***eLife’s* transparent reporting form**

We encourage authors to provide detailed information *within their submission* to facilitate the interpretation and replication of experiments. Authors can upload supporting documentation to indicate the use of appropriate reporting guidelines for health-related research (see [EQUATOR Network](http://www.equator-network.org/%20)), life science research (see the [BioSharing Information Resource](https://biosharing.org/%22%20%5Ct%20%22_blank)), or the [ARRIVE guidelines](http://www.plosbiology.org/article/info%3Adoi/10.1371/journal.pbio.1000412) for reporting work involving animal research. Where applicable, authors should refer to any relevant reporting standards documents in this form.

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**Sample-size estimation**

* You should state whether an appropriate sample size was computed when the study was being designed
* You should state the statistical method of sample size computation and any required assumptions
* If no explicit power analysis was used, you should describe how you decided what sample (replicate) size (number) to use

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

As this study focused on RNAseq, sample size was limited by cost. The number of replicates was chosen based on experience.

**Replicates**

* You should report how often each experiment was performed
* You should include a definition of biological versus technical replication
* The data obtained should be provided and sufficient information should be provided to indicate the number of independent biological and/or technical replicates
* If you encountered any outliers, you should describe how these were handled
* Criteria for exclusion/inclusion of data should be clearly stated
* High-throughput sequence data should be uploaded before submission, with a private link for reviewers provided (these are available from both GEO and ArrayExpress)

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

Reproducibility of viability results is discussed in the Results section. The numbers of replicates are detailed in Methods.

**Statistical reporting**

* Statistical analysis methods should be described and justified
* Raw data should be presented in figures whenever informative to do so (typically when N per group is less than 10)
* For each experiment, you should identify the statistical tests used, exact values of N, definitions of center, methods of multiple test correction, and dispersion and precision measures (e.g., mean, median, SD, SEM, confidence intervals; and, for the major substantive results, a measure of effect size (e.g., Pearson's r, Cohen's d)
* Report exact p-values wherever possible alongside the summary statistics and 95% confidence intervals. These should be reported for all key questions and not only when the p-value is less than 0.05.

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

Statistical methods are described in the Methods section. Results of statistical tests are reported in the figures and the Results section.

(For large datasets, or papers with a very large number of statistical tests, you may upload a single table file with tests, Ns, etc., with reference to sections in the manuscript.)

**Group allocation**

* Indicate how samples were allocated into experimental groups (in the case of clinical studies, please specify allocation to treatment method); if randomization was used, please also state if restricted randomization was applied
* Indicate if masking was used during group allocation, data collection and/or data analysis

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

Groups in our experiments were control, single treatments, and combination treatments.

**Additional data files (“source data”)**

* We encourage you to upload relevant additional data files, such as numerical data that are represented as a graph in a figure, or as a summary table
* Where provided, these should be in the most useful format, and they can be uploaded as “Source data” files linked to a main figure or table
* Include model definition files including the full list of parameters used
* Include code used for data analysis (e.g., R, MatLab)
* Avoid stating that data files are “available upon request”

Please indicate the figures or tables for which source data files have been provided:

Data described in the Results section but not in a figure is in:

Supplementary File 1 Tamoxifen and Mefloquine.xlsx

Supplementary File 2 Tamoxifen and Withaferrin.xlsx

Viability data for (Figure 1-figure supplement 1) and (Figure 1) is in these supplementary files:

Supplementary File 3 MCF7 Combination Viability.xlsx

Supplementary File 4 LNCap Combination Viability.xlsx

Supplementary File 5 LNCap Combinations.xlsx

Supplementary File 6 Dose Combination.csv

Log cpm tables that are the source for heatmaps and PCA plots in (Figure 1) and (Figure 1-figure supplement 2) can be found in these files:

Source Data File 1 mcf7\_log\_cpm.csv

Source Data File 2 lncap\_expression.csv

Source Data File 3 ss\_log\_cpm.csv

Raw RNAseq data is available at [ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE149428](https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE149428). Specifically, raw data from the MCF7 and LNCaP experiments have been uploaded to GEO as noted in the paper. Unfortunately, the raw RNAseq data from the dose experiments was lost due to hard drive failure.

Code is available at [github.com/jennifereldiaz/drug-synergy](https://github.com/jennifereldiaz/drug-synergy).