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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☒	☐	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Leginon v3.3 beta was used to collect single particle micrographs and tilt-series. SerialEM was used to collect tilt-series.
Data analysis	CryoSPARC v0.6.5 was used for single particle alignment and classification. Appion-Protomo, using Appion v3.3 beta and Protomo v2.4.1, was used to align tilt-series.

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/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Single particle half maps, full sharpened maps, and masks for insulin-bound insulin receptor (200 ms spot-to-plunge time), insulin-bound insulin receptor (800 ms), and hemagglutinin (100 ms) have been deposited to the Electron Microscopy Data Bank (EMDB) with accession codes EMD-7788, EMD-7791, and EMD-7792,

respectively. The full single particle collection of hemagglutinin (100 ms and 500 ms) has been deposited to the Electron Microscopy Pilot Image Archive (EMPIAR) with accession codes EMPIAR-10175 and EMPIAR-10197, respectively. Single particle cryoET tomograms have been deposited to the EMDB with accession codes EMD-7623, EMD-7624, EMD-7625, EMD-7150, EMD-7627, EMD-7628, EMD-7629, and EMD-7630. Single particle cryoET tilt-series, cryoET tilt-series alignment runs with Appion-Protomo, cryoET tomograms, and apoferritin particle picks have been deposited to the EMPIAR with accession codes EMPIAR-10169, EMPIAR-10170, EMPIAR-10171, EMPIAR-10141, EMPIAR-10172, EMPIAR-10129, EMPIAR-10173, and EMPIAR-10174.

Field-specific reporting

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

☒ Life sciences ☐ Behavioural & social sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences

Study design

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

Sample size	Three samples (apoferritin, hemagglutinin, and insulin-bound insulin receptor) were selected from in-house projects due to their observed behavior when plunging faster, as described in the manuscript. No sample size calculation was performed. Three samples were chosen in order to show applicability to: 1) a pathologically preferentially-oriented particle (hemagglutinin), 2) a novel particle (insulin-bound insulin receptor), and 3) a canonically-shaped particle (apoferritin).
Data exclusions	No data was excluded.
Replication	Both insulin receptor and hemagglutinin were used to show reproducibility with regards to reducing preferred orientation issues. Both apoferritin and apoferritin with 0.5mM TCEP were used to show reproducibility with regards to increasing the density of non-adsorbed particles. All attempts to replicate these two results with these samples have thus far been successful.
Randomization	This is not relevant in this study because protein structural data could not be randomized.
Blinding	Blinding is not relevant to this study because the relevant tests - preferred orientation and a change in non-adsorbed particle density - were performed in a manner that does not introduce bias. Preferred orientation was analyzed with exclusively software-based 2D classification and 3D reconstruction. Non-adsorbed particle density was analyzed by explicitly counting non-adsorbed particles and measuring the volume they occupy. The raw data together with the particle picks are provided together with the manuscript.

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☒	☐ Unique materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Research animals
☒	☐ Human research participants

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ Magnetic resonance imaging