8.1.0 software was used for all other data analysis, including box and whiskers plot, 2-tailed t-tests, paired t-test, correlation analyses, volcano plots, ROC curves, bar charts) |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

## Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Raw and processed Z-score values of the transcriptomic data from Trial 1 and Trial 2 are deposited in ArrayExpress database (www.ebi.ac.uk/arrayexpress) under accession number E-MTAB-7928 and E-MTAB-7931 respectively. The CE-MS/MS metabolite expression data was deposited in the NIH Metabolomics Workbench under accession number ST001176.

# Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

# Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

| | |
|---|---|
| Sample size | Sample size for trial 1 provided 80% power to investigate effects of cross-reactive antibodies on vaccination (Low et al., Trials, 2015). All patients enrolled in trial 2 were used for validation studies. |
| Data exclusions | No data was excluded |
| Replication | All findings were replicated in a second trial independent of the first where the discovery was made. |
| Randomization | Randomization was not relevant to our study, as all subjects received the same vaccine. |
| Blinding | Blinding was not necessary as all subjects received the same vaccine. |

# Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ Antibodies |
| ☒ | ☐ Eukaryotic cell lines |
| ☒ | ☐ Palaeontology |
| ☒ | ☐ Animals and other organisms |
| ☐ | ☒ Human research participants |
| ☐ | ☒ Clinical data |

### Methods

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ ChIP-seq |
| ☒ | ☐ Flow cytometry |
| ☒ | ☐ MRI-based neuroimaging |

## Human research participants

Policy information about studies involving human research participants

| | |
|---|---|
| Population characteristics | All subjects recruited were flaviviral serology negative healthy adults, ages 30-50 years old. Symptomatic outcome did not correlate with covariates such as gender, age, BMI and ethnicity. For more details on the population characteristics for trial 1, please refer to Chan et al., Nature Microbiology, 2016 and Supplementary Table 1. Population characteristics for trial 2 are in Supplementary Tables 5-6. |
| Recruitment | Healthy volunteers were recruited in both trials. All subjects were flaviviral serology negative healthy adults. There were no other selection biases. |
| Ethics oversight | SingHealth Centralised Institutional Review Board |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

| | |
|---|---|
| Clinical trial registration | NCT01943305 (Trial 1) and NCT03116802 (Trial 2) |
| Study protocol | Full trial protocol can be assessed at clinicaltrials.gov (ID: NCT01943305 and NCT03116802 for Trial 1 and 2 respectively) |
| Data collection | Healthy adults, prescreened to be negative for anti-dengue antibodies, were enrolled on receiving informed consent. Study was conducted at SingHealth Investigational Medicine Unit in Singapore. A subject is considered to be symptomatic when systemic adverse events (AEs) are reported at or after 24 hours post-vaccination, in accordance with CTCAE version 4.03 recommendations. Participants were educated to use a daily diary to record any local and systemic symptoms for 1 month following vaccination. At each study visit after YFLAV immunization on days 1, 3, 7, 15 and 28, subjects underwent physical examination, measurement of vital signs (blood pressure, temperature, pulse and respiratory rate) and diary review by a team of trained physicians, who were part of the study team. Blood is drawn on days 0, 1, 3 and 7 for transcriptomic, proteomic and metabolomic studies. Full details are described in Low et al., Trials, 2015 and Chan et al., JCI Insight, 2017. Subjects from Trial 1 are recruited from October 2013 to December 2015.<br><br>For Trial 2, blood was taken at days 0, 1, 3, 7, 1 month and 1 year post YF-vaccination. For validation of the Trial 1 results, only the 34 control subjects (non-statin group) were used. Day 0 blood was used for baseline transcriptomic analyses, measured by either nCounter or qPCR. The control subjects from Trial 2 are recruited from March 2017 to March 2018. |
| Outcomes | Results from Trial 1 was based on an exploratory analysis of the clinical trial described in Chan et al., Nature Microbiology, 2016 and Low et al., Trials, 2015. The primary objectives were fulfilled and the data was presented in Chan et al., Nature Microbiology, 2016. One of the secondary objectives of the trial was to characterize the innate immune responses to YF vaccination in subjects that had prior JE vaccination. The transcriptomics analysis reveal that the induction of innate immune responses at day 3 post-YF vaccination was associated with vaccine immunogenicity (Chan et al., Nature Microbiology, 2016). In contrast, day 1 post-YF vaccination innate immune responses was associated with adverse event outcome described in Chan et al., JCI Insight, 2017. This current study extends the work described by Chan et al., JCI Insight, 2017 and characterized the baseline transcriptomic and metabolomic signatures that were correlated with adverse event or symptomatic outcome, showing that metabolic perturbations and cellular stress underpin susceptibility to symptomatic outcome.<br><br>The primary objective for Trial 2 was to study the effects of YF vaccine on statin or non statin subjects. To validate the baseline signatures observed in Trial 1, we used the 34 control subjects, which are the non statin subjects and processed the whole blood for nCounter analyses. The results validated the Trial 1 observations, which reinforced the role of metabolic perturbations and cellular stress in determining susceptibility to symptomatic outcome. |