**Supplementary Figures**

**Figure S1. The comparison of predicted and measured pharmacodynamics of bevacizumab and ABT-510 in cancer patients.** The dots are measured data in clinical trials using bevacizumab (40) or ABT-510 (42) as single-agent treatment. The solid lines are predictions from the whole-body systems biology model.

**Figure S2. The sensitivity indices of model parameters.** We report the eFAST sensitivity indices for three groups of parameters (horizontal axis): (A) receptor numbers on tumor cells (“Tumor cell”), normal and diseased endothelial cells (“Norm EC” and “Tumor EC”) and parenchymal cells in the normal compartment (“Norm Cell”, representing muscle fiber cells); (B) inter-compartmental transport rate; and (C) the kinetic parameters: *koff* is the dissociation rate of the complex and *kc* is the coupling rate of the complex. We examined nine outputs in three compartments (vertical axis): proMMP9:MMP3 (proMMP9 bound to MMP3), TSP1:MMP3 (TSP1 bound to MMP3), TSP1:VEGF (TSP1 bound to VEGF), proMMP9, MMP3, MMP9, TSP1, VEGF and Angio-Ratio (the angiogenic ratio).

**Figure S3. The effect of anti-angiogenic therapy on angiogenic complexes in tumor.**  The left panel shows the changes of absolute concentrations of the angiogenic complexes. The right panel shows the percentages of individual angiogenic complexes relative to the total. (A) Bevacizumab promotes the decrement of pro-angiogenic complexes involving VEGFR1. (B) ABT-510 promotes the formation of anti-angiogenic complexes involving CD36. (C) Combination therapy decreases pro-angiogenic complexes and increases anti-angiogenic complexes. Anti-angiogenic complexes: *B1* represents the TSP1-bound B1 receptors; *CD36* includes TSP1-bound and ABT-510-bound CD36 receptors; *CD47* represents TSP1-bound CD47 receptors; and *LRP1* represents TSP1-bound LRP1 receptors. Pro-angiogenic complexes: *R1* represents the VEGF-bound VEGFR1 receptors; *R2* represents the VEGF-bound VEGFR2 receptors; *N1* and *N2* represent the VEGF-bound neuropilin co-receptors. The tertiary complex of VEGF, VEGFR2, and neuropilin is counted as VEGF-bound neuropilin.

**Figure S4. The dynamics of VEGF, TSP1, and the angiogenic ratio with combination therapy.** The solid line indicates the average of the simulation results of 1,000 sampled tumor receptor profiles. The shaded area shows the 90% confidence interval.

**Figure S5. The fold-changes of the angiogenic complex with combination therapy.** The numbers of the various receptor complexes change following combination treatment. Dark grey area indicates a fold-change higher than 1, and light grey denotes a fold-change lower than 1. *B1-complex,* the TSP1-bound B1 receptors; *CD47-complex,* TSP1-bound CD47 receptors; *LRP1-complex*, TSP1-bound LRP1 receptors; *N1-complex*, VEGF-bound neuropilin-1;and *N2-complex*,VEGF-bound neuropilin-2; *R1-complex,* VEGF-bound VEGFR1 receptors; *R2-complex,* VEGF-bound VEGFR2 receptors that do not involved ligand bound TSP1 receptors; *R2-complex (inactive),* VEGF-bound VEGFR2 receptors coupled with ligand-bound TSP1 receptors; *CD36-complex,* TSP1-bound and ABT-510-bound CD36 receptors. The tertiary complex of VEGF, VEGFR2 and neuropilin is counted as VEGF-bound neuropilin.

**Figure S6. The comparison of the predicted responses from the PLSR model and the mechanistic model.** Our optimal PLSR model has two principal components and shows good performance (Q2Y = 0.94; R2Y = 0.93). The dashed line represents a 100% match between predicted values from the PLSR model and the responses predicted by the three-compartment systems biology model.

**Figure S7. The association between angiogenic receptors and response to combination anti-angiogenic therapy.** The normalized receptor level is plotted versus the response to combination therapy (fold-change in the angiogenic ratio for tumor tissue) for all 16 receptors varied in our simulations. The orange line is the locally weighted scatterplot smoothing (LOWESS).

**Supplementary Files**

**Supplementary File S1.** Detailed description of BioNetGen model formulation and parameters.

**Supplementary File S2.** This zipped file contains the computational model used to generate the results presented in this paper: “TSP1\_VEGF\_Model.m”, the MATLAB *m*-file containing the whole-body TSP1-VEGF model; “run\_baselinedynamics.m”, “run\_MCsimulations.m”, the MATLAB scripts to run the baseline model and Monte Carlo simulations, respectively; and “findParamValue\_Rec.m” the MATLAB script to randomly generate the receptor number.