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Supplemental Conflicts of Interest:

IMPACC Network Competing Interests

The Icahn School of Medicine at Mount Sinai has filed patent applications related to SARS-CoV-2 serological assays, NDV-based SARS-CoV-2 vaccines, influenza virus vaccines, and therapeutics, listing Florian Krammer and Viviana Simon as co-inventors. Mount Sinai has spun out Kantaro to market SARS-CoV-2 serological tests and Castlevax to develop SARS-CoV-2 vaccines, with Florian Krammer as co-founder and scientific advisory board member of Castlevax. Florian Krammer has consulted for Merck, Curevac, Seqirus, GSK, Pfizer, 3rd Rock Ventures, Sanofi, Gritstone, and Avimex. His laboratory collaborates with Dynavax on influenza vaccine development and with VIR on influenza virus therapeutics development. Ofer Levy is a named inventor on patents held by Boston Children's Hospital related to vaccine adjuvants and human in vitro platforms that model vaccine action. His laboratory has received research support from GlaxoSmithKline (GSK) and Pfizer, he is a consultant to GSK and Sanofi, and he is a co-founder and advisor to ARMR Sciences (formerly Ovax, Inc.), which develops technologies to detect illicit substances and prevent overdose. Charles Cairns consults for bioMérieux and receives grant funding from the Bill & Melinda Gates Foundation. James A. Overton is a consultant at Knocean Inc. Jessica Lasky-Su is a scientific advisor for Precion Inc. Scott R. Hutton, Greg Michelloti, and Kari Wong are employees of Metabolon Inc. Vicki Seyfer-Margolis is employed by MyOwnMed. Nadine Rouphael reports grants or contracts with Merck, Sanofi, Pfizer, Vaccine Company, and Immorna. She has served on data safety monitoring boards for Moderna, Sanofi, Seqirus, Pfizer, EMMES, ICON, BARDA, and CyanVan Micron. She has received travel support from Sanofi and Moderna and honoraria from Virology Education and Krog Consulting. Chris Cotsapas is employed by Vesalius Therapeutics. Adeeb Rahman is employed by Immunai Inc. Steven Kleinstein consults for Peraton related to the ImmPort data repository. Nathan Grubaugh consults for Tempus Labs and the National Basketball Association. Akiko Iwasaki consults for 4BIO, Blue

