**Supplemental Methods**

CyTOF: Cryopreserved PBMC samples were thawed and stained as described previously (Subrahmanyam PB,Maecker HT. CyTOF measurement of immunocompetence across major immune cell types. Curr Protoc Cytom 2017;82:9.54.1–9.54.12). Briefly, frozen PBMC were thawed in a 370C water bath and washed twice in complete medium (RPMI with 10% FBS, PennStrep and L-glutamine) with benzonase (PierceTM Universal Nuclease, Thermo Fisher Scientific). Cells were re-suspended in complete medium without benzonase, counted, and 2 × 106 or maximum available cells were placed in each well of a 96-well U-bottom plate. The cells were rested overnight at 370C, 5% CO2. After resting, secretion inhibitors brefeldin A and monensin, and stimulating agents phorbol 12-myristate 13-acetate (PMA) and ionomycin were added for 4 hours (Sigma-Aldrich). Anti-CD107a-151Eu (Fluidigm) was also added during stimulation. After stimulation, samples were washed twice in staining buffer (Ca/Mg-free PBS, 0.1% BSA, 2 mM EDTA, and 0.05% Sodium azide). The surface staining antibody cocktail prepared in staining buffer was added for 45 min on ice (Table 1). Cells were washed twice and 115In-DOTA Maleimide live/dead stain diluted 1:3000 in Ca/Mg-free PBS was added for 30 min on ice. Cells were washed three times and fixed in 2% paraformaldehyde overnight at 40C. The fixed cells were washed twice in 1× permeabilization buffer (eBioscience). Intracellular staining cocktail prepared in permeabilization buffer was added for 45 min on ice, and then washed three times in staining buffer (Below Table). For DNA staining, Ir Intercalator (Fluidigm) was added per the manufacturer’s instructions for 20 min at room temperature. Cells were washed twice in staining buffer and three times in 18.2 Ω MilliQ-grade water. Finally, cells were resuspended in MilliQ-grade water with EQ Four Element Calibration beads, and data were acquired on a HeliosTM version mass cytometer (Fluidigm).

**CyTOF Surface and Intracellular Staining Panel**

| Metal Tag | Specificity | Clone | Source (Fluidigm or in-house conjugated) |
| --- | --- | --- | --- |
| 113In | CD57 | HCD57 | in-house |
| 115In | Dead\* | - | - |
| 140Ce | Beads\* | - | - |
| 141Pr | HLA-DR | G46-6 | in-house |
| 142Nd | CD19 | HIB19 | Fluidigm |
| 143Nd | IL-10 | JES3-9D7 | in-house |
| 144Nd | IL-4 | MP4-25D2 | Fluidigm |
| 145Nd | CD4 | RPA-T4 | Fluidigm |
| 146Nd | CD8 | RPA-T8 | Fluidigm |
| 147Sm | CD20 | 2H7 | Fluidigm |
| 148Nd | CD40 | 5C3 | in-house |
| 149Sm | CTLA-4 | 14D3 | in-house |
| 150Nd | MIP1β | D21-1351 | Fluidigm |
| 151Eu | CD107a | H4A3 | Fluidigm |
| 152Sm | TNFα | Mab11 | Fluidigm |
| 153Eu | CD45RA | HI100 | Fluidigm |
| 154Sm | CD3 | UCHT1 | Fluidigm |
| 155Gd | CD28 | L293 | in-house |
| 156Gd | CD38 | HB-7 | in-house |
| 157Gd | CD25 | MA251 | in-house |
| 158Gd | CD33 | WM53 | Fluidigm |
| 159Tb | GM-CSF | BVD2-21C11 | Fluidigm |
| 160Gd | CD14 | M5E2 | Fluidigm |
| 161Dy | IFNγ | 4S.B3 | in-house |
| 162Dy | CD69 | FN50 | Fluidigm |
| 163Dy | TCRγδ | B1 | in-house |
| 164Dy | IL-17 | N49-853 | Fluidigm |
| 165Ho | CD127 | A019D5 | Fluidigm |
| 166Er | IL-2 | MQ1-17h12 | Fluidigm |
| 167Er | CD27 | L128 | Fluidigm |
| 168Er | CD40L (CD154) | 24-31 | Fluidigm |
| 169Tm | CCR7 | 150503 | in-house |
| 170Er | PD-1 | EH12.1 | in-house |
| 171Yb | Granzyme B | GB11 | Fluidigm |
| 172Yb | PD-L2 | 24F.10C12 | Fluidigm |
| 173Yb | Perforin | B-D48 | in-house |
| 174Yb | CD21 | Bu32 | in-house |
| 175Lu | PD-L1 | 29E.2A3 | Fluidigm |
| 176Yb | CD56 | NCAM16.2 | Fluidigm |
| 193Ir | DNA1\* | - | - |
| 195Ir | DNA2\* | - | - |
| 209Bi | CD16 | 3G8 | Fluidigm |

