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Chiral transformers: reconfigurable nanoassemblies for single-step enrichment of low-abundance biomarkers

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Once assembled, chiral and achiral inorganic nanostructures are typically static^{1–4} because rigid cores and strong van der Waals interactions lock their building blocks into thermodynamically stable configurations.⁵ In contrast, biological assemblies are dynamic and reorganize across multiple length scales to acquire diverse functions. To bridge this gap between irreversible inorganic constructs and adaptive biological systems, we show that penicillamine-functionalized chiral CuS nanosheets reversibly self-assemble into supraparticles with media-responsive organization and multiscale reconfigurability. By tuning attractive and repulsive interactions through pH, temperature, and chemical additives, these hierarchical microstructures undergo repeated assembly–disassembly cycles and access a broad family of isomorphs spanning nanometer-to-micron length scales. In biological fluids, these reconfigurable, high surface area supraparticles enable rapid, non-denaturing, chirality-dependent protein capture, achieving 10- to ~1,000-fold enrichment of low-abundance disease markers essential for disease diagnostics and biotechnology.^{6,7}

Colloidal chiral nanostructures from metals, ceramics, and semiconductors display a rich variety of geometries, resembling self-organized cellular components and biomineralized tissues.^{3,8–11} Their surfaces, functionalized with amino acids, peptides, lipids, or sugars, can engage in

collective supramolecular interactions with biomacromolecules. Multiple cases of chirality-specific interactions with proteins, cells, and organisms have also been reported.^{9,12,13} The bioinspired asymmetry of chiral nanostructures has motivated their exploration in therapeutics,^{14–16} and their high chiroptical activity has enabled advances in biosensing.^{17–20} However, nearly all known chiral inorganic nanostructured assemblies are structurally static. Their inorganic metallic or semiconducting cores lack the nano- and meso-scale dynamics of biological structures with similar dimensions. Biological assemblies dynamically reconfigure, assembling and disassembling across a spectrum of complex morphologies and length scales, to acquire new properties and functions. Beyond limiting biosimilarity, the lack of reconfigurability in response to media composition restricts the spectrum of accessible morphologies. Their structural rigidity also diminishes their technological relevance.^{21,22} For example, protein coronas formed on inorganic nano-, meso-, and microparticles are only weakly selective, producing soft and hard layers of biomolecules with mixed composition.^{2,23–25} Such nano- and microparticles also cause denaturation of many proteins upon adsorption, even at physiological pH.^{26–30}

Unless reconfigurability is introduced extrinsically by flexible biopolymers such as DNA,^{31–33} inorganic assemblies generally lack structural reconfigurability and media responsiveness because attractive forces between inorganic building blocks are much stronger than those typical of organic biomolecules in biological systems.^{34,35} The combined contribution of favorable enthalpy and entropy locks these assemblies into local energy minima, whose depth increases with the size and mass of the building blocks. Even in the smallest inorganic nanoclusters (~1.5 nm) that form chiral assemblies,¹ van der Waals (vdW) and other forces prevent reconfiguration once assembly occurs.⁵ These energy constraints become more severe as size and architectural complexity increase.

Here we report a family of nanostructured isomorphs that reversibly assemble from and disassemble into CuS nanosheets (NSs)³⁶ functionalized with penicillamine (Pen),³⁷ bridging this gap between biological and inorganic systems. Variations in pH (**Fig. 1a**), temperature, surfactants, and media components induce pronounced changes in the molecular-scale organization of the NSs, leading to extensive reconfiguration at larger scales through a continuum of simple and complex isomorphs. These include chiroptically active particles with varying size, complexity, and composition, governed by inter-NS repulsion. The high surface area, combined with pH-triggered

release and adaptive reconfiguration of the NSs, enables efficient capture of proteins and peptides, followed by rapid on-demand release, resulting in $\sim 10\text{--}1,000\times$ enrichment of disease markers.

Supraparticles from CuS-Pen nanosheets

Supraparticles (SPs, **Fig. 1b**) are microscale assemblies of nanoscale components whose dimensions and architecture are restricted by electrostatic forces. They represent one of the isomorphs self-assembled from Cu_3S_3 NSs (formed in situ, **Fig. S1–S3**) when, for instance, 16.7 mM CuCl_2 with 6.5 molar equivalents of Pen are mixed with an aqueous 400 mM solution of cetyltrimethylammonium chloride (CTAC) (Methods and SI). The resulting SPs exhibit strong red fluorescence, with intensity increasing as NSs form and self-assemble into SPs (**Fig. S2**). Different enantiomeric ratios, $\chi = \frac{[D\text{-Pen}] - [L\text{-Pen}]}{[D\text{-Pen}] + [L\text{-Pen}]} \times 100\%$, along with other conditions, result in widely variable morphologies (**Fig. 1b, Fig. S3–S26**). For simplicity, when *D*-Pen ($\chi = +100\%$), *L*-Pen ($\chi = -100\%$), or a racemic (*rac*, $\chi = 0$) mixture of these enantiomers are used, the resulting particles are denoted as *D*-, *L*-, and *rac*-SPs, respectively. Transmission electron microscopy (TEM) and high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) images confirm that NSs are the primary building blocks of these microparticles (**Fig. 1d, Fig. S9, Fig. S26**).

Depending on the media conditions, including χ , temperature, [Pen], [CTAC], and the presence of other surfactants and polyelectrolytes (**Fig. S11, S15, S16, S19**), more than a hundred distinct microscale morphologies and complex macroscale phases can be produced. Among these isomorphs, spiky spheroids predominantly form when $\chi > +80\%$ or $\chi < -80\%$ (**Fig. 1b, Fig. S16**). As the composition approaches racemic conditions ($-20\% < \chi < 20\%$), SPs acquire smooth spheroidal shapes (**Fig. S16**). Asymmetric beaded spheroids, an unusual morphology for SPs, form when $-80\% < \chi < -20\%$ and $+20\% < \chi < +80\%$ (**Fig. S17**). In all cases, the SPs exhibit remarkably high size uniformity (**Fig. S4, S11, S16**) reflecting the constraints imposed on self-assembly by electrostatic forces.³⁸

At the atomic scale, the constituent NSs are crystalline when synthesized at $T > 40^\circ\text{C}$, adopting a graphene-like covellite lattice (**Fig. 1h**). They have a triangular shape with surfaces coated by Pen ligands (**Fig. 1d–h**). High-resolution TEM and selected-area electron diffraction (SAED) confirmed (**Fig. S26**) the formation of a two-dimensional (2D) honeycomb lattice from

Cu₃S₃ hexagonal units. The composition of NSs was further confirmed by X-ray photoelectron spectroscopy (XPS) (**Fig. S8**). Sulfur atoms from Pen simultaneously form covalent bonds with copper atoms in the inorganic lattice and anchor the ligands, producing a chemically continuous interface within each NS. By testing a variety of surface ligands, we found that the tertiary thiol and two adjacent methyl groups of Pen provide steric protection and hydrophobic stabilization to the lattice (**Fig. S10**).

