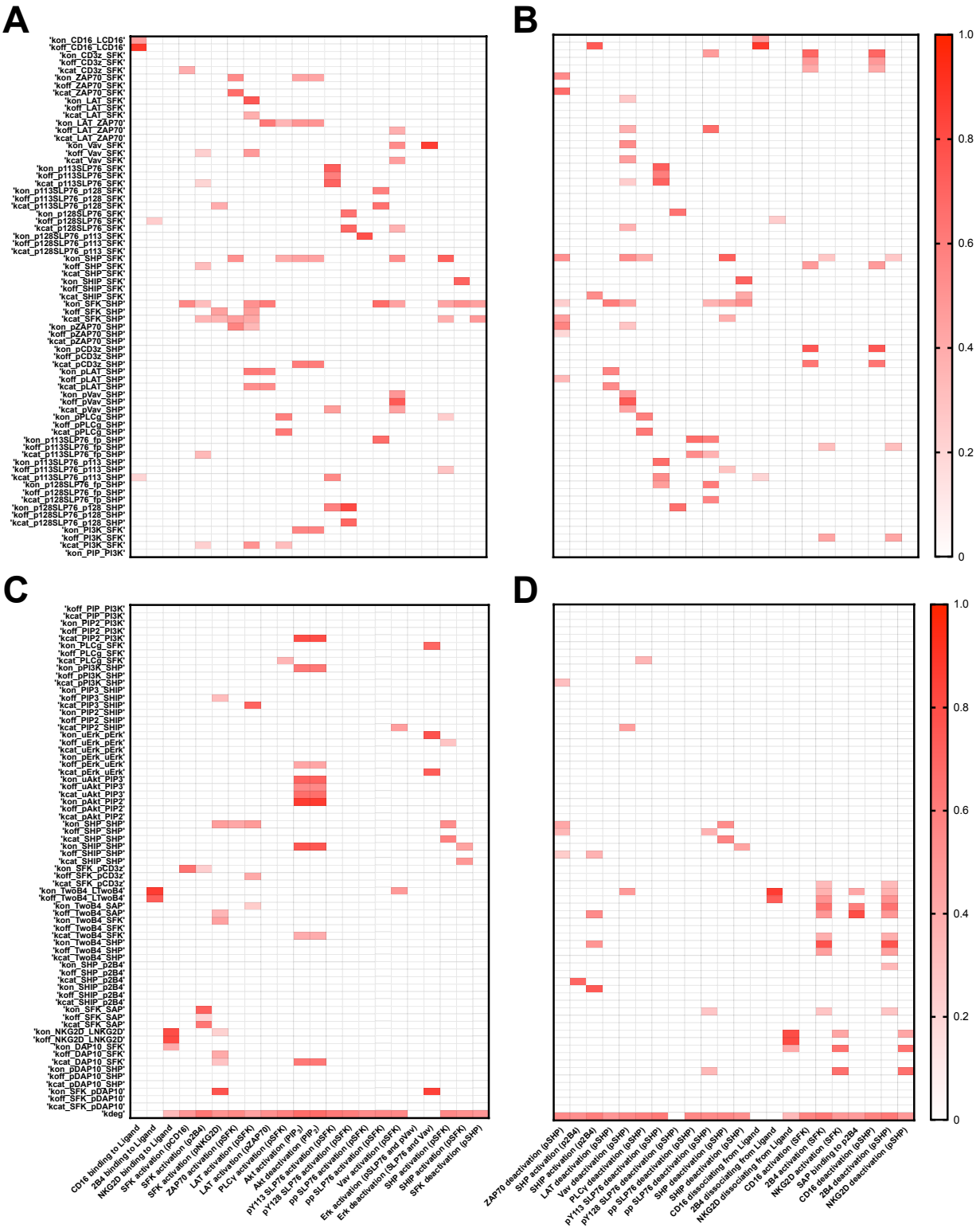

Figure S1. Results of eFAST sensitivity analysis. We performed a global sensitivity analysis to determine how sensitive the upstream reaction rates (44 outputs, horizontal-axis) are to variance in the kinetic parameters (138 inputs, vertical-axis). A total of 138 kinetics parameters (equally split into quadrants (A-D) for visualization) were varied. The color bar corresponds to the total FAST index, S_{Ti}, values. Parameters with an $S_{Ti} \geq 0.5$ were selected for fitting (56 in total), which can be identified in **Figure S2, A-B**.