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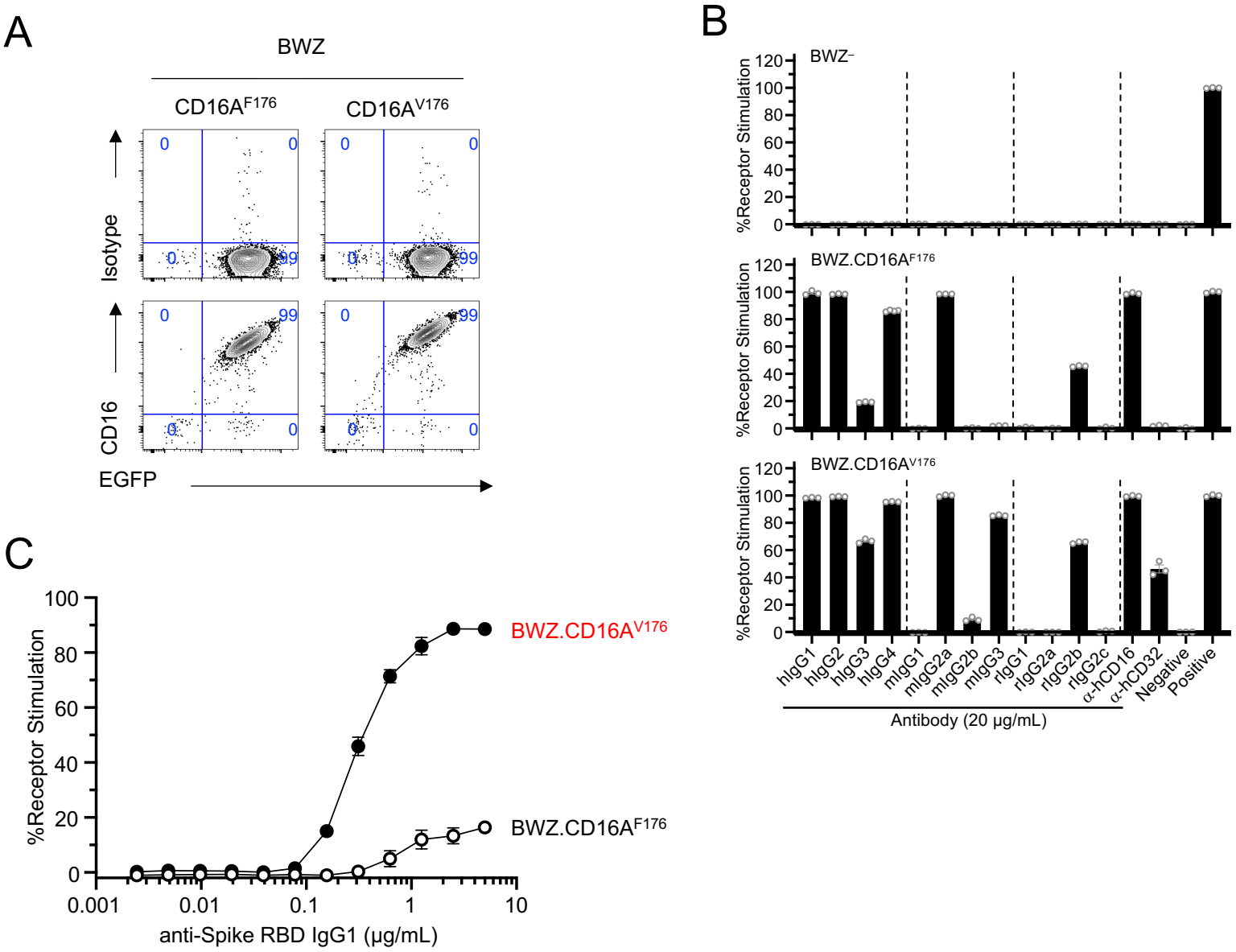
Supplemental Figure 1. Generation and validation of BWZ.CD16A reporter cells. A) BWZ cells expressing chimeric CD16A-z receptors were generated and confirmed to express cell surface receptor using flow cytometry. **B**) Stimulation of BWZ.CD16A reporter cells using platebound purified antibodies of shown isotypes. **C**) Titration curve showing dose response of antibody coated Spike RBD stimulating BWZ.CD16A reporter cells.

Supplemental Figure 2. The CD16A V176 allele remains associated with lower anti-SARS-CoV-2 titers and improved respiratory status at visit 4. A) Respiratory status breakdown by CD16A genotype at visit 4 (14 days from hospital admission), P=0.025. 1= not hospitalized + no limitations, 2= not hospitalized + limitations, 3= hospitalized + no O2, 4= hospitalized + required O2, 5= non-invasive ventilation or high flow O2, 6= mechanical ventilation or ECMO, 7= death. **B)** Mortality stratified by CD16A genotype (OR=0.963, 95% CI=0.726-1.268, P=0.788). **C-D)** Visit 4 antibody titers of RBD **(C)** and spike **(D)** stratified by CD16A genotype (P=0.01 and 0.006, respectively). **E)** Viral rpM at visit 4 split by CD16A genotype (P=0.246).

Supplemental Figure 3. Individuals homozygous for the CD16A V176 allele have a weakened correlation between anti-spike titers and viral rpM as well as viral rpM and COVID-19 severity. A-B) Correlation plots for viral rpM and spike titers **(A)** or RBD titers **(B)** split across CD16A genotypes. Black line is for that specific genotype, and red line is all patients together. Dashed lines are 95% confidence intervals. **C)** Box-and-whisker plots of viral rpM for mild (TG123) versus severe (TG45) COVID-19 trajectory groups split by CD16A genotype.