At the nanoscale, the planarity of Cu₃S₃ hexagons makes them analogous to graphene (**Fig. 1j,k, Fig. S41**) and many other 2D materials. Accordingly, they share properties such as a pronounced tendency to self-assemble into stacked structures. However, face-to-face attraction between NS stacks is weakened because individual NSs are separated by Pen ligands, reducing vdW forces. For these reasons, the chirality transfer mechanism in Pen-CuS SPs differs from that in noble metal NPs,^{10,11,39} their assemblies,⁴⁰ SPs based on AuS NSs,³ Cu_xS_y nanostructures,^{41,42} and chiral copper nanoclusters.⁴³

Instead of arising from twisting of nanoribbons or from restricted growth of specific chiral phases, the molecular chirality of Pen is translated into SP chirality via the consistent twist in stacks of triangular NSs (**Fig. 1e,f**). This can be directly observed in electron microscopy images (**Fig. 1g,h, Fig. S22**), where angular displacement of NSs is left-handed (clockwise) for *D*-SPs and right-handed (counterclockwise) for *L*-SPs. Molecular Dynamics (MD) simulations (**Fig. 1i, Fig. S41**) confirm that Pen-stabilized Cu₃S₃ stacks adopt relative twists that originate from interactions between homochiral Pen ligands with oppositely oriented amine and carboxylate groups (**Fig. 2g,h**). Consistent with the stack-and-twist chirality transfer mechanism, MD simulations of *rac*-SPs do not show a consistent twist (**Fig. S41**), explaining their altered morphology and broadened X-ray diffraction (XRD) peaks (**Fig. 1c**). Interestingly, binding between NSs with oppositely chiral Pen ligands is stronger ($-50.1 \text{ kJ} \cdot \text{mol}^{-1}$) than between NSs with homochiral ligands ($-41.8 \text{ kJ} \cdot \text{mol}^{-1}$), which accounts for the smoother surfaces of *rac*-SPs. Indeed, the basal spacing between homochiral ligands is larger than that between heterochiral NSs (**Fig. 1c**): $d = 1.28 \text{ nm}$ ($2\theta = 6.89^\circ$) versus 1.25 nm ($2\theta = 7.06^\circ$), respectively. The experimentally determined XRD data closely match those obtained from MD simulations (**Fig. 1i, Fig. 2k**).

Optical properties of NSs

The CuS-Pen NSs serving as building blocks of the nano- and microstructures are quantum confined. Thus, nearly all isomorphs assembled from them exhibit strong absorptivity and emissivity, provided that the NSs are crystalline. The corresponding UV absorption and photoluminescence peaks are observed at ~360 nm (**Fig. S26**) and ~670 nm (**Fig. S13**), respectively. With a quantum yield of ~40%, SPs can be visualized without luminescent stains using a confocal microscope (**Fig. 2a–f**). The fluorescence is retained over a pH range of 1.7–6.2 (**Fig. S24**). Their ~2 mg mL⁻¹ dispersions display similarly bright luminescence in water and common organic solvents (**Fig. S7**), indicating the chemical stability of the Cu₃S₃ network regardless of surface solvation.

The chirality of the ligands, NSs, and their twisted stacks manifests as strong chiroptical activity across infrared, visible, and UV spectral regions (**Fig. 2g,h**). Comparison with SEM images (**Fig. S11**) indicates that isomorphs prepared at ≥50 °C exhibit improved NS crystallinity and stacking, resulting in enhanced chiroptical activity across all spectral windows.

The vibrational circular dichroism (VCD) bands appearing in the near-infrared region at 1566, 1623, and 1648 cm⁻¹ correspond to C=O stretching and N–H bending modes formed between Pen ligands in adjacent NSs within the stack (**Fig. 1I, Fig. 2k,l, Fig. S44b**). The computed VCD spectra (**Fig. 2j**) show close agreement with experimental spectra for SPs synthesized at ≥50 °C, consistent with a well-defined hexagonal Cu₃S₃ network.

A rich set of circular dichroism (CD) peaks is observed from 200 nm to 800 nm (**Fig. 2h**). The bands in the 200–350 nm range correspond to hybridized states of Pen and the Cu₃S₃ framework, including localized transitions in Pen stereocenters and crystallinity-dependent metal-to-ligand transitions. Broad features in the visible and near-infrared regions arise from isomorph-dependent Mie scattering. As a related optical phenomenon, strong birefringence of spiky SPs produces complex optical patterns with multicolor ‘hot spots’ observed under a polarization microscope (**Fig. S6**), originating from anisotropic refractive indices due to NS stacking combined with local chirality.

Strong emissivity of the NSs and their stacks (**Fig. 2a–f**) gives rise to circularly polarized light emission (CPLE, **Fig. 2i, Fig. S13, Fig. S21**).³⁷ This can originate both from chiral quantum states induced by distortions of the Cu₃S₃ framework by Pen enantiomers (**Fig. 2m**) and from post-emission polarization rotation due to photon interactions with twisted NS stacks. The increase in

CPLE intensity with crystallinity indicates contributions from both atomic- and nanoscale chirality to the ellipticity of emitted photons.

Reversible reconfiguration of nanosheet assemblies

Reconfigurability of the NSs at nano-, meso-, and microscales originates from atomic-scale dynamics and media responsiveness of the Cu_3S_3 frameworks. One key contributor to atomic-scale reconfiguration is the relatively low dissociation energy of the Cu–S bond ($\sim 285 \text{ kJ mol}^{-1}$) compared to other transition and noble metals, enabling the formation of multiple structural units, such as Cu_4S_6 and $\text{Cu}_{136}\text{S}_{80}$.⁴³ Another key contributor is pH-dependent electrostatic repulsion between NSs arising from Pen protonation and conformation (**Fig. 1a, 3a**). Due to the simplicity and universality of electrostatic tuning, it is described here in detail.

Electrostatic repulsion depends on the net formal charge of surface ligands, δ , defined as $\delta = +1$ for fully protonated, 0 for zwitterionic, -1 for fully deprotonated Pen. The charge on NSs and δ also affect the multiscale structure of the isomorphs, because SP formation and packing are governed by competition between electrostatic repulsion and inter-sheet vdW attraction augmented by hydrogen bonding (**Fig. 1i, 2l**). At $\text{pH} < 1.7$ ($\delta > +0.8$) or $\text{pH} > 6.9$ ($\delta < -0.35$), electrostatic repulsion between CuS-Pen NSs is sufficiently strong that only $\sim 2 \text{ nm}$ individual NSs form (**Fig. 3c**). Mass spectrometry indicates coexistence of NSs with $\text{Cu}_x(\text{SPen})_y$ nanoclusters with molecular weights of $\sim 2\text{--}20 \text{ kDa}$ (**Fig. S27,28**), composed of units as large as $[\text{Cu}(\text{SPen})]_{95}$, indicating the presence of free NSs $< 3 \text{ nm}$ in size at these pH values.

At pH between 1.7 and 3.1, the net formal charge on Pen decreases markedly ($+0.6 > \delta > \sim 0.0$), and NSs initially assemble into thicker planar isomorphs and then into SPs (**Fig. 1b**), driven by hydrogen bonding and vdW interactions. Assembly leads to progressive accumulation of charge within the NS assembly, increasing with isomorph size, even as $|\delta|$ decreases. Repulsion between homochiral NSs is counteracted by supramolecular interactions that are weaker than those in heterochiral NS pairs, preventing tight packing and leading to spiky morphologies. The circumference of SPs increases with pH within this window due to decreasing repulsion, reaching $\sim 20 \text{ }\mu\text{m}$ for *D*- and *L*-SPs and $\sim 15 \text{ }\mu\text{m}$ for *rac*-SPs at pH 3.1 (**Fig. S4**).