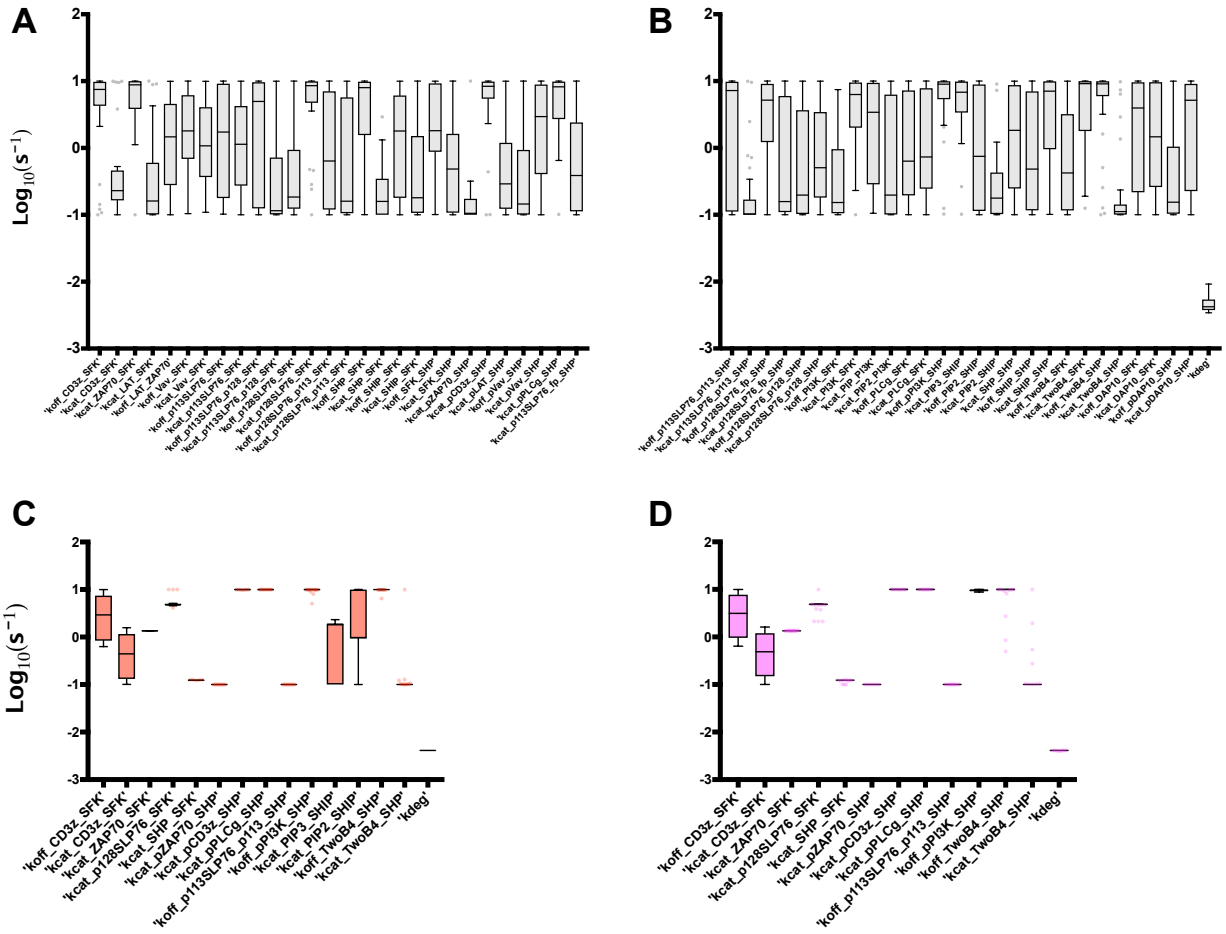

Figure S2. Estimated parameter values. We estimated the kinetic parameter values using PSO. Fifty-six parameters were found to be influential to our model outputs via eFAST sensitivity analysis. These 56 parameters were varied from their baseline value $\pm$ 10-fold. The results are shown in panels A (28 parameters) and B (28 parameters). Results from the second and third iteration of fitting are shown in panels C and D, respectively. Points represent outliers according to Tukey's method.

