Supplemental Methods

List of clinical study sites. As described in the Methods, all trials were conducted under protocols approved by the institutional review boards for each study site. The full list of sites follows.

1. University of Arizona, Tucson, Arizona, USA
2. University of Southern California / Children's Hospital Los Angeles, Los Angeles, California, USA
3. Children's Hospital and Research Center, Oakland, California, USA
4. Diabetes Center at University of California San Francisco, San Francisco, California, USA
5. University of California at San Diego / San Diego Children's Hospital, San Diego, California, USA
6. Stanford University, Stanford, California, USA
7. Barbara Davis Center for Childhood Diabetes, Aurora, Colorado, USA
8. Yale University, New Haven, Connecticut, USA
9. University of Florida, Gainesville, Florida, USA
10. University of Miami, Miami, Florida, USA
11. Emory Children's Center, Atlanta, Georgia, USA
12. Medical College of Georgia, Augusta, Georgia, USA
13. Indiana University / Riley Hospital for Children, Indianapolis, Indiana, USA
14. University of Iowa Hospital & Clinics, Iowa City, Iowa, USA
15. University of Maryland, Baltimore, Maryland, USA
16. Joslin Diabetes Center, Boston, Massachusetts, USA
17. Massachusetts General Hospital, Boston, Massachusetts, USA
18. University of Minnesota, Minneapolis, Minnesota, USA
19. Children's Mercy Hospital, Kansas City, Missouri, USA
20. Creighton University, Omaha, Nebraska, USA
21. Columbia University / Naomi Berrie Diabetes Center, New York, New York, USA
22. University of North Carolina, Durham, North Carolina, USA
23. University of Pennsylvania / Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
24. University of Pittsburgh / Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, USA
25. University of Texas Southwestern Medical Center, Dallas, Texas, USA
26. Benaroya Research Institute, Seattle, Washington, USA
27. Pacific Northwest Research Institute / University of Washington, Seattle, Washington, USA
28. Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia
29. Hospital for Sick Children, Toronto, Ontario, Canada
30. San Raffaele Hospital, Milan, Italy

