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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), life science research (see the BioSharing Information Resource), or the ARRIVE guidelines for reporting work involving animal research. Where applicable, authors should refer to any relevant reporting standards documents in this form.

If you have any questions, please consult our Journal Policies and/or contact us: editorial@elifesciences.org.

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:

We chose a sample size of 65,536 for the CR-9114 library and 2,048 for the CR-6261 library to measure the impact of all possible combinations of mutations on binding affinity for each antibody. The library design is explained in the Mutation Selection section of the Methods and is illustrated in Figure 1.

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:

The replicate structure (and definition) is described in lines 522-524 of the Methods section for the Tite-seq assays, and in lines 620-621 for the Isogenic validation assays. For the Tite-seq assays, the removal of outliers is explained in lines 651-654 of the Methods section. Figure 1—Source Data Files 1 and 2 contain measurements for all replicates.

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:

All statistical tests used are described in the associated figure legends and Methods sections.

(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:

Experimental groups contain a random sampling of each combinatorially complete library, as production of the library via Golden Gate cloning, transformation, and microbial growth is inherently random. For all experimental steps, random sampling of the libraries was kept at 10-fold excess of the library diversity to ensure adequate sampling of all library variants. This information is described in the Golden Gate assembly and Yeast library production sections of the Methods.

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:

Figure 1—source data 1. CR-9114 library -logK_D to H1, H3, and influenza B.
Figure 1—source data 2. CR-6261 library -logK_D to H1 and H9.
Figure 1—source data 3. Isogenic flow cytometry measurements of $-\log_{10}K_D$ for select CR-9114 and CR-6261 variants.
Figure 2—source data 1. Interaction model coefficients for CR-9114.
Figure 2—source data 2. Interaction model coefficients for CR-6261.
Figure 2–source data 3. Tabulated contact surface area, number of HA contacts, and pairwise distances for
mutations in CR9114 and CR6261.
Figure 5—source data 1. Total log probability of mutational trajectories for CR-9114 under different antigen selection scenarios.
Figure 5—source data 2. Total log probability of mutational trajectories for CR-6261 under different antigen selection scenarios.

Data and code used for this study are available at https://github.com/klawrence26/bnab-landscapes. FASTQ files from high-throughput sequencing have been deposited in the NCBI BioProject database with accession number PRJNA741613, and will be publicly released upon acceptance.