Supplementary Material

Methods

Mice:
C57BL/6 (000664), NOD/ShiLtJ (001976), B6.TIGER (008379), and B6.Nur77-GFP (016617) mice were obtained from The Jackson Laboratory and bred in-house. B6.GREAT mice were a gift from Dr. Lee Reinhardt and NOD.GREAT mice were a gift from Dr. Jeffrey Bluestone. All animal procedures were approved by the Institutional Animal Care and Use Committee at National Jewish Health and University of Colorado Anschutz Medical Campus. Mice were housed in standard ventilated mice cages under specific pathogen free conditions and maintained at an ambient temperature of 22°C. Mice were provided bedding, nesting material and huts to improve quality and reduce fighting between male mice. Mice were placed in same-sex groups of 5 or less using a 12h dark/light cycles with ad libitum food and water. Both male and female mice between ages 12-40 weeks of age were analyzed for C57BL/6 background mice. Female NOD mice between the ages of 12-20 weeks of age were analyzed, as male NOD mice do not have a high penetrance of autoimmune diabetes with greater variability in progression to overt diabetes[1]. Mice were monitored daily for general health and well-being.

Diet-Induced Obesity (DIO) Mice
Diet-induced obesity (DIO) mice were generated in-house by feeding 4-6 week mice ad libitum a diet containing 60% of calories from fat (Research Diets, D12492) or a control diet containing 10% of calories from fat (Research Diets, D12450B) until euthanasia at 16-40 weeks of age. At or within 2 weeks of weaning, male littermates were randomized when assigned to a diet. Male mice were exclusively used for DIO studies as female mice have reduced capacity to gain appropriate weight on a high-fat diet. Weight and blood glucose levels were monitored weekly. At 16 weeks of age, mice were challenged by intraperitoneal injection of 2g glucose/kg in PBS and blood glucose levels were monitored every 15 minutes for 2 hours post injection. DIO mice were excluded from the study if weight gain was not within one standard deviation of the weight curve from The Jackson Laboratory[2].

Flow Cytometry:
Flow Cytometry Panels and Antibody Information:

| Marker   | Fluor   | Vendor   | Catalog Number | Dilution |
|----------|---------|----------|----------------|----------|
| Resident T cell Panel |         |          |                |          |
| CD45     | BUV395  | BD       | 564279         | (1:400)  |
| CD90.2   | FITC    | Biolegend| 105306         | (1:200)  |
| CD19     | PE      | Biolegend| 115508         | (1:200)  |
| CD4      | AlexaFluor594 | Biolegend| 100446         | (1:200)  |
| CD8a     | BV650   | Biolegend| 100741         | (1:200)  |
| CD69     | PE-Cy7  | Biolegend| 104511         | (1:200)  |
| CD11b    | APC-Cy7 | Biolegend| 101225         | (1:200)  |
| CD103    | BV785   | Biolegend| 121439         | (1:200)  |
| CD49d    | AlexaFluor647 | Biolegend| 103613         | (1:200)  |
| CD44     | BV510   | Biolegend| 103043         | (1:200)  |
| B cell subset Panel |         |          |                |          |
| CD45     | BUV395  | BD       | 564279         | (1:400)  |
| CD19     | BUV737  | BD       | 612781         | (1:200)  |
|    | Antigen   | Color | Supplier     | Catalog Number | Concentration |
|----|-----------|-------|--------------|----------------|---------------|
| B220 | B220      | BV421 | Biolegend    | 103239         | (1:200)       |
| IgM | BV750     | BD    | Biolegend    | 747333         | (1:200)       |
| IgD | AlexaFluor700 | PerCP | Biolegend    | 405729         | (1:200)       |
| CD5 | BV711     | BD    | Biolegend    | 100615         | (1:200)       |
| CD11d | PE        | BD    | Biolegend    | 123510         | (1:200)       |
| CD138 | BV605    | BD    | Biolegend    | 142515         | (1:200)       |
| CD80 | APC       | BD    | Biolegend    | 121214         | (1:200)       |
| CD90.2 | FITC    | BD    | Biolegend    | 105328         | (1:200)       |
| Nur77-GFP Reporter Panel | | | | | |
| CD45 | BUV395    | BD    | Biolegend    | 564279         | (1:200)       |
| CD90.2 | PE-Cy7  | BD    | Biolegend    | 105326         | (1:200)       |
| CD4 | BV711     | BD    | Biolegend    | 100447         | (1:200)       |
| CD8a | APC-eFluor780 | BD | Thermo-Fisher | 47-0081-82    | (1:200)       |
| CD19 | BUV737    | BD    | Biolegend    | 612781         | (1:200)       |
| CD62L | Pacific Blue | BD | Biolegend | 104424         | (1:200)       |
| CD44 | BV510     | BD    | Biolegend    | 103043         | (1:200)       |
| MHCII (I-A/I-E) | APC | Biolegend | eBioscience | 17-5321-82 | (1:600)       |
| IL-10-GFP Reporter Panel | | | | | |
| CD45 | BUV395    | BD    | Biolegend    | 564279         | (1:200)       |
| CD90.2 | PE-Cy7  | BD    | Biolegend    | 105326         | (1:200)       |
| CD4 | BV711     | BD    | Biolegend    | 100447         | (1:200)       |
| CD8a | APC-eFluor780 | BD | Thermo-Fisher | 47-0081-82    | (1:200)       |
| CD11b | BUV395   | BD    | Biolegend    | 101236         | (1:100)       |
| CD19 | PE        | BD    | Biolegend    | 115508         | (1:200)       |
| B6.GREAT Reporter Panel | | | | | |
| CD45 | BUV395    | BD    | Biolegend    | 564279         | (1:200)       |
| CD90.2 | PE-Cy7  | BD    | Biolegend    | 105326         | (1:200)       |
| CD4 | BV711     | BD    | Biolegend    | 100447         | (1:200)       |
| CD8 | eFluor660 | BD    | Biolegend    | 101236         | (1:100)       |
| CD19 | PE        | BD    | Biolegend    | 115508         | (1:200)       |
| Intracellular IFNγ Panel | | | | | |
| CD45 | BUV395    | BD    | Biolegend    | 564279         | (1:200)       |
| CD90.2 | FITC    | BD    | Biolegend    | 105306         | (1:200)       |
| CD4 | BV711     | BD    | Biolegend    | 100447         | (1:200)       |
| CD8 | eFluor660 | BD    | Biolegend    | 101236         | (1:100)       |
| CD19 | PE        | BD    | Biolegend    | 115508         | (1:200)       |
| IFNγ | PE-Cy7    | BD    | Biolegend    | 505825         | (1:100)       |
| FoxP3 Panel | | | | | |