Between pH 3.1 and 4.5 ($\sim 0 > \delta > -0.05$), SPs change geometry from spiky spheroids to concave microplates (**Fig. 1b**). Their dissymmetry increases as δ becomes more negative,

indicating gradual recovery of electrostatic forces between negatively charged NSs. Increasing pH to 6.0 leads to formation of individual short stacks, while discrete ~ 2 nm NSs reappear at pH 6.9 ($\delta = -0.35$) as electrostatic repulsion overcomes attractive interactions.

Multiscale reconfiguration of Cu-Pen isomorphs in response to pH can be inferred from their chiroptical activity. CD spectra (**Fig. 3c**) show that pH alters surface ligand conformation, stack twisting, and overall isomorph configuration, reflected in shifts in intensity and spectral position of CD peaks corresponding to atomic (200–300 nm), nanoscale (300–600 nm), and microscale (600–800 nm) structural changes.

Importantly, pH-induced disassembly and reconfiguration are reversible: SPs can be repeatedly reassembled without morphological degradation, as evidenced by reversible changes in CPL (**Fig. 3d**, **Fig. S24**). Upon adjusting pH between 1.5 and 2.3 with HCl or between 6.9 and 2.3 with KOH at 50 °C, SPs can be repeatedly assembled and disassembled into NSs. Fidelity of reassembly is supported by similarity of microscopy images before and after reassembly (**Fig. S29**). Assembly–disassembly cycles can also be triggered by temperature, reflecting sensitivity of inter-NS hydrogen bonding and Cu-S interactions (**Fig. S30**). For example, SPs reversibly disassemble into ~ 2 nm NSs at 90 °C and gradually reassemble into ~ 15 μ m SPs upon cooling to 20 °C (**Fig. S30**) in the case of dispersions in acidified ethanol or at high ionic strength (4 M KCl).

This reversibility enables access to a wide range of new isomorphs using disassembled NSs as intermediates (**Fig. 3f,g**, **Fig. S31**, **Fig. S34–S36**). For example, spiky *D*-SPs can be disassembled and reassembled in media containing CTAC to yield laminar assemblies (**Fig. 3f**) with distinct organizational patterns previously observed for chiral mesogens in liquid crystals but not for chiral nanoparticles. Similarly, SPs can be reshaped into flat hexagonal microcrystals by neutralizing dispersions to pH 2.3 in superionic CsCl, which screens electrostatic repulsion (**Fig. 3g**). These can be further disassembled into 2 nm NSs and converted into ~ 5 μ m corrugated spheres by adding isopropanol, which weakens hydrogen bonding. Additionally, iodide doping of disassembled 2 nm NSs produces CuI–Pen nanoribbons upon reassembly at pH 2.3 (**Fig. S32**), representing an isomorph common in biological assemblies but not previously observed for chiral nanoparticles. Similarly, cyanide doping during NS formation yields yet another isomorph of SPs (**Fig. S38**).

We note that such facile transitions between multiple complex architectures represent a unique property that differentiates the CuS–Pen system from previously reported self-assembled microscale particles or films derived from ceramics, semiconductors, metals, MOFs, COFs, and perovskite nanoparticles or clusters. Many of these systems decompose with pH or fail to rearrange due to strong interparticle interactions. By contrast, phase transitions in polymer coacervates or NP superlattices, whether or not organic ligands drive those transitions, generally involve continuous phases. Biological assemblies often undergo irreversible denaturation under similar conditions.

Protein separation and analysis

The high surface area, media responsiveness, and reversible disassembly of CuS–Pen isomorphs motivated their use as a platform for biomolecular isolation and enrichment, which is central to state-of-the-art proteomics^{6,7,44,45}. Various isomorphs were incubated with 2 mL aliquots of human or bovine serum for 5 minutes and the resulting NS assemblies were separated by low-speed centrifugation (**Fig. 4a**). Adsorbed biomolecules were released by dissolving the $(\text{Cu}_3\text{S}_3)_n$ inorganic framework in phosphate-buffered saline (PBS) containing 75 mM ethylenediaminetetraacetic acid (EDTA) at pH 7.4. This was followed by proteomic analysis focused on disease markers for cardiovascular and neurodegenerative diseases (**Fig. 4b–d**).

Multiple isomorphs with various chiralities, surface ligands, pH conditions, and anion dopants were tested (**Fig. 4c**, **Fig. 5a**, **Fig. S47–S52**, **Tables S1–3**). Indicating biomimetic selectivity, as high as several orders-of-magnitude differences in the protein enrichment factor, $K = \frac{[c_{final}]}{[c_{initial}]}$, (**Supplementary Note 2**) between different isomorphs was observed. Representative examples of isomorphs with such selectivity labeled as isomorph 1, 2, 3... are given in **Fig. 5** and **Fig. S38**: *D*-CuS–Pen SPs (1), *D*-CuS–Pen NSs (1'), *rac*-CuS–Pen SPs (2), *rac*-CuS–Pen NSs (2'), *D*-CuCN–Pen SPs (3), *rac*-CuCN–Pen SPs (4), *D*-CuI–Pen SPs (5), *rac*-CuI–Pen SPs (6), *D*-CuS–Cys SPs (7), and *rac*-CuS–Cys SPs (8). All isomorphs reconfigure during interactions with proteins in response to changes in media conditions and interparticle interactions, as exemplified by disassembly of SPs into NSs. Some isomorphs, such as CuI–Pen SPs, reconfigure into nanowires (**Fig. S47**), pointing to intrinsic connection between their multiscale reconfigurability and isolation functionality.

While strong agglomeration is often observed for gold and other NPs with strong vdW attraction^{26,29,30,46}, this is not the case for SPs and other isomorphs of CuS–Pen (**Fig. 5c,g, Fig. S50**). Furthermore, they exhibit high protein loading capacity with protein layer thickness ranging from 1.2 to 9.6 nm (**Fig. 5h, Fig. S48**). The high surface area leads to total protein uptake of 1.8–9.2% by mass for homochiral SPs and 1.4–16.4% for *rac*-SPs (**Fig. S48**). To assess protein integrity, trypsin was isolated from serum using *D*- and *L*-CuS–Pen SPs, and its enzymatic activity toward hydrolysis of an AMC-labeled peptide was tested (**Fig. S51**). The enzyme remained active after release from SPs and NSs, confirming preservation of its tertiary structure.

In contrast to rigid nano-, meso-, and microparticles, NSs constituting SPs can adapt and deform in response to protein adsorption (**Fig. 5i, Fig. S49**), contributing to high isolation efficiency. In addition to XRD and CD data (**Fig. 1 and Fig. 2**) capturing molecular and nanoscale reconfigurability, the response of both homochiral and racemic CuS–Pen SPs to protein adsorption was confirmed by CD spectra before and after protein capture (**Fig. 5i, Fig. S49**).