Supplementary Figure 4. No difference in blood NK cell counts based on CD16A genotype in the IMPACC cohort. A-E) CyTOF was performed on whole blood of N=788 participants and immune cell counts were determined. **(A)** CD56low CD16hi NK cell counts (P=0.095), **(B)** CD56hi CD16low NK cell counts (P=0.086), **(C)** monocyte counts (P=0.034), **(D)** neutrophil counts (P=0.618), and **(E)** CD39high CD4+ Treg counts (P=0.192) were recorded split by CD16A genotype.

Supplemental Figure 1



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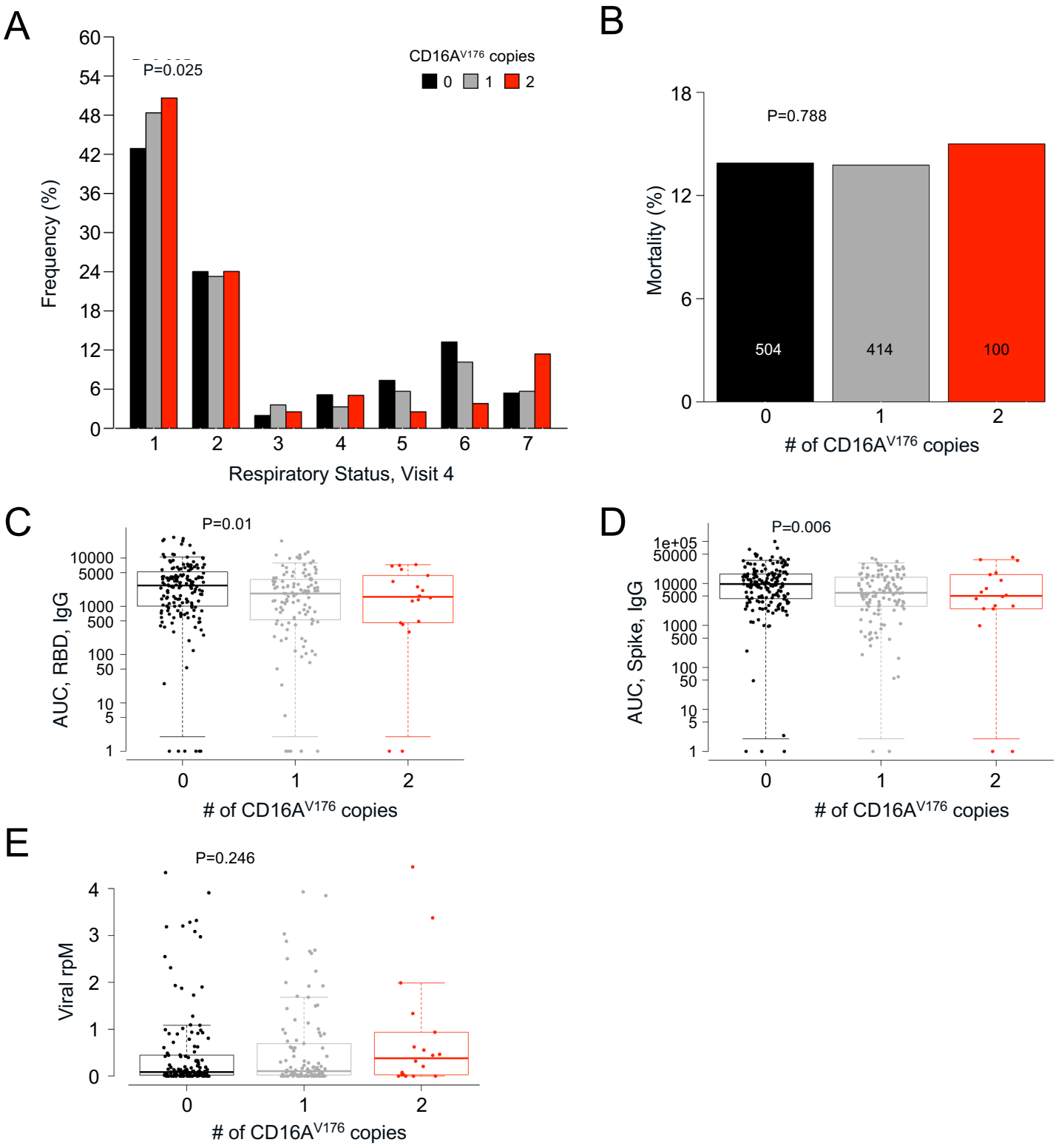
Supplemental Figure 2



