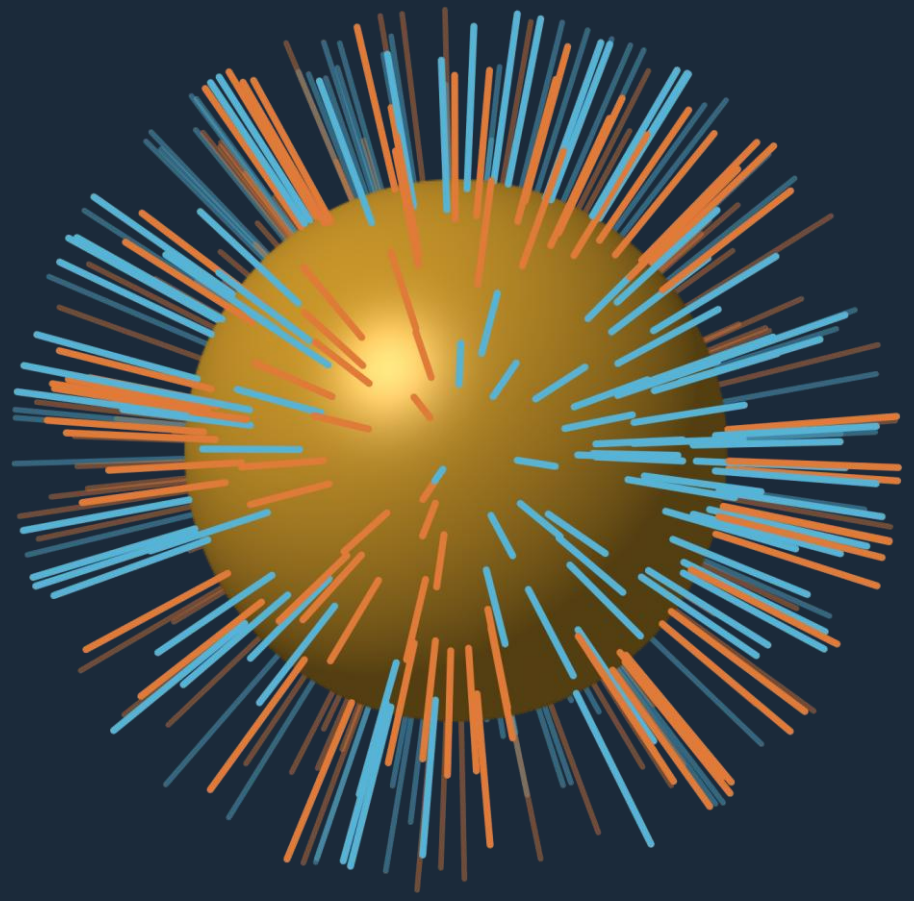
GUEST LECTURE 3 OF 3

Nanoparticles in Action

Applications, and what hydrophobic interactions do at the nano–bio interface



Francesco Stellacci · EPFL

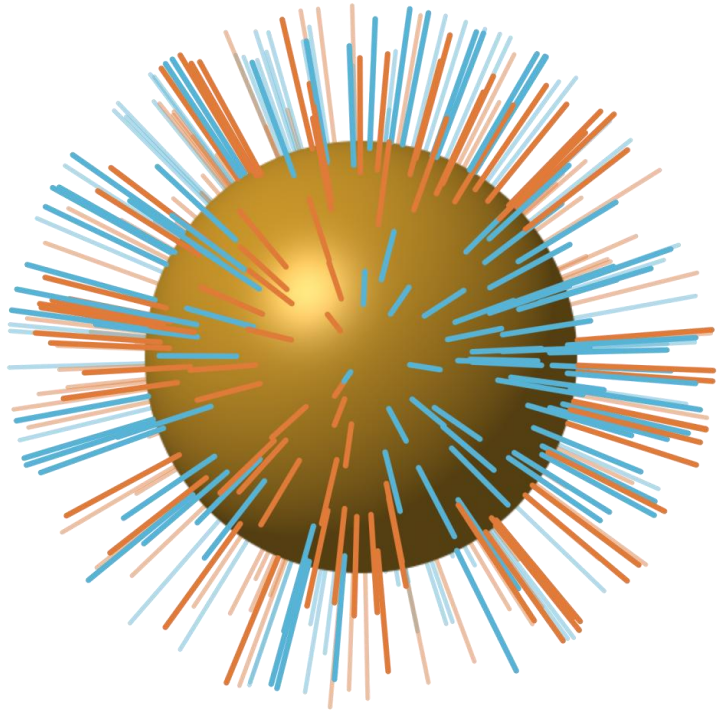
Outline

Part I · What they are used for

1. Why gold
2. Colour as a readout: DNA, barcodes, strips
3. Enzyme and array sensing
4. Spherical nucleic acids and delivery
5. Catalysis in the monolayer
6. Gold in the clinic
7. Programmable matter