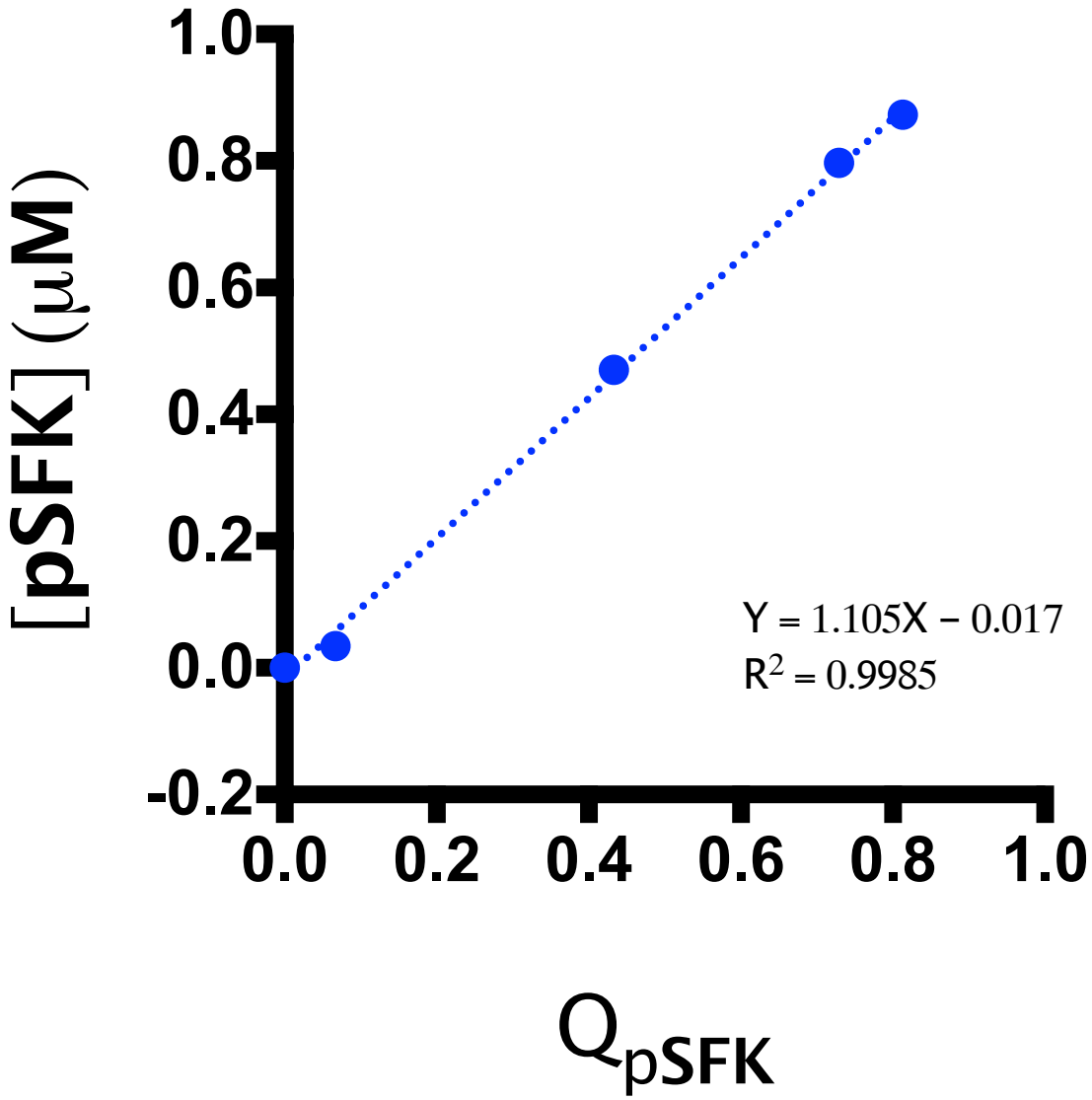

Figure S3. Relationship between predicted absolute concentrations and signal intensity values. Since the molecular perturbation data includes only one or two data points, normalization according to the methods described above is not possible. Thus, we generated a standard curve between the predicted absolute concentration of a phosphorylated species (pX) and its corresponding measured signal intensity (Q_{pX}) values at the discrete time points of experimental measurement. After model fitting, the signal intensity values of a species (horizontal axis) were plotted against the model's predicted absolute concentration of the same species (vertical axis). Using linear regression analysis in Prism (GraphPad), a mathematical relationship between signal intensity and species concentration was derived. Next, we used the equation to calculate the predicted absolute concentration from signal intensity data. These predicted concentration values were plotted as points in **Figure 3, E-H** and compared to the model simulations. We generated such figures and mathematical relationships for each panel in **Figure 3, E-H**. Here, we show the case for pSFK as an illustration. Circles: data points; dashed line: best-fit line.

