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	Network Setup Wizard version 3.1.0 (Kistler Instrument, Amherst, NY, USA)
Data analysis	Phoenix Datos|x version 2.3.2 (GE Measurement & Control, Billerica, MA, USA) VGStudio MAX version 2.2 (Volume Graphics, Heidelberg, Germany) MATLAB version 9.4 (MathWorks, Natick, MA, USA) GraphPad Prism version 8 (GraphPad Software, San Diego, CA, USA)

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

All data that support the findings of this study are available within this paper, its Supplementary information and the Source data that are provided with this paper. Any additional information is available upon request.

Human research participants

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

Reporting on sex and gender	Not applicable
Population characteristics	Not applicable
Recruitment	Not applicable
Ethics oversight	Not applicable

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	Sample sizes were not determined due to the proof-of-concept study nature of this work. Herein we are exploring small-scale experiments and exploratory investigations to assess the device concept feasibility and viability. The primary focus here is to gather initial evidence or insights rather than determining a sample size based on statistical considerations.
Data exclusions	No data were excluded.
Replication	Jetting performance study: n=3 technical replicates per condition Ex vivo tissue jetting - characterisation study: n=4-8 tissue samples per condition Ex vivo tissue jetting - organ comparison study: n=2-8 tissue samples per tissue type and ampule pressure Ex vivo tissue jetting - heatmap study: n=2-8 tissue samples per tissue type, nozzle size and ampule pressure Histology (organ comparison study): n=1 tissue sample for each control and n=4-8 independent tissue samples following jetting (for each tissue type [depot location]: cheek, oesophagus, antrum [submucosal and intraperitoneal], jejunum [submucosal and intraperitoneal], colon, rectum) Force profile testing of proof-of-concept jetting devices: n=2-4 technical replicates In vivo testing with proof-of-concept jetting devices: n=3-8 animals per condition Specific n values are provided in each figure legend. All attempts at replication were successful and all experimental data were reproducible between independent experiments.
Randomization	Randomization of animals was conducted to minimize physiological bias and increase validity of experimental results. Additionally, controlled experimental conditions (i.e., animal pre-treatment) and counterbalancing (weight, dose normalization) were introduced where assessed meaningful (see Methods).
Blinding	No blinding was conducted as the studies focused on objective measurements and observations where inanimate objects were studied.

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

Antibodies

Antibodies used

HUI-018 (1212-0000-0087; Novo Nordisk; Clone name 02A2; IgG1; Mouse; specificity for human insulin).
NN454-1F31 (1212-0000-0096; Novo Nordisk; Clone name A6; IgG1; Mouse; specificity for gGlu-fatty diacid protraction).
4F1 (M-hinsulin-4F1A3B1; 1212-0000-0257; Novo Nordisk; IgG1; Mouse; no cross-reactivity to dog and pig insulin).
S1 (1212-0000-0107; Novo Nordisk; Clone name C3D3E3; IgG1; Mouse; specificity for human insulin; cross-reactivity for dog, pig, and rat insulin <1%).

Validation

The antibodies were produced at Novo Nordisk. Their identity and quality have been checked by Nanodrop, SEC-HPLC, LC-MS and SDS Page. The combination of antibodies used in the human insulin assay was qualified for purpose by covering the following issues: 1) selectivity, 2) sensitivity and range, 3) inter- and intra-assay variability, 4) dilution linearity and 5) interference.

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

Ex vivo jet injection study: Female Yorkshire pigs, 3-5 months old, 35-80 kg.
In vivo pharmacokinetic exposure studies with MiDeAxAuto, MiDeRadAuto and MiDeAxEndo (small intestine delivery): Female Yorkshire pigs, 35-80 kg.
In vivo pharmacokinetic exposure study with MiDeAxEndo (gastric delivery): Female Beagle dogs, from 10 months old, 8-13 kg.
In vivo pharmacokinetic exposure negative control study: Female LYD (Landrace Yorkshire Duroc) pigs, 50-70 kg.
In vivo pharmacokinetic exposure inactive GLP-1 tablet control study: Male Beagle dogs, 2.8-3.5 years old, 9.9-14.5 kg.

Wild animals

This study did not involve wild animals.

Reporting on sex

The primary objective of the studies conducted was focused on investigating the mechanistics of jetting and pharmacokinetics, with a specific emphasis on toxicology being out of scope for the research. Furthermore, the study design aimed to minimize potential confounding factors and sources of variation that could influence the outcomes. By selecting a more controlled and standardized experimental setup, enhancing the ability to detect and evaluate the effects of the specific jetting parameters or intervention under investigation. While recognizing that sex can play a significant role in certain areas of research, the specific study at hand did not involve aspects where sex-specific findings were expected or directly relevant to the research objectives.

Field-collected samples

This study did not involve samples collected in fields.

Ethics oversight

Committee on Animal Care at MIT and the Animal Experiment Inspectorate, Ministry of Justice, Denmark.

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