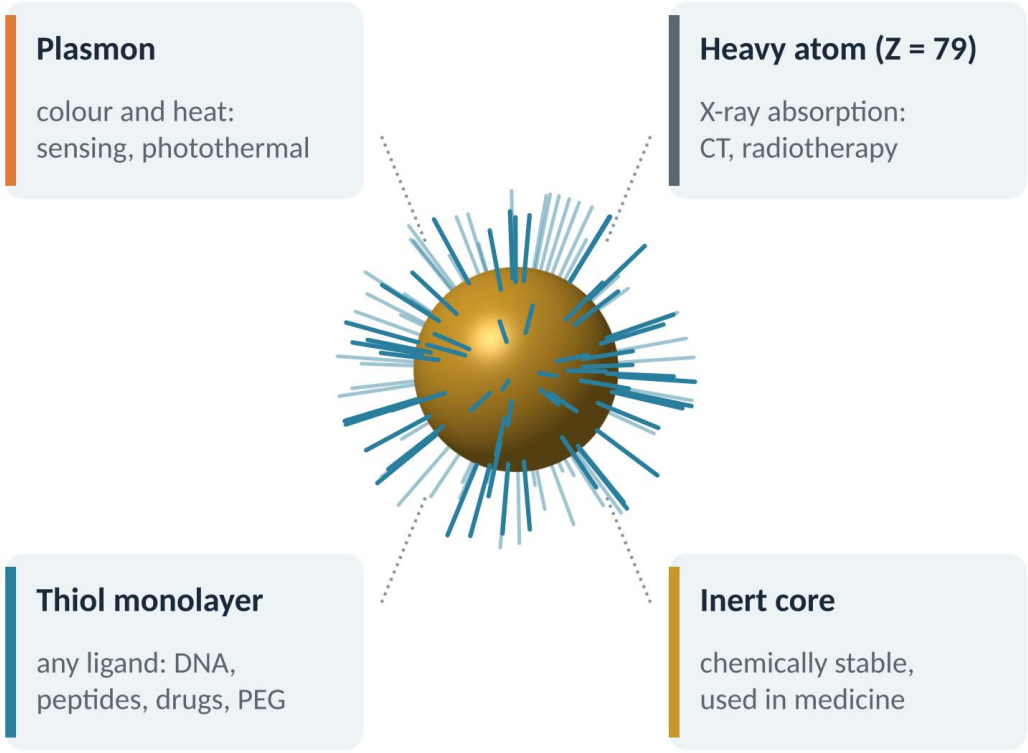
Part II · Hydrophobic interactions

8. A length scale for hydrophobicity
9. Crossing cell membranes
10. Fusing membranes
11. Labelling amyloids
12. Breaking viruses