Supplementary Figures

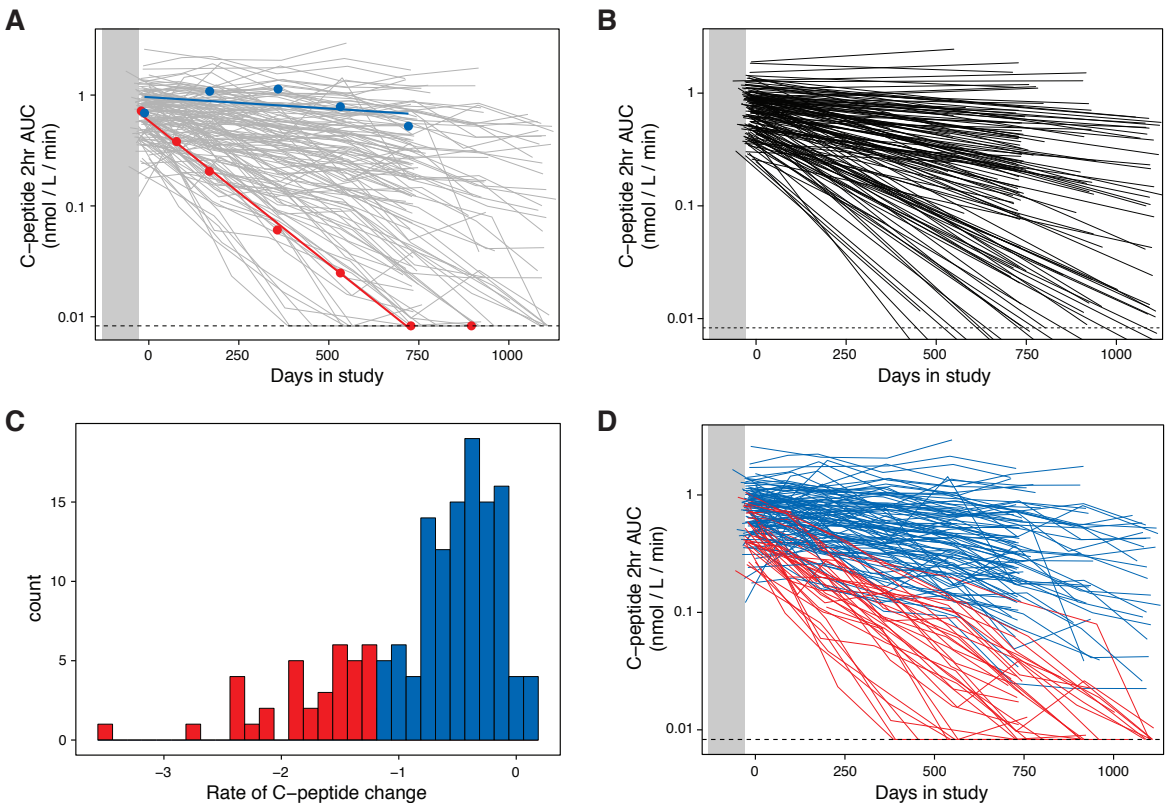

Figure S1. Distribution of C-peptide AUC values and modeled rates of change. (A) Example of individual-specific models of rates of C-peptide change for two representative subjects. Colored points represent C-peptide AUC at individual study visits, colored lines represent fitted models. Observed C-peptide AUC values for all subjects are shown in pale gray. (B) Model fits for C-peptide AUC values from all subjects. Each line represents the modeled values for a single subject. The extent of lines on the x-axis corresponds to the timeframe of measurements for a given subject. Pseudo-R^2 calculated as the squared Pearson correlation between observed and fitted values. N=846 measurements from 152 subjects. (C) Histogram of rates of C-peptide change from linear models. Red, fast progressors; blue, slow progressors. N=152 subjects. (D) C-peptide AUC values over time for each subject, with lines colored by subject classification as slow or fast progressors as shown in Fig. S1C. N=846 measurements from 152 subjects.

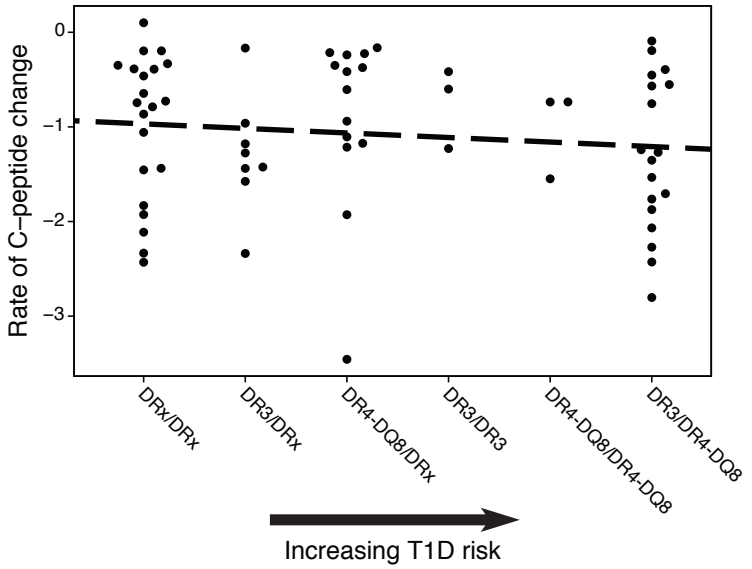

Figure S2. Rate of C-peptide change does not vary consistently with HLA genotypes that confer T1D risk, when restricting to subjects aged below 15 years at diagnosis. Dashed line shows linear model fit (p=0.32). Genotype categories are from Winkler et al. (27); DRx represents alleles that are not DR3 or DR4-DQ8. N=67 subjects.