|    | Antigen   | Color | Supplier     | Catalog Number | Concentration |
|----|-----------|-------|--------------|----------------|---------------|
|    | B6.GREAT Reporter Panel | | | | |
|    | IFNγ Panel | | | | |
|    | FoxP3 Panel | | | | |
| CD45 | BUV395 | BD | 564279 | (1:200) |
|------|--------|----|--------|---------|
| CD90.2 | FITC | Biolegend | 105306 | (1:200) |
| CD4 | BV711 | Biolegend | 100447 | (1:200) |
| CD8 | PerCP-Cy5.5 | Biolegend | 100734 | (1:200) |
| CD25 | Biotin | Biolegend | 102004 | (1:200) |
| CD19 | BV510 | Biolegend | 115545 | (1:200) |
| FoxP3 | PE | eBioscience | 12-5773-82 | (1:100) |

**CyTOF Analysis from Human Pancreas Analysis Program (HPAP) Database**

Human CyTOF data was obtained from deidentified patient samples sourced from the Human Pancreas Analysis Program. Study size was based upon available number of patient data. Because the database was deidentified, potential sources of bias were removed.

Demographic information for donors used in the study:

| Donor Number | Group | Age (years) | Sex | BMI (kg/m²) | Race |
|--------------|-------|-------------|-----|-------------|------|
| HPAP-034     | Control | 13          | Male | 18.6         | Caucasian |
| HPAP-035     | Control | 35          | Male | 26.91        | Caucasian |
| HPAP-037     | Control | 35          | Female | 21.9 | Caucasian |
| HPAP-040     | Control | 35          | Male | 23.98        | Caucasian |
| HPAP-052     | Control | 27          | Male | 38.72        | African American |
| HPAP-053     | Control | 58          | Female | 24.2 | Caucasian |
| HPAP-054     | Control | 40          | Female | 30.85 | Caucasian |
| HPAP-059     | Control | 35          | Male | ----          | Caucasian |
| HPAP-051     | T2D    | 43          | Female | 45.49 | African American |
| HPAP-057     | T2D    | 50          | Female | 30.49 | Caucasian |
| HPAP-061     | T2D    | 59          | Female | 38.27 | African American |
| HPAP-020     | T1D    | 14          | Male | 13.2         | Caucasian |
| HPAP-021     | T1D    | 13          | Female | 21.4 | Caucasian |
| HPAP-023     | T1D    | 17          | Female | 21.35 | Caucasian |
| HPAP-028     | T1D    | 4           | Male | 17.3         | Caucasian |
| HPAP-032     | T1D    | 10          | Female | 16.3 | Caucasian |
| HPAP-055     | T1D    | 24          | Male | 27.9         | Caucasian |
| HPAP-064     | T1D    | 24          | Male | 16.98        | African American |
| HPAP-087     | T1D    | 15          | Female | 19.3 | Caucasian |

**References:**

1. Leiter EH (1997) The NOD Mouse: A Model for Insulin-Dependent Diabetes Mellitus. Curr Protoc Immunol 24(1):15.9.1-15.9.23. https://doi.org/10.1002/0471142735.IM1509S24
2. Laboratory J PHENOTYPE INFORMATION FOR DIET-INDUCED OBESE C57BL/6J (380050). https://www.jax.org/jax-mice-and-services/strain-data-sheet-pages/phenotype-information-380050#