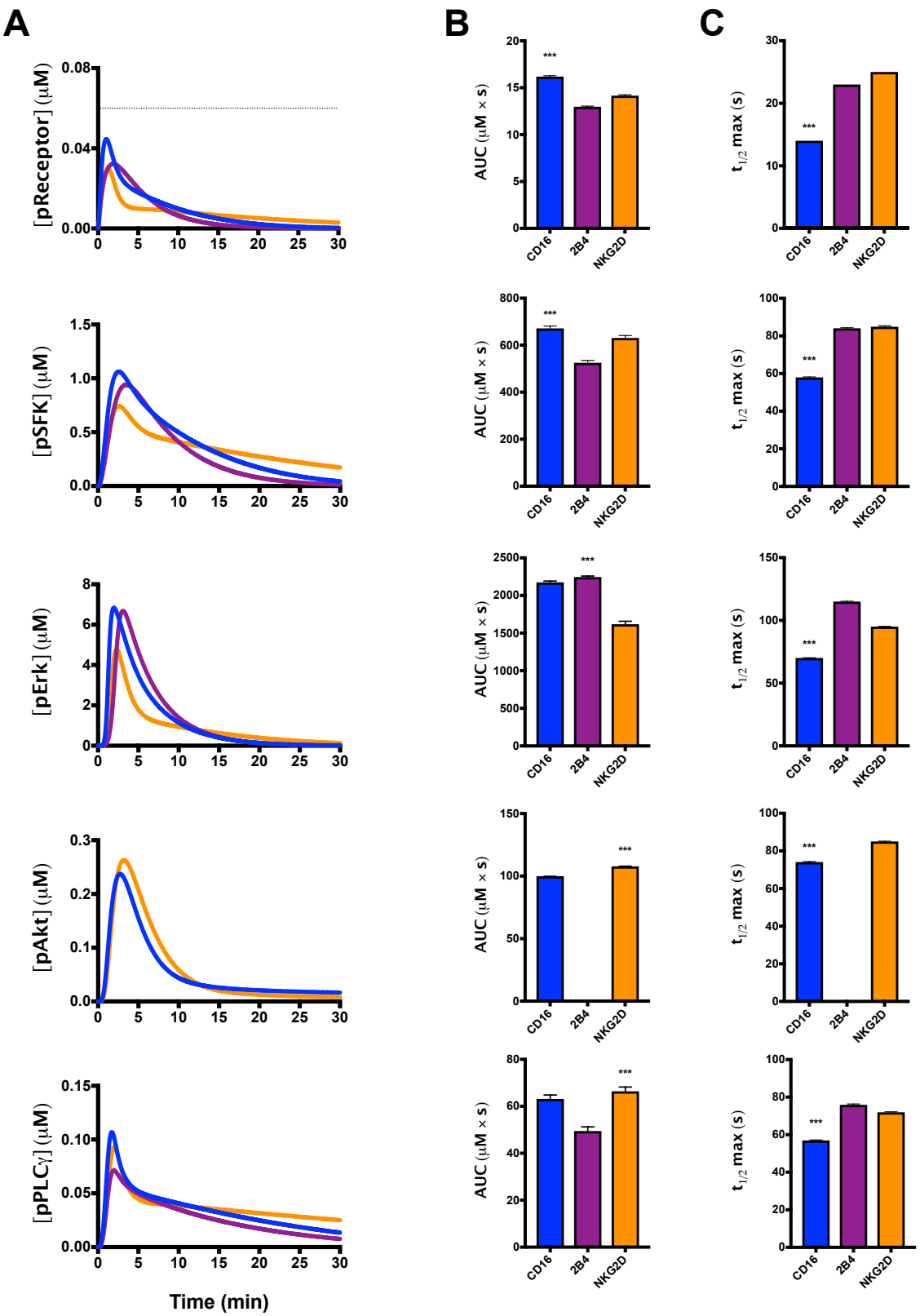

Figure S4. Characteristic signaling differences when CD16 is reduced 100-fold. (A) Concentration profiles for activation-influencing species: pReceptor, pSFK, pErk, pAkt, and pPLCγ. (B) Magnitude of activation for the corresponding species in panel A via AUC analysis. (C) Time to reach half-maximal concentration for the corresponding species in panel A. Blue: CD16 pathway. Purple: 2B4 pathway. Orange: NKG2D pathway. Asterisks signify the highest AUC or lowest $t_{1/2}\,max$ based on *t*-test ($p < 0.001$).

