***eLife’s* transparent reporting 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

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We did not use sample size estimation methods. The number of replicates, where applicable, were determined arbitrarily to constitute a convincing dataset.

**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)

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Details on experimental replicates, where applicable, are reported in the Materials and Methods section. Technical replicates are multiple measurements performed on the same sample, or as identical treatments on a multiwell plate (e.g. four wells receiving the same concentration of the same nanobody), whereas biological replicates are a repetition of the experiment on different days using different cells.

**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.

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Statistical reporting is provided, where appropriate, in the figure legends, results and discussion, and in the supplemental tables. **No data were excluded**.

(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

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Not applicable in this study.

**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: data in Figure1\_source\_data.xlsx with ms dataset deposited at zenodo.org with doi: 10.5281/zenodo.5236816.

Figure 2: data provided as supplemental Figure 2—figure supplement 1, and 2; and Tables 1, 2, and 3.

Figure 3: data in Figure3\_source\_data.xlsx with additional supporting data provided as as Figure 3—figure supplement 1.

Figure 4: data provided in Tables 1, 2, 4, and 5.

Figure 5: data in Figure5\_source\_data.xlsx

Figure 6: data in pbd files (S1-1.pdb, S1-6.pdb, S1-23.pdb, S1-36.pdb, S1-37.pdb, S1-46.pdb, S1-48.pdb, S1-49.pdb, S1-62.pdb, S1-RBD-9.pdb, S1-RBD-15.pdb, S1-RBD-16.pdb, S1-RBD-21.pdb, S1-RBD-22.pdb, S1-RBD-23.pdb, S1-RBD-24.pdb, S1-RBD-29.pdb, S1-RBD-35.pdb, S1-RBD-40.pdb, S2-10.pdb, S2-40.pdb) with ms dataset deposited at zenodo.org with doi: 10.5281/zenodo.5236816 and summarized in Table 8 with additional supporting data provided as Figure 6—figure supplement 1, 2, and 3. Files containing input data, scripts and output results are available at https://github.com/integrativemodeling/nbspike.

Figure 7: data in Figure7\_source\_data.xlsx with modeling parameters provided as Table 9, additional supporting data provided as Figure 7—figure supplement 1.