Interestingly, Cu–Pen SPs concentrate multiple low-abundance proteins and peptides (**Fig. 4c**) with enrichment factors K as high as 1000, while concomitantly reducing the content of high-abundance proteins with enrichment factors K as low as 0.001 (**Fig. 4b,c, Tables S1–S3**). Examples of the latter include albumin ($K = 0.011$), serotransferrin ($K = 0.007$), immunoglobulins ($K = 0.006$), α -2-HS-glycoprotein ($K = 0.014$), and A1AT ($K = 0.001$). Examples of the former include low-abundance cardiovascular disease markers, such as PEDF ($K = 3,800$), kininogen-1 ($K = 948$), and tropomyosin ($K = 356$). Notably, the assemblies showed strong selectivity for apolipoproteins (Apo, **Fig. 5a,d**), which serve as disease markers. For example, *L*-CuS–Pen and *rac*-CuS–Cys achieve 52.8% ApoA-I and 46.6% ApoB purity of the isolates, respectively, in a single-step extraction from serum. CuI–Pen, CuCN–Pen, and CuS–Cys SPs enrich the lipoprotein fractions of ApoA-I (87.1%), ApoA-II (20.6%), ApoB (88.2%), and ApoE (43.8%) (**Fig. 5j, Fig. S50**).

CuS–Pen isomorphs also enable selective isolation of neurodegenerative disease markers (**Fig. 4d**). High enrichment factors were observed for serum amyloids SAP ($K=52$), SAA-4 ($K=94$), and proteoglycan 4 ($K=108$). We also evaluated isolation of A β 42 and α -synuclein (**Supplementary Section 10**) – key proteins associated with Alzheimer’s and Parkinson’s

diseases^{47,48}. Starting from concentrations as low as 2 ppm in serum, these proteins were enriched with $K=220$ and $K=250$ using CuCN-Pen SPs and CuI-Pen SPs, respectively (**Fig. S50**).

Conclusions: We show that nanoscale assemblies reversibly transform into a broad family of isomorphs with distinct multiscale organization in response to changes in pH, temperature, ionic environment, biomolecules, polymers, dopants, and surface ligands. These isomorphs exhibit properties found in both biological and inorganic materials, including multiscale reconfigurability, strong chiroptical activity, and intrinsic luminescence. The reconfiguration space bridges both continuous (e.g. lamellar) and discrete (e.g. supraparticles) phases, which have not been previously observed for chiral nanoparticles. By dynamically adapting their structure and surface organization, these assemblies enable selective, non-denaturing enrichment of low-abundance biomarkers associated with cardiovascular and neurodegenerative diseases by 10–1,000-fold. Coupled with high-throughput proteomics, the structural diversity of these assemblies and their optical responses to protein–particle interactions provide a foundation for selective biomolecular isolation and analysis in complex biological fluids.

References

1. Ugras, T. J. *et al.* Transforming achiral semiconductors into chiral domains with exceptional circular dichroism. *Science* **387**, eado7201 (2025).
2. Zhang, Q. *et al.* Unraveling the origin of chirality from plasmonic nanoparticle-protein complexes. *Science* **365**, 1475–1478 (2019).
3. Jiang, W. *et al.* Emergence of complexity in hierarchically organized chiral particles. *Science* **368**, 642–648 (2020).
4. Shevchenko, E. V., Talapin, D. V., Kotov, N. A., O’Brien, S. & Murray, C. B. Structural diversity in binary nanoparticle superlattices. *Nature* **439**, (2006).
5. Bergström, L. Hamaker constants of inorganic materials. *Adv. Colloid Interface Sci.* **70**, 125–169 (1997).

6. Bi, C. *et al.* Chromatographic Studies of Protein-Based Chiral Separations. *Separations* **3**, 27 (2016).
7. Gregorich, Z. R. & Ge, Y. Top-down proteomics in health and disease: Challenges and opportunities. *Proteomics* **14**, 1195–1210 (2014).
- 5 8. Cho, N. H. *et al.* Bioinspired chiral inorganic nanomaterials. *Nat. Rev. Bioeng.* **1**, 88–106 (2023).
9. Ma, B. & Bianco, A. Regulation of biological processes by intrinsically chiral engineered materials. *Nat. Rev. Mater.* **8**, 403–413 (2023).
10. Xie, Y., Krasavin, A. V., Roth, D. J. & Zayats, A. V. Unidirectional chiral scattering from single enantiomeric plasmonic nanoparticles. *Nat. Commun.* **16**, 1125 (2025).
11. Mark, A. G., Gibbs, J. G., Lee, T.-C. & Fischer, P. Hybrid nanocolloids with programmed three-dimensional shape and material composition. *Nat. Mater.* **12**, 802–7 (2013).
12. Cho, N. H. *et al.* Chiral inorganic nanomaterials for biomedical applications. *Chem* **10**, 1052–1070 (2024).
- 15 13. Xu, L. *et al.* Enantiomer-dependent immunological response to chiral nanoparticles. *Nature* **601**, 366–373 (2022).
14. Zhang, H. *et al.* Light-Induced Chiral Iron Copper Selenide Nanoparticles Prevent β -Amyloidopathy In Vivo. *Angew. Chem. Int. Ed.* **59**, 7131–7138 (2020).
15. Hou, K. *et al.* Chiral gold nanoparticles enantioselectively rescue memory deficits in a mouse model of Alzheimer's disease. *Nat. Commun.* **11**, 4790 (2020).
- 20 16. Huang, Y. *et al.* Chirality-Driven Transportation and Oxidation Prevention by Chiral Selenium Nanoparticles. *Angew. Chem.* **132**, 4436–4444 (2020).
17. Probst, P. T. *et al.* Mechano-tunable chiral metasurfaces via colloidal assembly. *Nat. Mater.* **20**, 1024–1028 (2021).

18. Tullius, R. *et al.* “Superchiral” Spectroscopy: Detection of Protein Higher Order Hierarchical Structure with Chiral Plasmonic Nanostructures. *J. Am. Chem. Soc.* **137**, 8380–8383 (2015).
19. Ma, W. *et al.* Attomolar DNA detection with chiral nanorod assemblies. *Nat. Commun.* **4**, 2689 (2013).
- 5 20. Kumar, J. *et al.* Detection of amyloid fibrils in Parkinson’s disease using plasmonic chirality. *Proc. Natl. Acad. Sci.* **115**, 3225–3230 (2018).
21. Mahmoudi, M., Landry, M. P., Moore, A. & Coreas, R. The protein corona from nanomedicine to environmental science. *Nat. Rev. Mater.* **8**, 422–438 (2023).
22. Johnson, A. P. *et al.* Bioinspired and biomimetic micro- and nanostructures in biomedicine. *J. Controlled Release* **343**, 724–754 (2022).
- 10 23. Baimanov, D. *et al.* In situ analysis of nanoparticle soft corona and dynamic evolution. *Nat. Commun.* **13**, 5389 (2022).
24. Pizzi, D. *et al.* Influence of chirality on protein corona formation of low-fouling chiral poly(2-oxazoline) coated nanoparticles. *Eur. Polym. J.* **210**, 112964 (2024).
- 15 25. Treuel, L. & Nienhaus, G. U. Toward a molecular understanding of nanoparticle–protein interactions. *Biophys. Rev.* **4**, 137–147 (2012).
26. Dominguez-Medina, S. *et al.* Adsorption and Unfolding of a Single Protein Triggers Nanoparticle Aggregation. *ACS Nano* **10**, 2103–2112 (2016).
27. Aubin-Tam, M.-E. & Hamad-Schifferli, K. Gold Nanoparticle–Cytochrome c Complexes: The Effect of Nanoparticle Ligand Charge on Protein Structure. *Langmuir* **21**, 12080–12084 (2005).
- 20 28. Lundqvist, M., Sethson, I. & Jonsson, B.-H. Protein Adsorption onto Silica Nanoparticles: Conformational Changes Depend on the Particles’ Curvature and the Protein Stability. *Langmuir* **20**, 10639–10647 (2004).