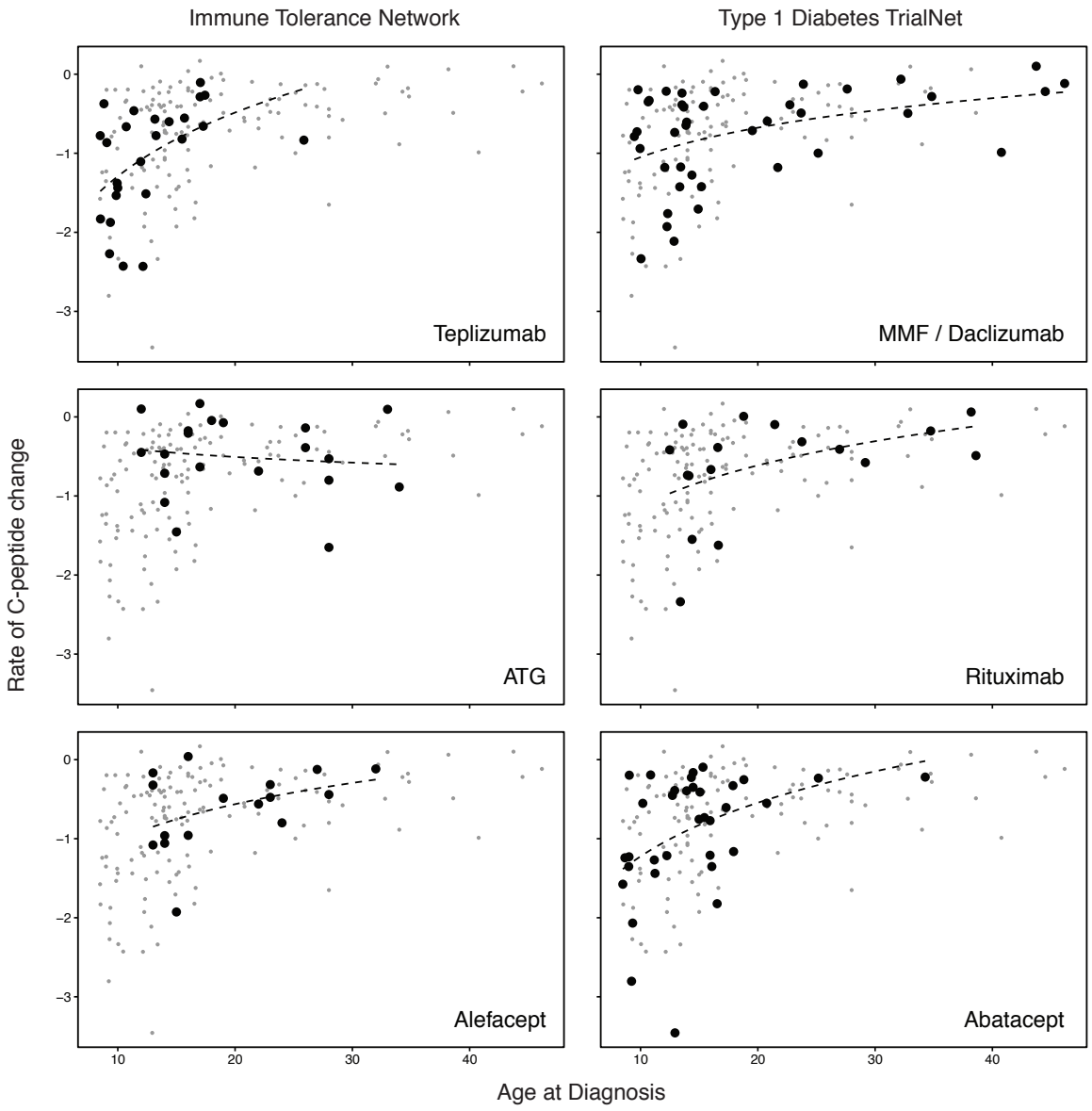

Figure S3. Individual clinical trials vary in patient population and distribution of T1D progression. Each plot shows the control patients from a single clinical trial, for ITN trials (left column) and TrialNet trials (right column). Dashed lines represent logarithmic function fit to the subjects from the focal trial only. Small gray dots show the control patients from all other trials. N=25, 20, 16, 40, 17, and 34 subjects for teplizumab, ATG, alefacept, MMF/daclizumab, rituximab, and abatacept trials, respectively.