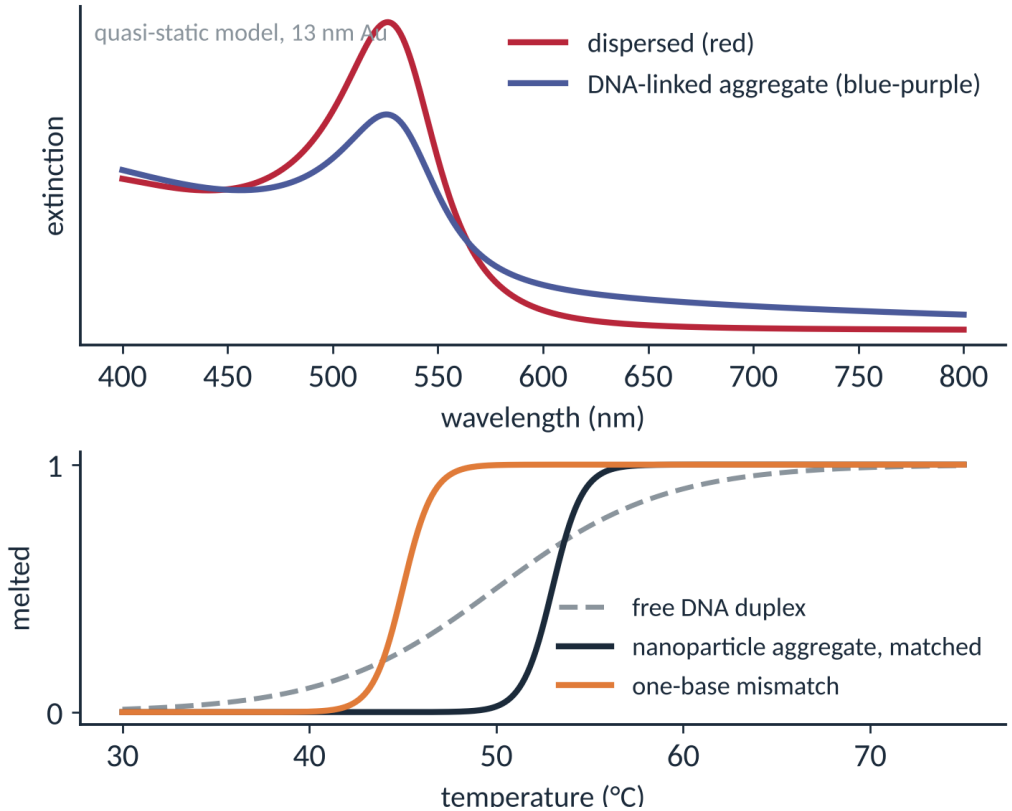
Why gold, and why a ligand shell

- **Plasmon.** A few nanometres of gold absorb light strongly in the visible; the colour depends on size, shape and, above all, on the distance to the next particle.
- **Chemistry.** Thiols bind firmly but exchangeably; mixed shells can be patterned.
- **Inert and dense.** Stable in biological media, easy to see in TEM, strongly X-ray absorbing.
- **Scale.** 1–100 nm spans proteins to viruses.



Colour as a readout: DNA detection

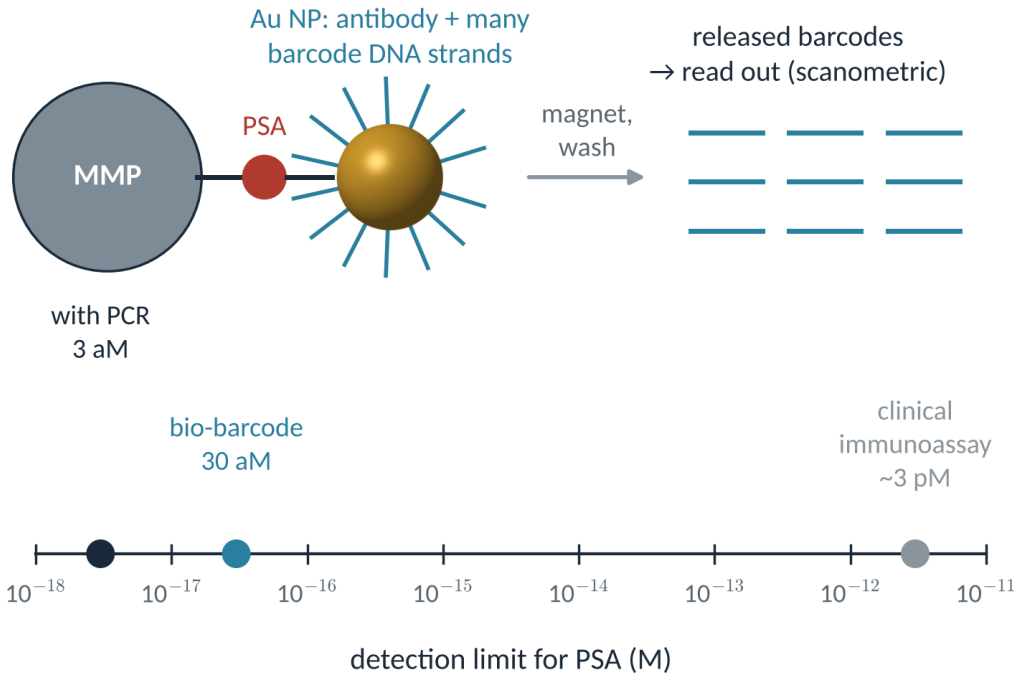
- Two batches of particles carry non-complementary probe strands.
- A target that is complementary to both cross-links them. Interparticle distance falls below roughly one diameter, the plasmons couple, and the suspension turns from red to blue.
- The aggregate melts over ~2 °C instead of ~20 °C, because many duplexes break cooperatively — so a single base mismatch is visible by eye.