29. Cedervall, T. *et al.* Understanding the nanoparticle–protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proc. Natl. Acad. Sci.* **104**, 2050–2055 (2007).
30. Zhang, D. *et al.* Gold Nanoparticles Can Induce the Formation of Protein-based Aggregates at Physiological pH. *Nano Lett.* **9**, 666–671 (2009).
31. Neubrech, F., Hentschel, M. & Liu, N. Reconfigurable Plasmonic Chirality: Fundamentals and Applications. *Adv. Mater.* **32**, 1905640 (2020).
32. Kuzyk, A. *et al.* DNA-based Self-Assembly of Chiral Plasmonic Nanostructures with Tailored Optical Response. *Nature* **483**, 311–314 (2012).
33. Aldaye, F. A., Palmer, A. L. & Sleiman, H. F. Assembling Materials with DNA as the Guide. *Science* **321**, 1795–1799 (2008).
34. Tenzer, S. *et al.* Rapid formation of plasma protein corona critically affects nanoparticle pathophysiology. *Nat. Nanotechnol.* **8**, 772–781 (2013).
35. Silvera Batista, C. A., Larson, R. G. & Kotov, N. A. Nonadditivity of nanoparticle interactions. *Science* **350**, 1242477 (2015).
36. Low, K.-H., Roy, V. A. L., Chui, S. S.-Y., Chan, S. L.-F. & Che, C.-M. Highly conducting two-dimensional copper(i) 4-hydroxythiophenolate network. *Chem Commun* **46**, 7328–7330 (2010).
37. Jin, Y. *et al.* Self-Assembled Chiral Copper Superstructures with Enhanced Circularly Polarized Light Emission. *Adv. Opt. Mater.* **11**, 2203068 (2023).
38. Xia, Y. *et al.* Self-assembly of self-limiting monodisperse supraparticles from polydisperse nanoparticles. *Nat. Nanotechnol.* **6**, 580–7 (2011).
39. Lee, H.-E. *et al.* Amino-acid- and peptide-directed synthesis of chiral plasmonic gold nanoparticles. *Nature* **556**, 360–365 (2018).

40. Chen, W. *et al.* Nanoparticle superstructures made by polymerase chain reaction: Collective interactions of nanoparticles and a new principle for chiral materials. *Nano Lett.* **9**, 2153–2159 (2009).
41. Gao, R. *et al.* Site-selective proteolytic cleavage of plant viruses by photoactive chiral nanoparticles. *Nat. Catal.* **5**, 694–707 (2022).
42. Young, H. L., McCormick, C. R., Butterfield, A. G., Gomez, E. D. & Schaak, R. E. Postsynthetic Thiol-Induced Reshaping of Copper Sulfide Nanoparticles. *Chem. Mater.* **34**, 11014–11025 (2022).
43. Baghdasaryan, A. & Bürgi, T. Copper nanoclusters: designed synthesis, structural diversity, and multiplatform applications. *Nanoscale* **13**, 6283–6340 (2021).
44. Aebersold, R. *et al.* How many human proteoforms are there? *Nat. Chem. Biol.* **14**, 206–214 (2018).
45. Wu, X. *et al.* Exosome-templated nanoplasmonics for multiparametric molecular profiling. *Sci. Adv.* **6**, eaba2556.
46. Pinals, R. L., Chio, L., Ledesma, F. & Landry, M. P. Engineering at the nano-bio interface: Harnessing the protein corona towards nanoparticle design and function. *Analyst* **145**, 5090–5112 (2020).
47. Fink, A. L. The Aggregation and Fibrillation of α -Synuclein. *Acc. Chem. Res.* **39**, 628–634 (2006).
48. Xia, Z. *et al.* Co-aggregation with Apolipoprotein E modulates the function of Amyloid- β in Alzheimer's disease. *Nat. Commun.* **15**, 4695 (2024).

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Author contributions: N.A.K. and M.S. led the conceptualization, investigation, and visualization of the study. Methodology was developed by N.A.K., M.S., and P.K., while modeling was performed by M.S. and P.K. N.A.K. was responsible for funding acquisition, project administration, and supervision. The original draft was written by N.A.K. and M.S., and both authors contributed equally to the subsequent review and editing of the final manuscript. All the authors read and approved the submitted manuscript.

Competing interests: M.S. and N.A.K. are inventors on a patent application covering the particles and protein-isolation protocols reported here (PCT/US2025/036835). The application is assigned to The Regents of the University of Michigan and The Board of Trustees of the University of Illinois. The authors declare no other competing interests.

Data, code, and materials availability: All experimental data are reported in the main text and Supplementary Information. Additional data, including full high-throughput proteomics datasets, are provided as separate files.

Supplementary Materials

This file contains Figs. S1-S51, Tables 1–3 and Supplementary References 1-5.