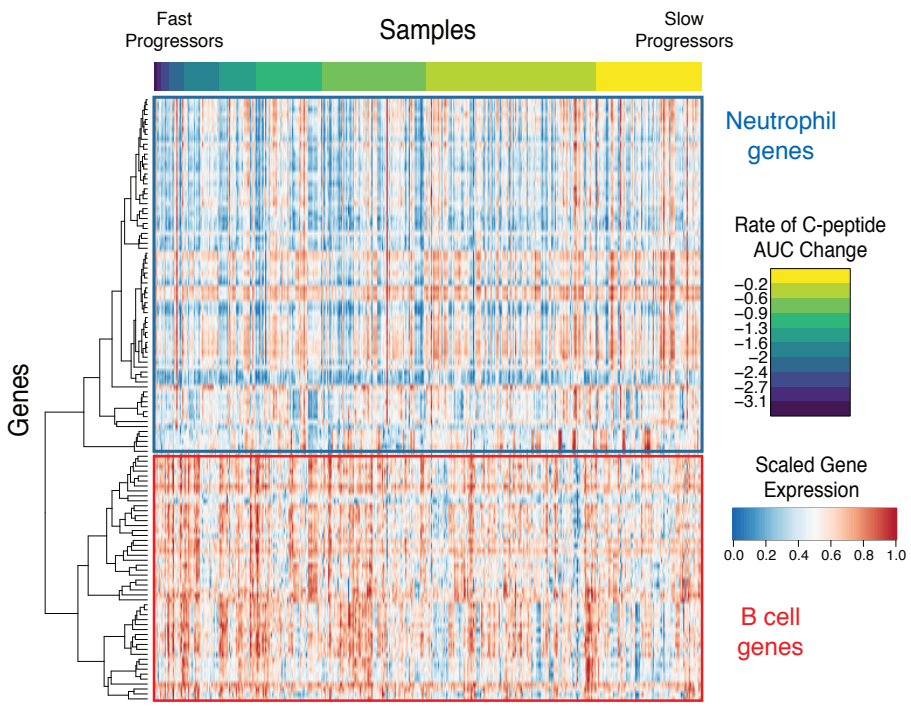

Figure S4. Genes differentially expressed with rate of C-peptide AUC change show consistent patterns despite individual variation. Genes shown in heatmap are differentially expressed at FDR < 0.05 and overlap the gene sets highlighted in Figure 2A. Each column represents one sample. Red and blue boxes show clusters of genes enriched for association with B cells and neutrophils. N=471 samples and 122 genes.

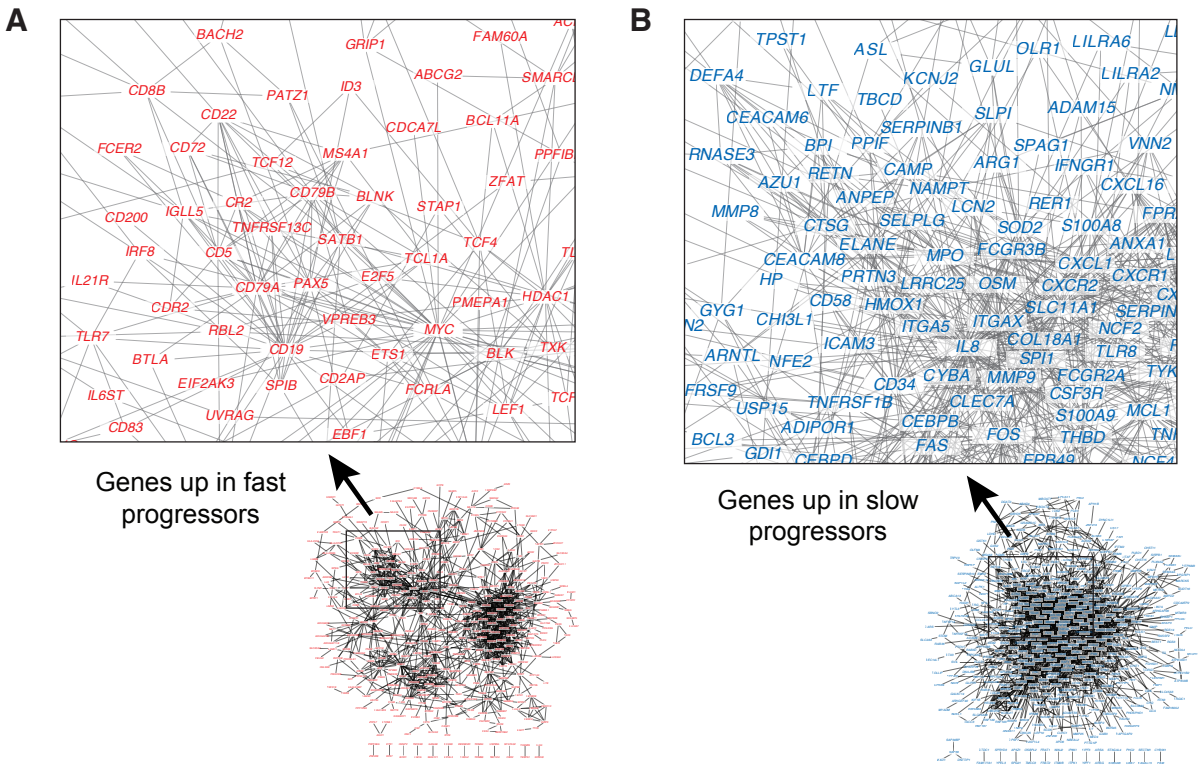

Figure S5. Genes differentially expressed with rate of C-peptide change form dense protein-protein interaction networks. Interaction networks from STRINGdb for genes up in fast progressors (A) and up in slow progressors (B). Insets show regions of the network containing genes from processes enriched in the full set. Genes shown are up-regulated at FDR < 0.05. N=600 and 656 genes, respectively.

