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	Custom hardware control code was used which makes use of various software packages and drivers that are available online or with the respective instrumentation. Our custom hardware control script is available on request. Hardware control and measurement parameters are described in detail in the manuscript.
Data analysis	Custom processing software written in Python and MATLAB was used and is available in an open-source repository under the MIT license at https://doi.org/10.5281/zenodo.8121099.

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

Main data is available via the University of St Andrews data repository at https://doi.org/10.17630/bec9180a-86e6-4157-822f-fa84249452dd, additional unprocessed large data sets are available as demo data sets in the code repository at https://doi.org/10.5281/zenodo.8121099. No accession codes are required.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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	At least n>40 laser particles were present in each field of view that were chosen at random, yielding typically n>10 spectra per laser particle. As our method is inherently high-throughput with routinely large sample sizes and samples are randomly selected from a batch of laser particles with very homogeneous quality and a rather narrow size distribution, no prior sample size calculation was deemed necessary.
Data exclusions	In the high-throughput sensing measurement, spectra were excluded when the asymptotic expansion fit failed to converge as judged by a high residual error (error > 40 pm which is comparable to the FWHM of the measured lasing peaks). In the cell tracking experiment, trajectories of cells that were not tracked over the majority of the measurement duration are excluded. No other data was excluded.
Replication	The microscope has been in routine operation for several years now. Imaging results are reliably replicated. Data sets shown in the present work were obtained specifically to represent the abilities of the microscope and to illustrate typical results or common errors.
Randomization	Randomization was not required as no comparisons between groups have been performed. All laser particles used to compare different measurement conditions stem from the same batch.
Blinding	No blinding has been applied as the study does not contain comparisons between different sample groups nor required data analysis that is affected by experience or subjective interpretation of a particular researcher.

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

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)	Experiment 1 (laser particle cell sorting): HEK293T cells were purchased from SigmaAldrich (Cat.No. 12022001), and modified in house to express CheRiff-EGFP. Experiment 2 (Cell tracking): Primary keratinocytes were isolated from newborn C57BL/6N mouse epidermis.
Authentication	Exp. 1: Authenticity was certified by supplier (ECACC). Exp. 2: Primary keratinocytes are isolated from dissected epidermis. Other epidermal cell types like tissue resident immune cells and melanocytes are depleted due to culture conditions and keratinocyte identity is verified through expression of keratinocyte specific keratins e.g. keratin14.
Mycoplasma contamination	Exp. 1: Cells were tested reguarly for mycoplasma contamination. No contamination was detected. Exp. 2: Primary keratinocytes were not tested for Mycoplasma due to regular fresh isolation.
Commonly misidentified lines (See ICLAC register)	HEK293T

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	HEK cells were maintained under standard tissue culture parameters (37 C, 5% CO2), and fed with DMEM, supplemented with 10% Fetal Bovine Serum (Gibco), 1% GlutaMAX (Gibco) and 1% Penicillin-Streptomycin (Gibco). Cells were passaged every 3-4 days at a confluence of approx. 70%. For FACS, cells were trypsinised, spun down, resuspended in FACS Buffer (DPBS without Ca2+ and Mg2+, 2% FBS) and transferred to the FACS facility. After sorting, cells were collected in DMEM and plated on a polymer cover slip imaging dish (Ibidi). Confocal imaging was performed 12 hrs after plating.
Instrument	BD FACSAria Fusion
Software	FACSDiva 8.0.1, FlowJo 10.8.1
Cell population abundance	The rate of false positive / false negative events was approximately < 2 %. This was determined by visual inspection of plated cell populations using an inverted Brightfield microscope.
Gating strategy	Gating of cells with laser particles was based on simple FSC-A/SSC-A gating, as three populations were clearly distinguishable. Cells with laser particles showed the highest SSC-A and FSC-A values, (approx. SSC-A 10^4, FSC-A 10^5). Laser particles on their own showed values around 10^4 SSC-A and 10^4 FSC-A. Cells on their own showed between 6x10^2 to 5x10^4 SSC-A and 2x10^4 to 10^5 FSC-A. Cells were further sorted into FSC and subsequently into SSC singlets. Lastly, only viable cells were sorted by gating for DAPI negative cells (BV421-A).

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.