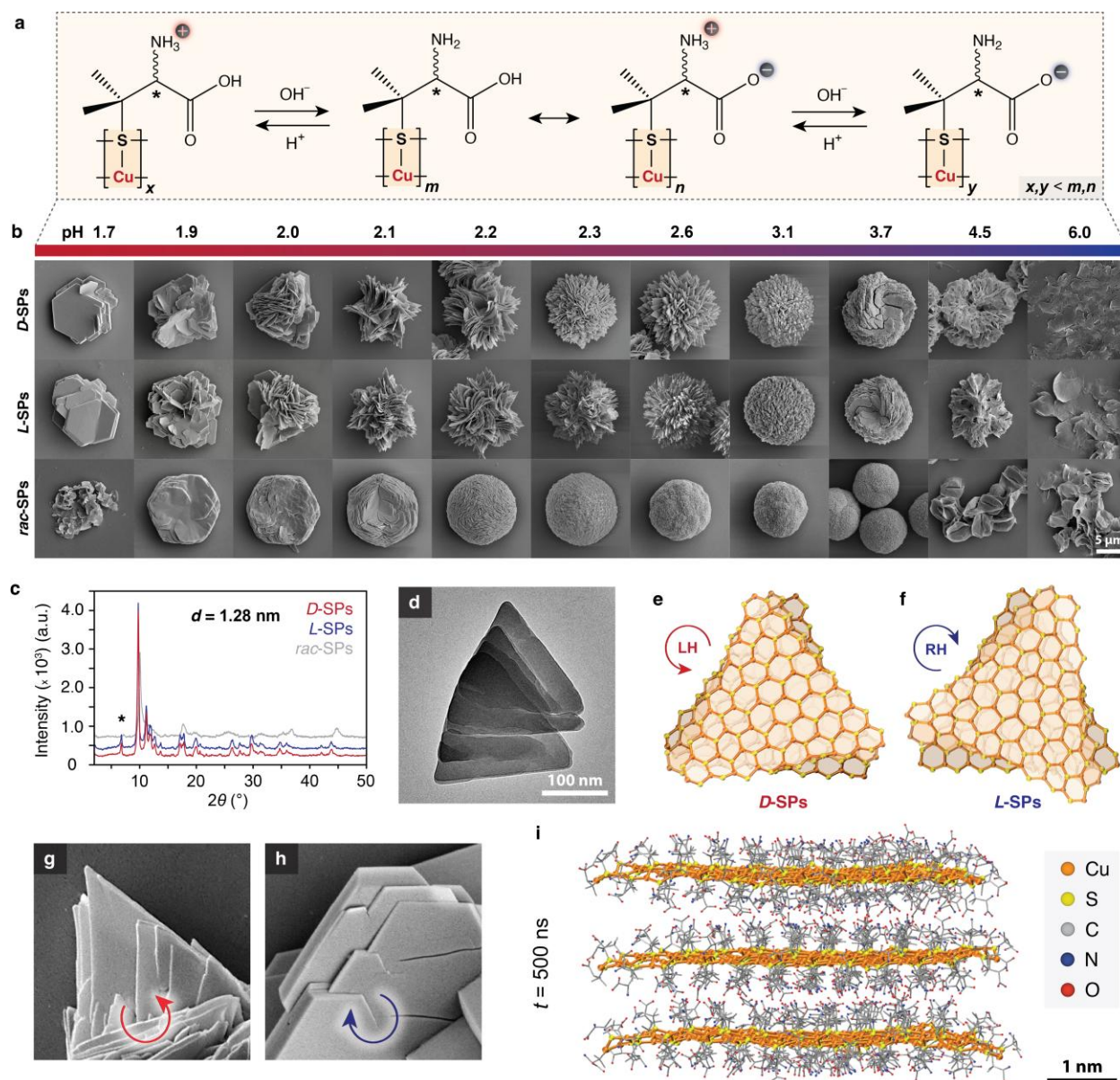


Fig. 1. Synthesis and structure of CuS-Pen isomorphs. (a) pH-dependent CuS-Pen building blocks participating in SP self-assembly. Generalized atomic scale reconfiguration of the NS surfaces under different media conditions. The parameters n and m indicate the number of CuS units in the assembly. The value of n can be orders of magnitude smaller than m because both pH extremes correspond to small NSs whose size is limited by the total positive (low pH) and negative (high pH) charge. (b) SEM micrographs *D*-, *L*-, and *rac*-SPs assembled at 50 °C under varying pH values, showing distinct morphologies governed by electrostatic repulsion. (c) Powder X-ray diffraction (XRD) patterns of *D*- (red), *L*- (blue), and *rac*-SPs (grey) prepared at 50 °C and pH 2.3. The principal resonance at $2\theta = 6.89^\circ$ corresponds to basal spacing of $d = 1.28$ nm. (d) TEM image of *D*-NSs forming SPs, showing hierarchical organization of NS lamellae. (e,f) MD-simulated 2.5 nm NS assemblies. Top views of *D*- and *L*-NSs reveal left- and right-handedness, respectively. (g,h) SEM images of sections of *D*- and *L*-SPs; their handedness is the same as observed in MD simulations. (i) Side view of an MD-simulated lamellar 5 nm *L*-NS assembly after 500 ns simulation time.

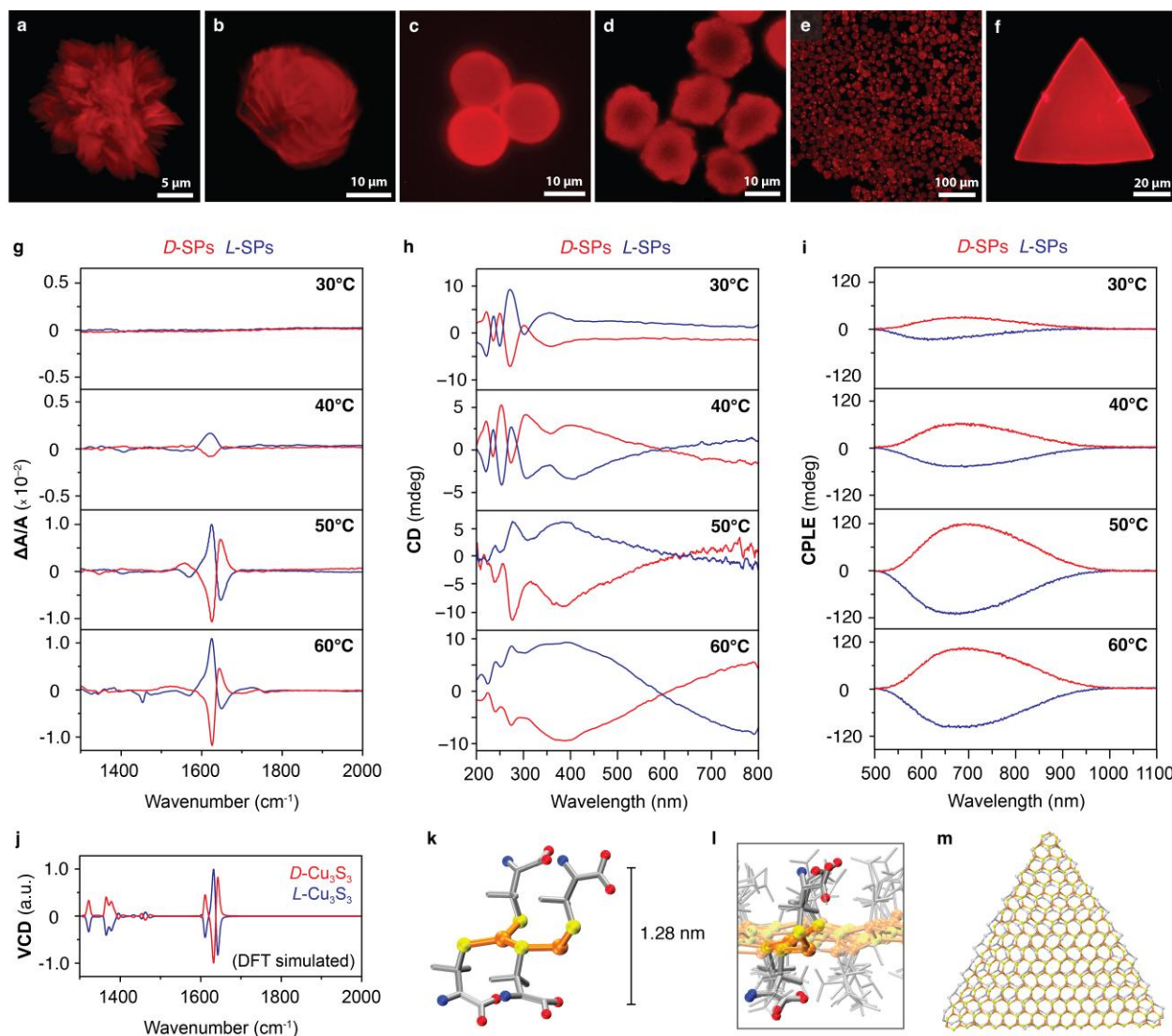


Fig. 2. Chiroptical properties of CuS-Pen isomorphs. (a-f) Confocal and inverted fluorescence microscopy images of representative SPs. (a) *D*-SPs at pH 2.3; (b) *D*-SPs at pH 1.9. (c) *rac*-SPs at pH 2.3; (d) SPs at $\chi = +40\%$; (e) large-area image of *D*-SPs at pH 2.3; (f) *D*-NS assembled in EtOH/1.5 equiv. HCl mixture. (g) VCD, (h) CD, and (i) CPL spectra of *D*- and *L*-SPs synthesized at different temperatures. Strong VCD signals originating from ordered packaging of Pen ligands at the nanoscale appear above 40 °C, while SPs synthesized below this temperature lack long-range order of chiral CuS-Pen units, as reflected in weaker CPL signals. (j) DFT-simulated VCD spectra of hexagonal Cu₃S₃(Pen)₃ units. (k, l) MD-simulated conformation of Pen ligands in NS assemblies (hydrogen atoms omitted for clarity). (m) Superimposed top views of MD-simulated achiral CuS lattices functionalized with 4-mercaptobenzoate (grey) and chiral CuS lattices functionalized with *D*-Pen. Ligands are omitted for clarity. The chiral distortion induced by *D*-Pen results in chiral quantum states contributing to the CPL shown in (i).