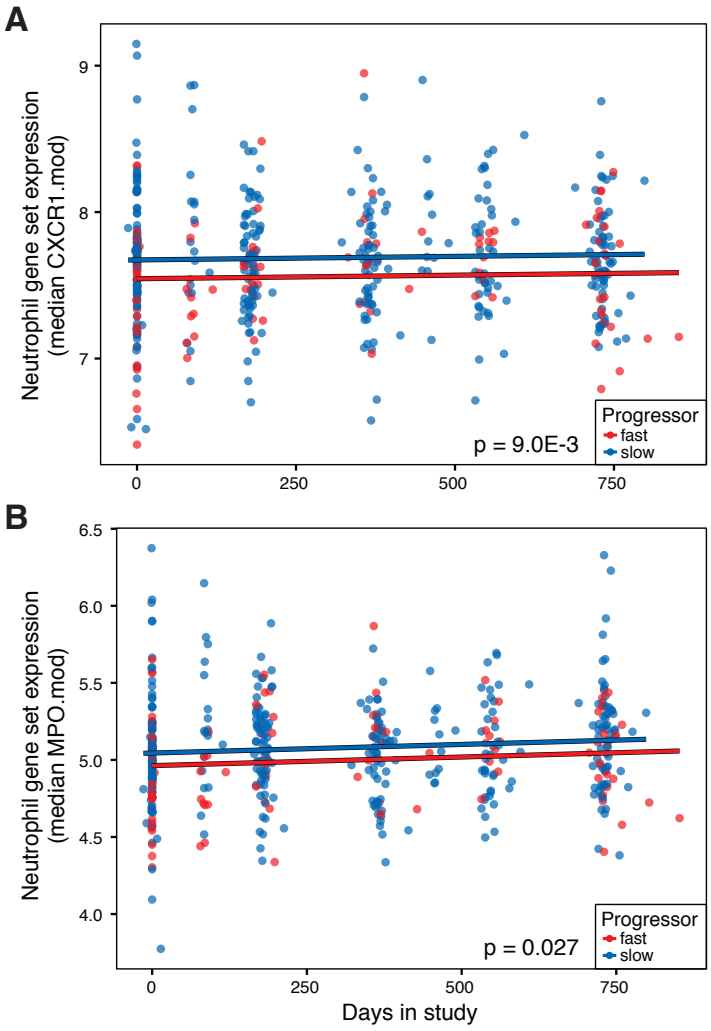

Figure S6. Median neutrophil gene expression levels from RNA-seq differ by progressor group but do not change significantly over time. Median expression of (A) general neutrophil genes, CXCR1.mod, and (B) neutrophil primary granules genes, MPO.mod. Points show individual subject values over the study timeframe; lines show model estimates for fast and slow progressors. Expression values were batch-corrected to remove differences by trial and RNA-seq batch. Fit lines have identical slopes, as there was no evidence of interactions between study day and progressor group; significance values are for difference in intercept between groups. N=470 measurements from 138 subjects.