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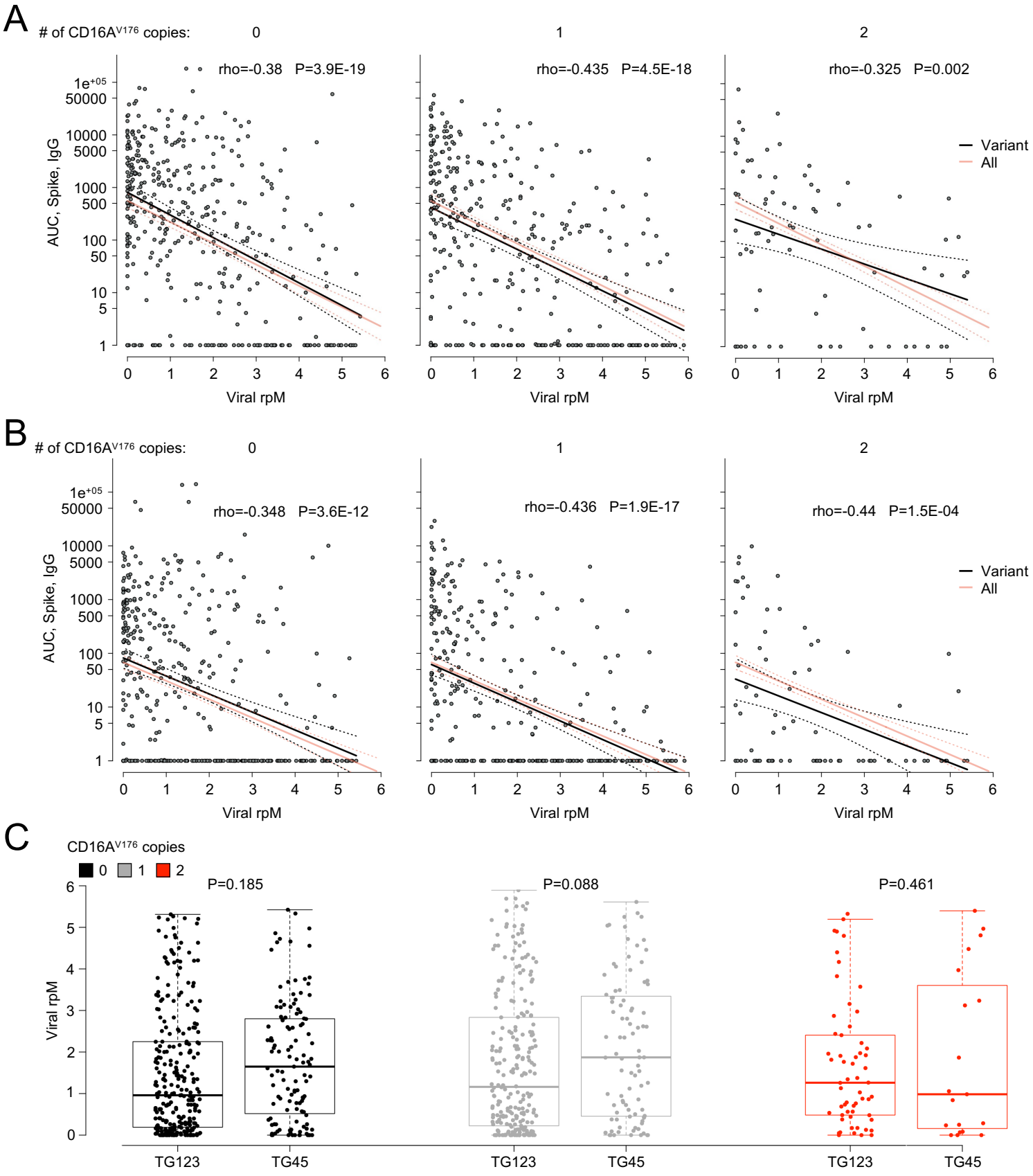
Supplemental Figure 3