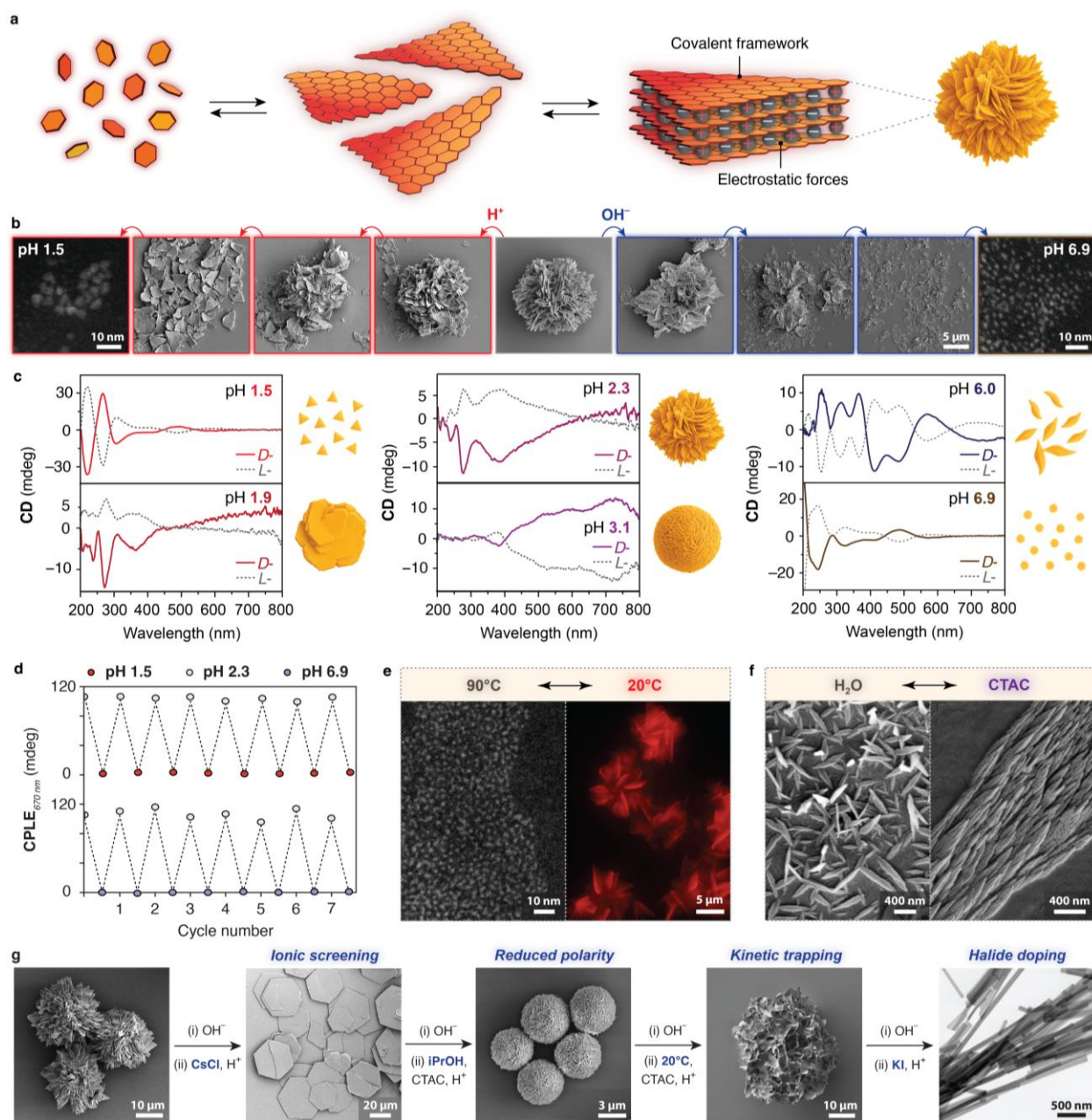


Fig. 3. Reversible disassembly and reconfiguration of SPs. (A) Schematic representation of reversible self-assembly of the CuS-Pen NSs governed by electrostatic and thermal interactions, controlled by Pen protonation state or temperature-driven disassembly. (B) SEM and HAADF-STEM images captured during gradual disassembly of *D*-SPs upon titration with hydrochloric acid (left) and potassium hydroxide (right). (C) Chiroptical activity of NSs and SPs synthesized at different pH values. (D) CPL intensity of *D*-SPs prepared at pH 2.3 during pH cycling between 1.5 and 6.9 at 50°C. (E) NSs reassembled in ethanol/CTAC mixture at 20°C after SPs disassembly at 90°C. (F) Free NSs in water and their lamellar assemblies with CTAC, both prepared at pH 6.0. (G) Reconfiguration of *D*-SPs into various superstructures through pH cycling under different conditions.

