

## Supplementary Data Guide

**Supplementary Data 1:** Drug-drug interaction Bliss scores for all strains. Each row contains the Bliss scores for the drug pair indicated in column 1. All concentration ratios tested in the screen are listed. There is a perfect well-to-well correspondence between the Bliss scores in this table and the expected fitness values from Supplementary Data 3. The name of the strains and the drug pairs corresponding to each distribution are indicated in the 1<sup>st</sup> and 2<sup>nd</sup> column, respectively.

**Supplementary Data 2:** p-values for drug-drug interactions for all strains. p-values from the statistical tests as described in Methods are listed. The name of the strains and the drug pairs are indicated in the 1<sup>st</sup> and 2<sup>nd</sup> column, respectively. Column 3 contains the p-values obtained using the complete distribution of Bliss interaction scores per drug combination. Columns 4 and 5 contain p-values after restricting the Bliss scores to those wells relevant for detecting antagonism or synergy, respectively (Methods). The number of wells used to assign antagonism and synergy upon restriction are listed in columns 6 and 7, respectively.

**Supplementary Data 3:** Expected fitness ( $f_a \cdot f_g$ ) for all drug combinations for all strains. Each row contains the expected fitness values for the strains and drug pair indicated in the 1<sup>st</sup> and 2<sup>nd</sup> column, respectively. All concentration ratios tested in the screen are listed. There is a perfect well-to-well correspondence between the expected fitness values in this table and the Bliss scores from Supplementary Data 1.

**Supplementary Data 4:** Fitness of double drug treatment for all strains. Columns and rows correspond to different array and query drugs, respectively. Query drugs are indicated in the 2<sup>nd</sup> column, while the array drugs used for a given strain are provided in the row preceding the data for that particular strain. The name of the strain is given in the 1<sup>st</sup> column. Drug concentrations are indicated as 1, 2 or 3 and correspond to the highest, middle and lowest (2-fold dilution series) concentration tested. The highest (1) concentration is given in Supplementary table 1. *rep* is a general indication of *replicate*. Control refers to when no query drug was added.

**Supplementary Data 5:** Fitness of single treatment with array drugs for all strains. The 1<sup>st</sup> and 2<sup>nd</sup> column represent the strain and array drug. Indication of drug concentrations follows the same principle as for Supplementary Data 4. When using single fitness data to calculate drug interactions, query and array batch indicators must be matched.

**Supplementary Data 6:** Fitness of single treatment with query drugs for all strains. The 1<sup>st</sup> and 2<sup>nd</sup> column represent the strain and query drug. Indication of drug concentrations follows the same principle as for Supplementary Data 4. When using single fitness data to calculate drug interactions, query and array batch indicators must be matched.

**Supplementary Data 7:** Fitness of all strains on drug-drug combinations in 8x8 checkerboards for validation dataset. The first two lines refer to the drug concentration ratios: increasing at equal steps from 1 to 7. 0 means no drug. 1 refers to the highest drug concentration used for that particular drug, listed in Supplementary Table 3.

**Supplementary Data 8:** Fitness of MDR *E. coli* and *K. pneumoniae* clinical isolates on drug-drug combinations in 8x8 checkerboards. The first two lines refer to the drug concentration ratios: increasing at equal steps from 1 to 7. 0 means no drug. 1 refers to the highest drug concentration used for that particular drug, listed in Supplementary Table 5.

**Supplementary Data 9:** Raw data (OD<sub>595nm</sub> over time) for all drug-drug combinations for the *E. coli* strains screened in this study.

**Supplementary Data 10:** Raw data (OD<sub>595nm</sub> over time) for all drug-drug combinations for the *S. Typhimurium* strains screened in this study.

**Supplementary Data 11:** Raw data (OD<sub>595nm</sub> over time) for all drug-drug combinations for the *P. aeruginosa* strains screened in this study.