nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Collected data was recorded on Microsoft Excel spreadsheets. Raw data was formatted for modeling using R version 4.3.1.
Data analysis	Data visualizations and simulations were done using R version 4.3.1. Modeling of data was done using NONMEM version 7.5.1 through Perl-speaks-NONMEM (PsN) version 5.3.0.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The rabbit pharmacokinetic data and models generated in this study are found in a Figshare database: https://figshare.com/s/302fef4734cd499c2b51?file=55374947. The code generated for preclinical data visualization, preclinical model diagnostics, and clinical simulations can be found on https://github.com/saviclab/lesion_pk_manuscript.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex information was available from the retrospective clinical data used for model validation. However, sex was not considered in the analysis, as it was not a relevant covariate to distinguish between easy-to-treat and hard-to-treat phenotypes.
Reporting on race, ethnicity, or other socially relevant groupings	Subject race and study site (country) were available from the retrospective clinical data used for model validation. However, this information was not considered in the analysis, as these were not relevant covariates to distinguish between easy-to-treat and hard-to-treat phenotypes.
Population characteristics	Population characteristics of the human research participants in the Phase 3 clinical trials (used for model validation) can be found in the trial-specific publications, referenced in Supplementary Table 5. Characteristics of the participants in the lesion resection study can be found in PMID 30939136.
Recruitment	Recruitment information can be found in the trial-specific publications, referenced in Supplementary Table 5, and in PMID 30939136.
Ethics oversight	Human tissue data not previously published was acquired and approved by the Institutional Review Board of the National Institute of Allergy and Infectious Diseases and by the institutional review boards of the hospitals conducting the study in the Republic of Korea. Subjects gave written informed consent to participate in the study and to have their resected tissue used for research.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	For animal studies, approximately three rabbits at three time points per drug (at Cmax, the end of the distribution phase, and Cmin) were selected to appropriately characterize PK via population PK modeling. The total number of rabbits varied depending on the proportion of animals with good pathology.
Data exclusions	No data were excluded from analyses.
Replication	In most experiments, multiple drug concentrations were taken for a given time point and dose level.
Randomization	Randomization was not relevant to this study, as the pharmacokinetic data were collected from animals.
Blinding	Investigators were not blinded to treatment allocation during data collection or analysis. Blinding was not relevant to this study, as the pharmacokinetic data were collected from animals. Drug and dose information were needed by data analysts for modeling.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	THP-1 macrophage-like cells
Authentication	Cell lines were purchased from ATCC, a reputable vendor that guarantees that cell lines are authenticated. New experiments were started from the seed stock.
Mycoplasma contamination	Cell lines were not tested for mycoplasma contamination; however, they were purchased from ATCC, a reputable vendor that guarantees that cell lines are free of contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	New Zealand White rabbits
Wild animals	The study did not involve wild animals.
Reporting on sex	All animals were female, as they are smaller, and thus compound requirements are lower. Furthermore, male rabbits are more aggressive, creating a significant added risk for the staff in a BSL-3 facility working with TB-infected animals. However, we expect this does not result in sex-specific results, as overall TB disease progression is very similar in male and female rabbits, with regards to the lesion types that develop and magnitudes of bacterial burden.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All research complied with relevant ethical regulations and was approved by the respective institution including the Institutional Animal Care and Use Committee of the Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, NJ.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	Retrospective clinical data from completed studies was utilized to validate model predictions. Trial registration numbers are found in Supplementary Table 5.
Study protocol	Information on the study protocols can be found in the associated references for each clinical trial in Supplementary Table 5.
Data collection	Data collection information can be found in the associated references for each clinical trial in Supplementary Table 5.
Outcomes	Outcome definitions for each clinical trial can be found in Supplementary Table 5.

Plants

Seed stocks	No seed stocks or other plant material were used in the study.
Novel plant genotypes	No novel plant genotypes were produced in the study.
Authentication	No authentication procedures were needed, as no plant material was used in the study.