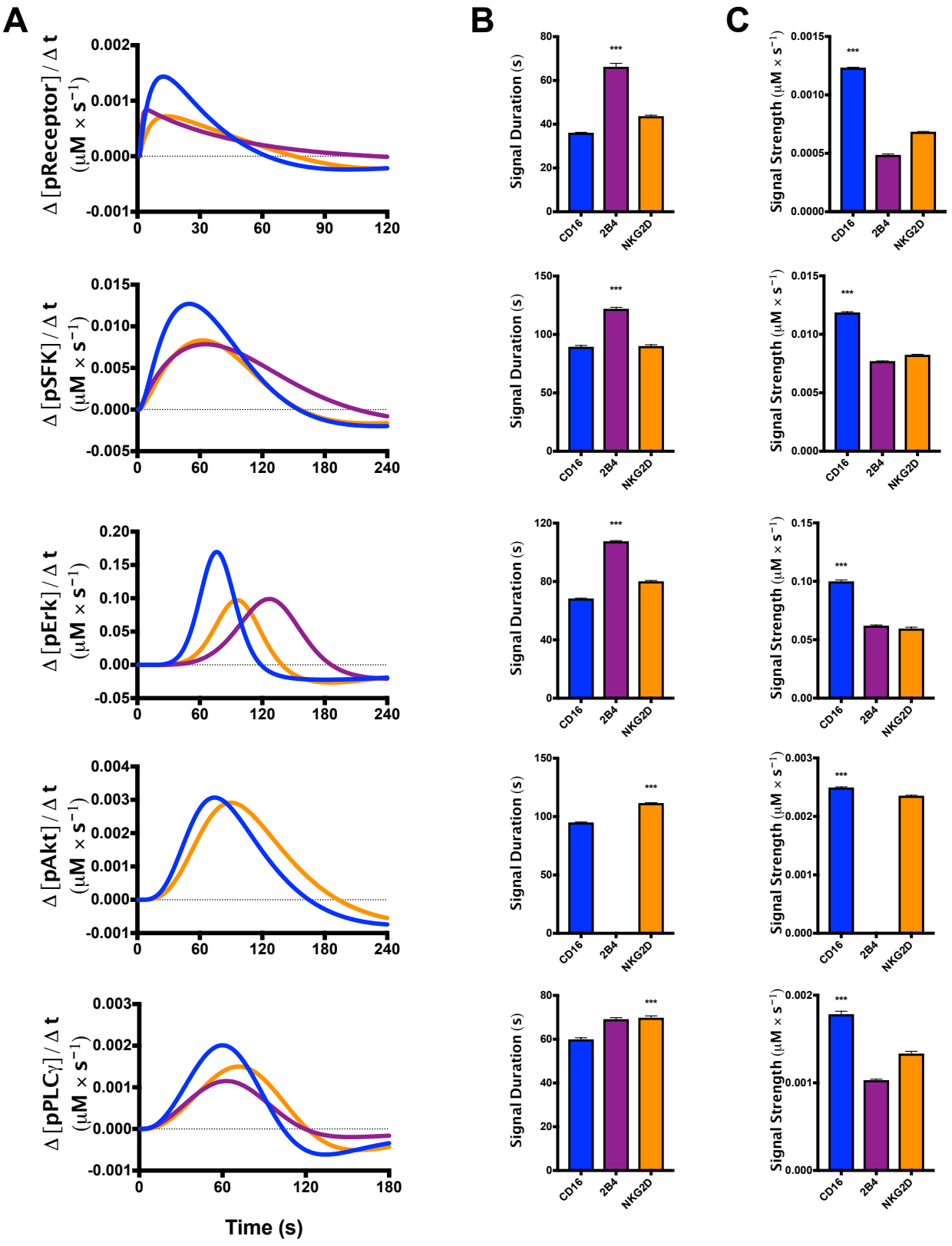

Figure S5. Kinetic analysis of species activation when CD16 is reduced 100-fold. (A) Time derivatives of the concentration profiles for activation-influencing species: pReceptor, pSFK, pErk, pAkt, and pPLCγ. (B) The calculated signal duration for the corresponding species in panel A. (C) The signal strength for the corresponding species in panel A. Blue: CD16 pathway. Purple: 2B4 pathway. Orange: NKG2D pathway. Asterisks signify the highest signal duration or signal strength based on *t*-test ($p < 0.001$).