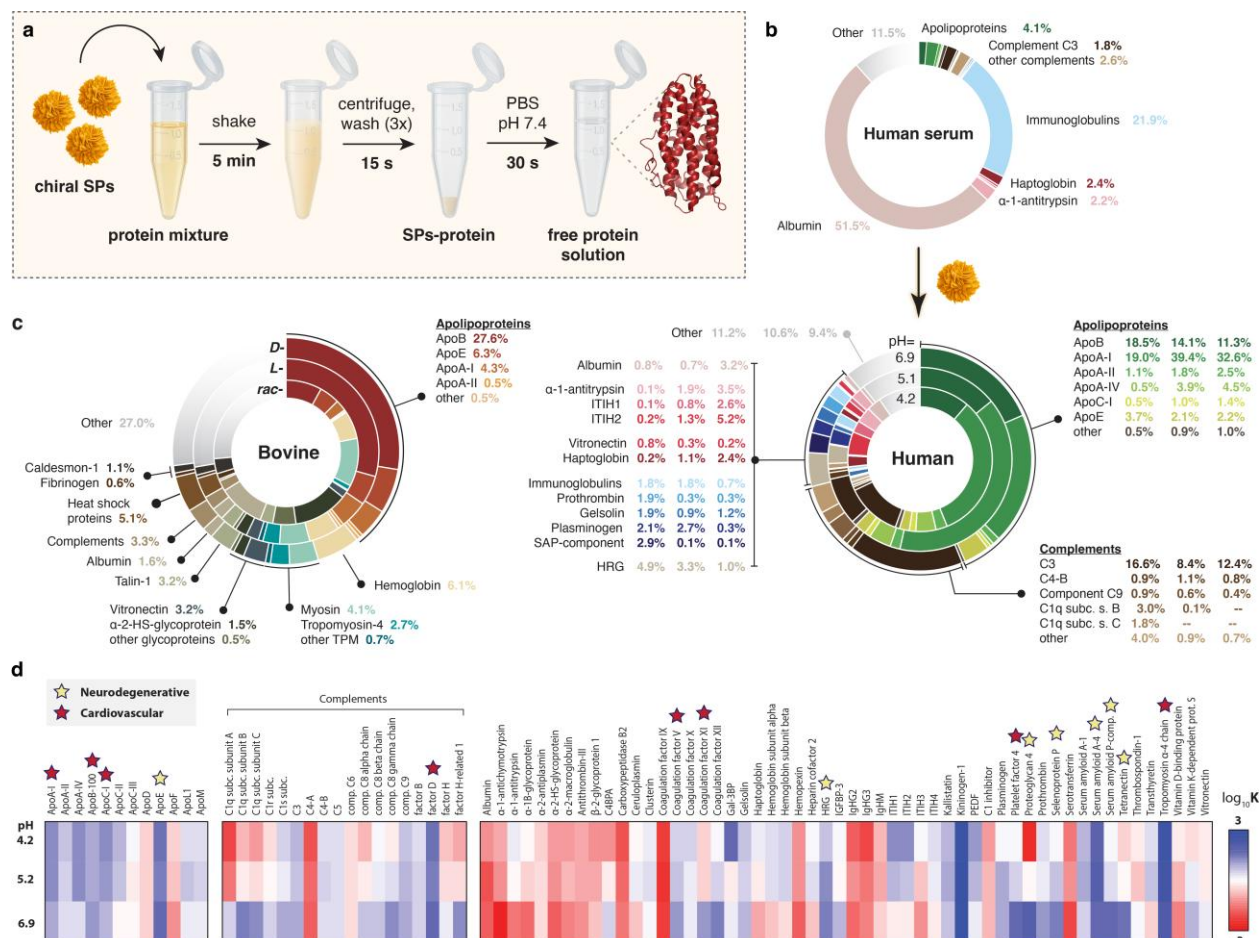


Fig. 4. Methodology of biomolecular separation using reconfigurable Cu-Pen isomorphs. (a) Schematic of the protein extraction procedure exemplified using SP isomorphs from serum. The entire process of protein isolation took 15 minutes. (b,c) Representative human (b) and bovine (c) proteomes after extraction from serum with *D*-SPs at different pH values (human) and *D*-, *L*-, and *rac*-SPs at pH 6.9 (bovine). (d) Human proteomes of the 90 most abundant proteins extracted using *D*-CuS-Pen SPs (as shown in panel b) at different pH values. Corresponding enrichment factors (*K*) are indicated by color intensity ($\log_{10}$ scale) for each protein. Stars denote biomarkers associated with neurodegenerative and cardiovascular diseases.

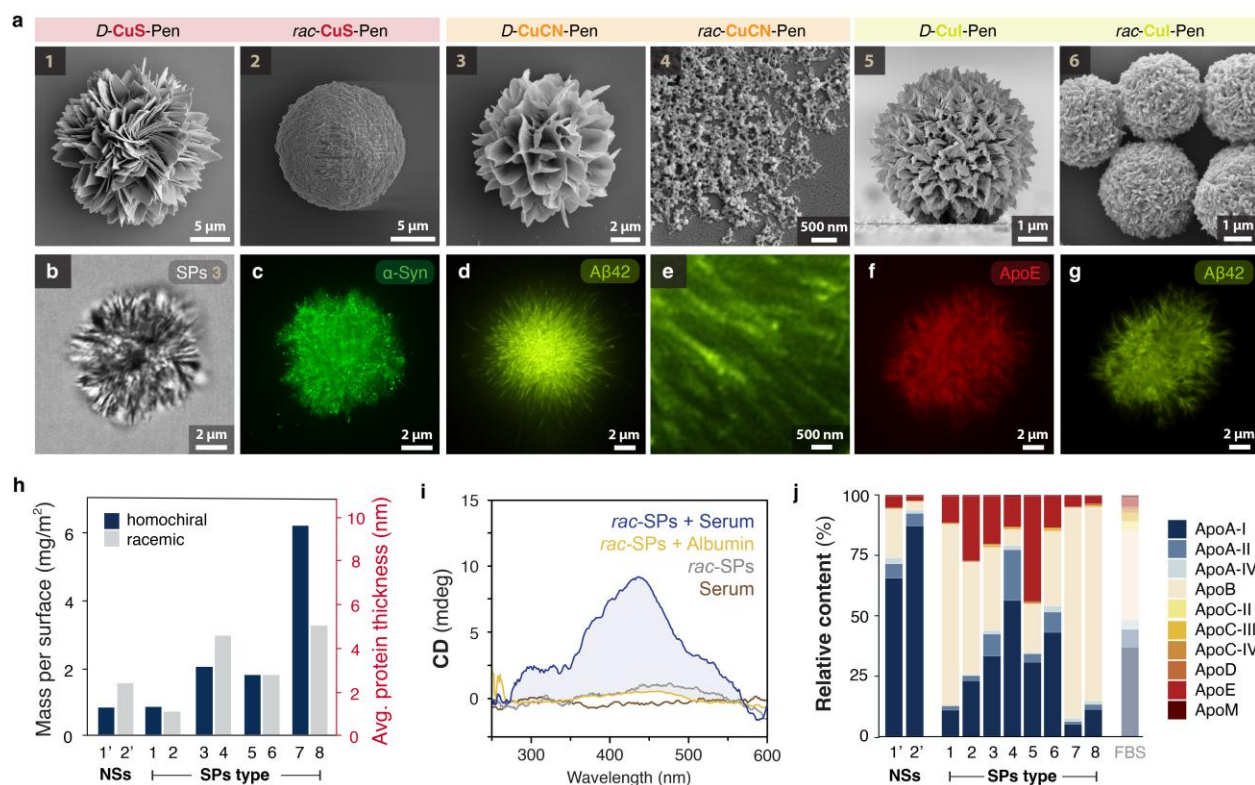


Fig. 5. Isomorph-dependent protein adsorption and isolation. (a) SEM images of representative isomorphs used for protein separation (see additional images in Fig. S38 B-G). (b,c) Confocal microscopy images of *D*-CuCN-Pen SPs (isomorph 3) capturing α -synuclein. (d,e) Confocal microscopy images of *D*-CuI-Pen SPs capturing A β 42 (isomorph 5). (f,g) Confocal microscopy images of *D*-CuCN-Pen SPs (isomorph 3) simultaneously capturing ApoE and A β 42 (see additional images in Fig. S51). (h) Average thickness of protein layer on the surface of different isomorphs after exposure to human serum. The isomorphs are labeled (1,2,3..) in accord with panel (A) and Fig. S38. Isomorphs 1' and 2' denote NSs disassembled from A and B SPs in panel (A). (i) CD spectra of *rac*-CuS-Pen NSs (isomorph 2') before and after adsorption of albumin and human serum proteins. (j) Isomorph-dependent enrichment of low-abundance apolipoproteins (Apo). The isomorphs are labeled (1,2,3..) in accord with panel (A) and Fig. S38. Isomorphs 1' and 2' denote NSs disassembled from A and B SPs in panel (a).

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