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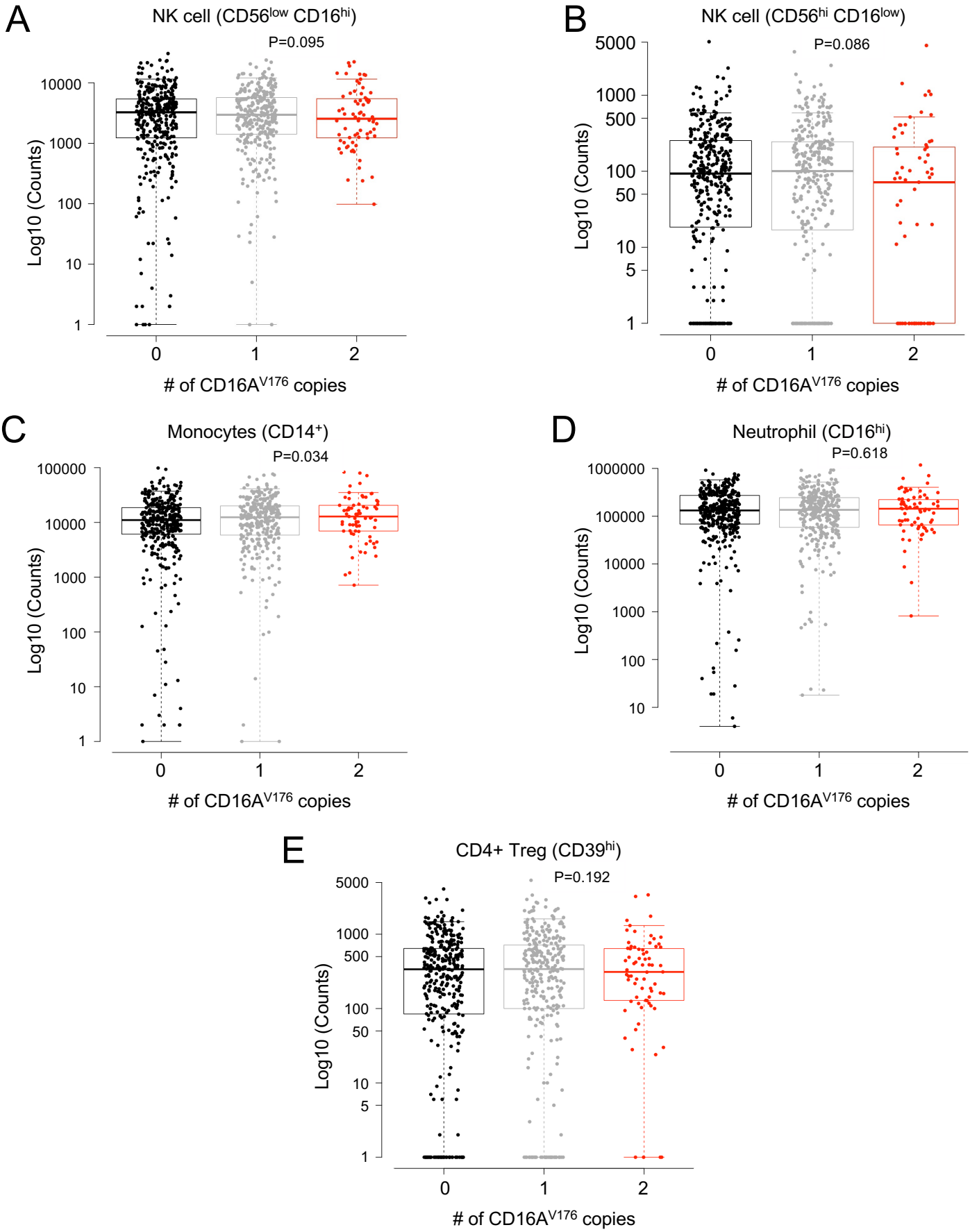

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