\* Non-protein subjects

Flow Cytometry: PBMC samples at the indicated visits pre- and post-treatment initiation were thawed and stained with a fixable Aqua viability dye (Invitrogen) and a cocktail of antibodies to the following surface markers: CD8–Qdot605 (Invitrogen, 3B5), CD4–Qdot655 (Invitrogen, S3.5), PD-1–PE (BD, MIH4), LAG-3–FITC (Enzo, 17B4), ICOS–PE-Cy7 (eBioscience, ISA-3), TIM-3–APC (R&D Systems, 344823). Cells were next fixed and permeabilized with the FOXP3/Ki67 Fixation/Permeabilization Concentrate and Diluent (eBioscience), and subsequently stained intracellularly with CD3–BV570 (Biolegend, UCHT1), Ki67–AlexaFluor700 (BD), FOXP3-eFluor450 (eBioscience), and CTLA-4–PerCP–eFluor710 (eBioscience). Stained cells were acquired on a BD Biosciences LSRFortessa and analysed using FlowJo software (FlowJo, LLC). Percentages of gated CD4 and CD8 T cell subsets within CD3+ lymphocytes expressing the various markers in the panel were determined using the appropriate fluorescence-conjugated isotype control antibodies after exclusion of non-viable cells and doublets.

TCR Sequencing: Peripheral blood CD8 T cells were purified and isolated from PBMCs using BD Aria Sorter. DNA extraction, amplification, library preparation, sequencing, and preliminary bioinformatics analysis was performed by Adaptive Biotechnologies. Amplification and sequencing of TCRB CDR3 was performed at a survey level resolution using the immunoSEQ Platform (Adaptive Biotechnologies). Clone frequencies were then calculated by dividing the total count of each TCRB CDR3 amino acid sequence by the overall counts. The clone frequencies were used to assess individual TCR diversity, specifically the Simpson index on any sample as the sum of the all frequencies squared in the sample. The Simpson index, which is the probability of choosing the same sequence twice when sampling from a population, was chosen as a diversity measure since it is less sensitive to sample depth. Strictly, it is a measure of clonality, with higher Simpson index for samples which are more dominated by large clones.

Luminex: Human 62-plex kits were purchased from eBiosciences/Affymetrix and used according to the manufacturer’s recommendations with modifications as described below. In brief, beads were added to a 96 well plate and washed in a Biotek ELx405 washer. Samples were added to the plate containing the mixed antibody-linked beads and incubated at room temperature for 1 hour, followed by overnight incubation at 4° C with shaking. Cold and room temperature incubation steps were performed on an orbital shaker at 500-600 rpm. Following the overnight incubation plates were washed in a Biotek ELx405 washer and then a biotinylated detection antibody was added for 75 minutes at room temperature with shaking. Plates were washed as above, and streptavidin-PE was added. After incubation for 30 minutes at room temperature, washing was performed as above and reading buffer was added to the wells. Each sample was measured in duplicate. Plates were read using a Luminex 200 instrument with a lower bound of 50 beads per sample per cytokine. Custom assay control beads by Radix Biosolutions were added to all wells.

List of cytokines tested: EGF, ENA7B, EOTAXIN, FGFB, GCSF, GMCSF, GROA, HGF, IFNA, IFNB, IFNG, IL10, IL12P40, IL12P70, IL13, IL15, IL17A, IL17F, IL18, IL1A, IL1B, IL1RA, IL2, IL21, IL22, IL23, IL27, IL31, IL4, IL5, IL6, IL7, IL8, IL9, IL10, LEPTIN, LIF, MCSF, MCP1, MCP3, MIG, MIP1A, MIP1B, PAI1, PGDFBB, RANTES, RESISTIN, CD40L, SCF, SDF1A, FASL, ICAM1, VCAM1, TGFA, TNFA, TNFB, TRAIL, VEGF, VEGFD