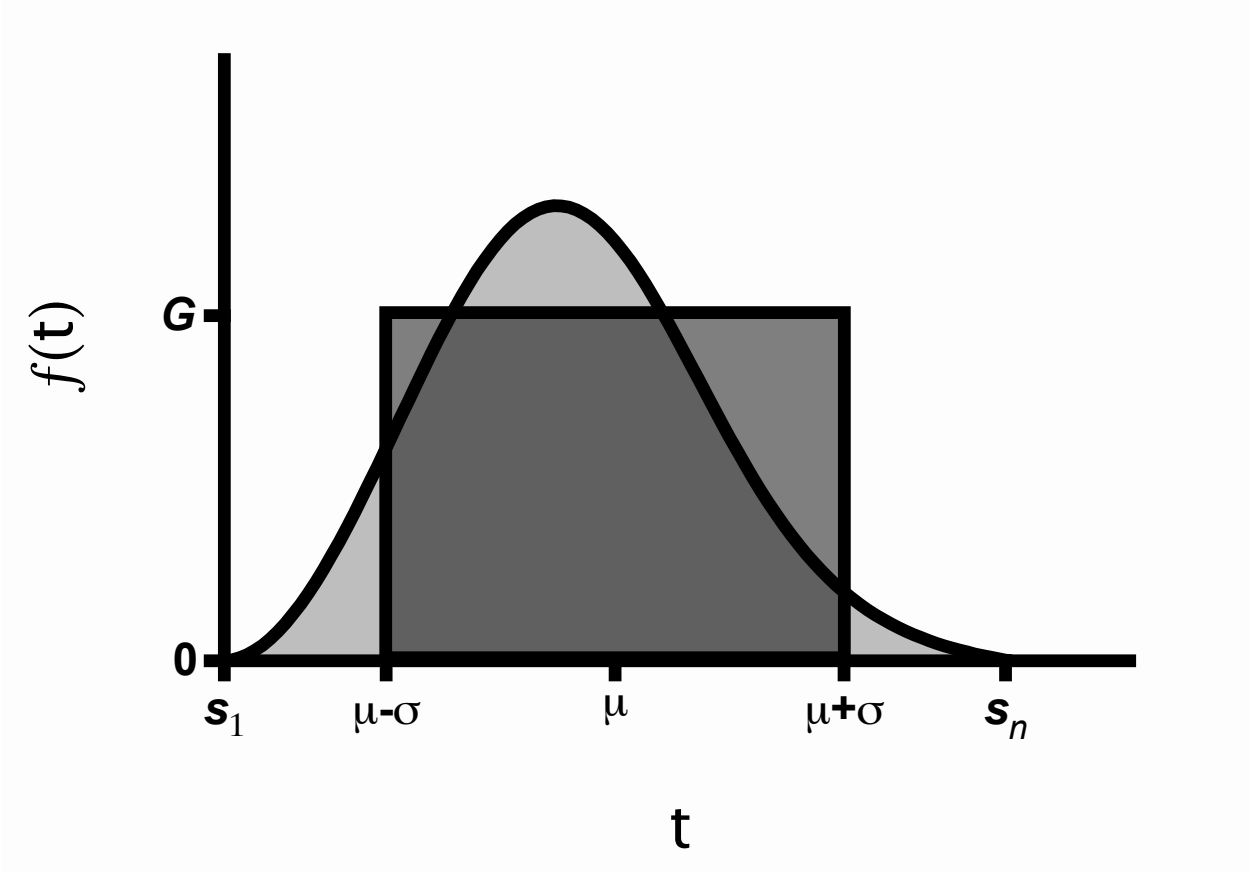

Figure S6. Signal duration and signal strength. The time derivative of a phosphorylated species, represented as $\boldsymbol{f}(t)$, plotted over time. The shaded area in the rectangle is equal to the shaded area under the curve. The height of the rectangle defines the curve's signal strength ($\boldsymbol{G}$) and the width of the rectangle defines the curve's signal duration ($\boldsymbol{\vartheta} = 2\sigma$).