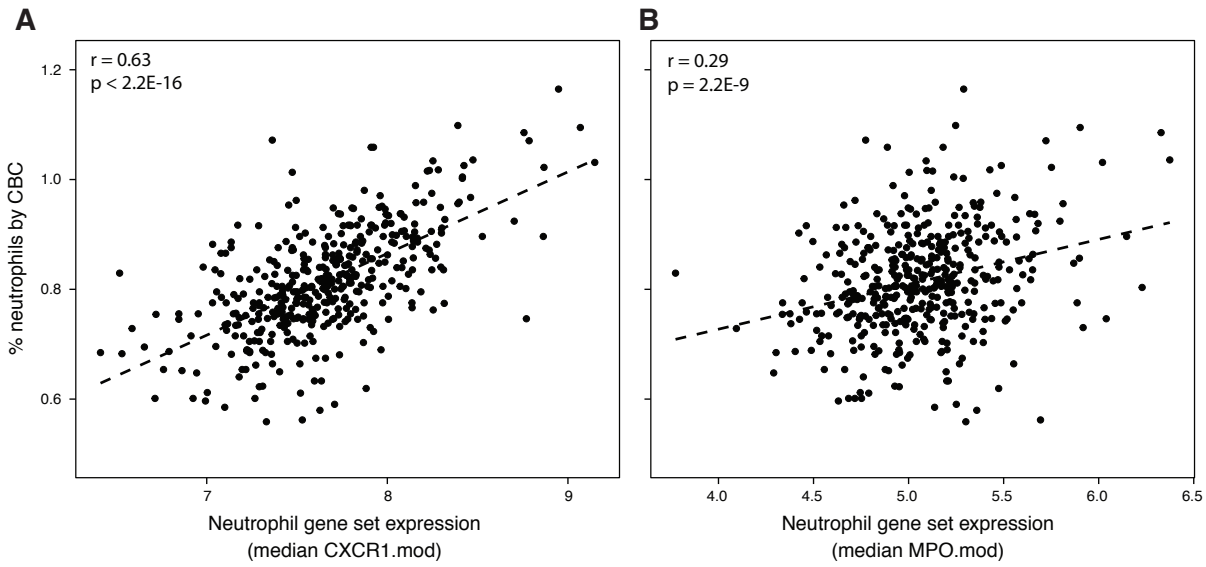

Figure S7. Expression of neutrophil genes is correlated with neutrophil percentages from cell blood counts. A) Expression of general neutrophil genes (CXCR1.mod) is highly correlated with neutrophil levels by CBCs. B) Expression of primary granule and neutrophil activation genes (MPO.mod) is less strongly correlated with neutrophil levels from CBCs, indicating that this gene set captures different information than quantity of neutrophils in the blood. Expression values were batch-corrected to remove differences by trial and RNA-seq batch. N=420 visits with both CBC and RNA-seq data.

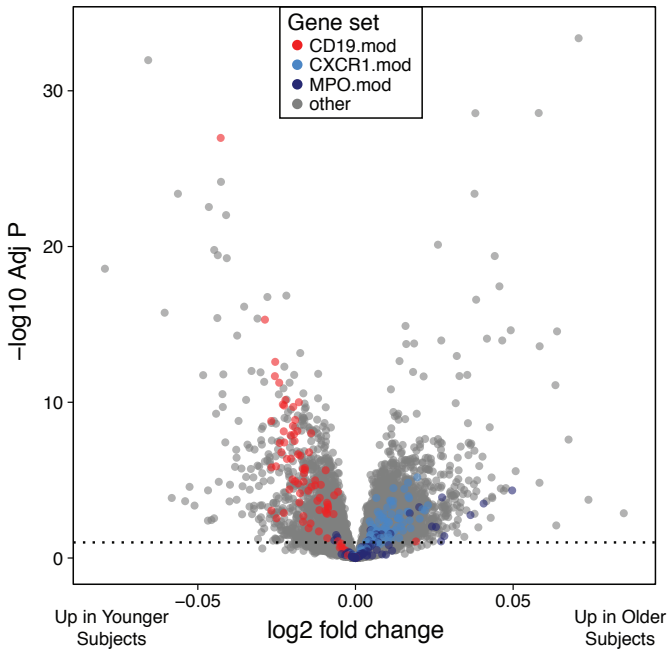

Figure S8. Differential gene expression by subject age as a continuous variable. Multiple neutrophil genes (CXCR1.mod) and neutrophil primary granule genes (MPO.mod) are significantly up-regulated with age. Model includes subject sex and RNA-seq batch as covariates. N=471 samples from 138 subjects.

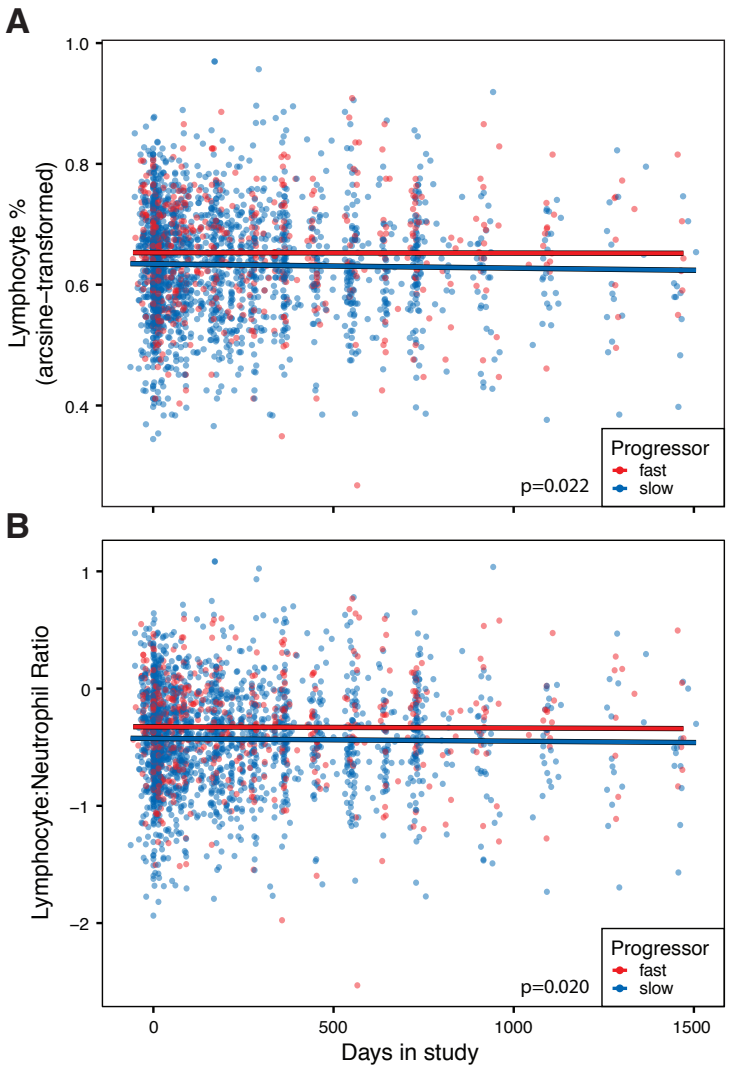

Figure S9. Lymphocyte levels from CBCs differ between progressors groups but do not change significantly over time, for (A) lymphocyte percentage and (B) lymphocyte-to-neutrophil ratio. Points show individual subject values over the study timeframe; lines show model estimates for fast and slow progressors. Fit lines have identical slopes, as there was no evidence of interactions between study day and progressor group; significance values are for difference in intercept between groups. N=2326 samples from 152 subjects.

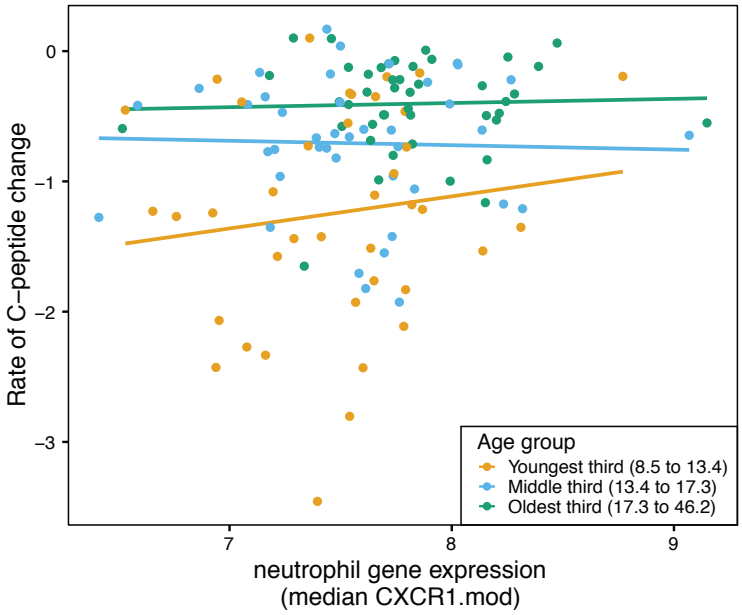

Figure S10. Rate of C-peptide change in relation to baseline neutrophil gene set expression by age tertile. The relationship does not differ significantly between the three age tertiles. N=39, 41, and 44 subjects, respectively.

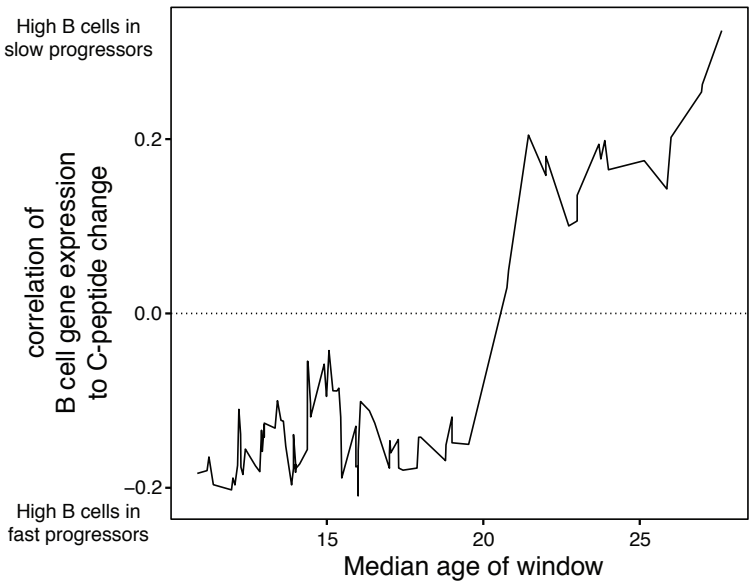

Figure S11. Sliding age window analysis of the relationship between baseline B cell gene expression (CD19.mod) and rate of C-peptide change. X-values represents the median age of the set of 35 subjects included in a given window. Y-values represent the correlation between baseline B cell gene expression and rate of C-peptide change within that set of subjects. Lower y-values indicate a negative relationship, where high B cell gene expression at baseline predicts more rapid loss of C-peptide; higher y-values indicate that B cell gene expression at baseline predicts slower loss of C-peptide. N=124 subjects, 90 windows.

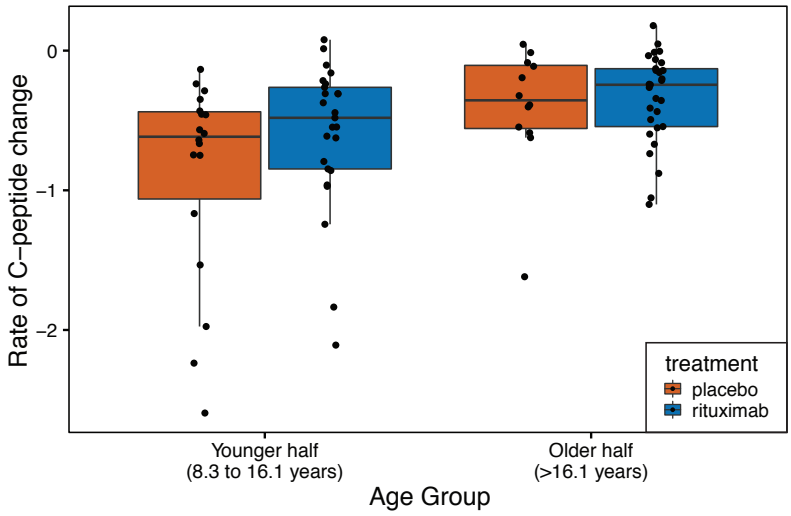

Figure S12. Effect of rituximab treatment on rate of C-peptide change by age. Subjects were split by median age across all patients. Rate of C-peptide is marginally different with treatment in younger subjects (p=0.083 by linear model contrast), but not in older subjects (p=0.72). Boxplots show median, first (Q1) and third (Q3) quartiles, and extent of values beyond Q1 and Q3 up to 1.5 times the interquartile range. N=18 placebo- and 25 active-treated patients in the younger half, and 12 placebo- and 29 active-treated in the older half.

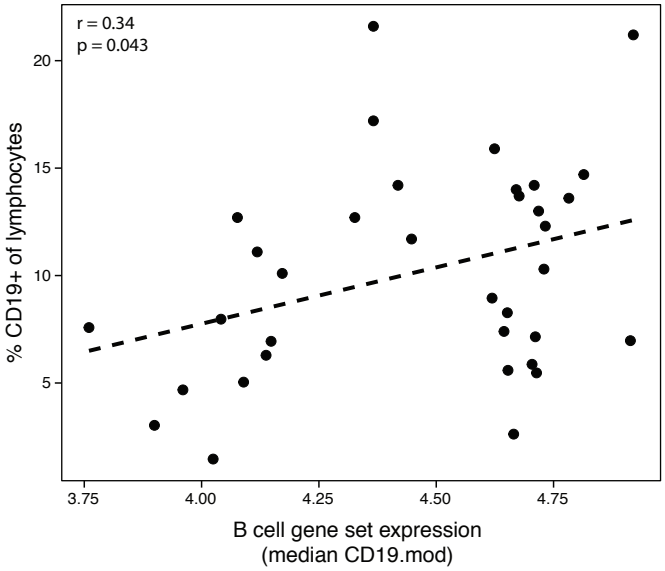

Figure S13. Expression of B cell genes is correlated with B cell percentages from flow cytometry. Gene expression values were batch-corrected to remove differences by trial and RNA-seq batch. N=35 visits with both flow cytometry and RNA-seq data.