Mirkin, Letsinger, Mucic & Storhoff, Nature 382, 607 (1996) · Elghanian et al., Science 277, 1078 (1997)

Amplification without PCR: the bio-barcode

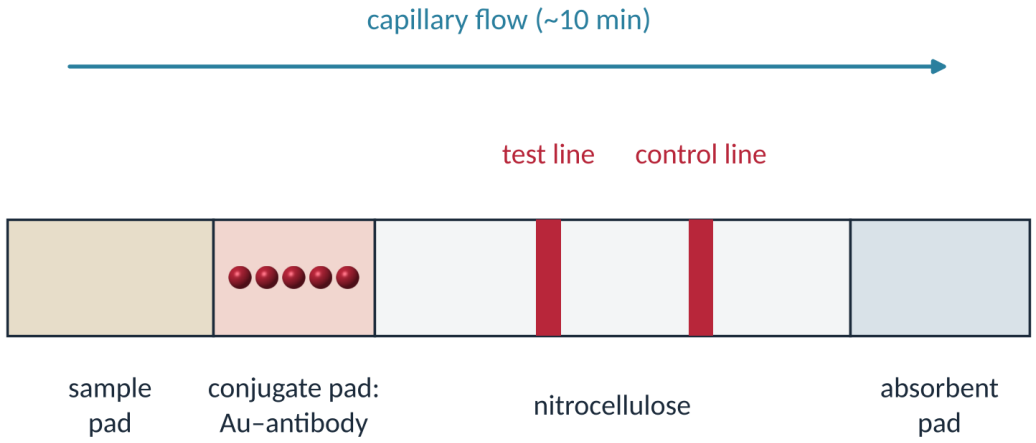
- A magnetic microparticle captures the target protein; a gold particle carrying an antibody **and** hundreds of identical short DNA strands binds the other side.
- Magnetically separate, release the DNA, and read the barcode instead of the target.
- Each binding event is reported by hundreds of strands — the surface area is the amplifier.
- PSA down to ~330 fg mL^{-1}; detects recurrence after prostatectomy years before standard assays.



Nam, Thaxton & Mirkin, Science 301, 1884 (2003) · Thaxton et al., PNAS 106, 18437 (2009)

The one in every home: lateral flow

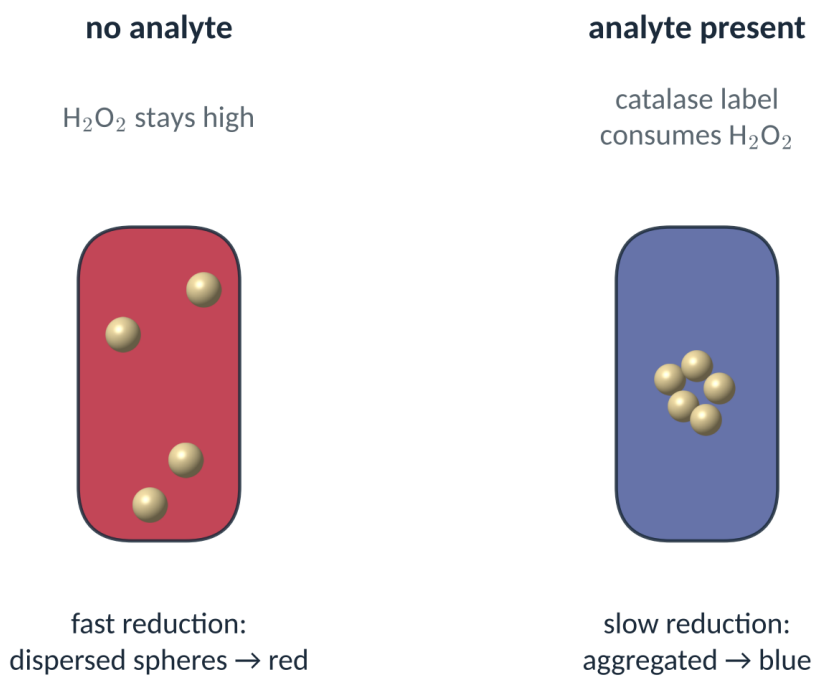
- About 40 nm citrate gold, conjugated to an antibody, dried onto a pad.
- Sample wicks along nitrocellulose, carries the conjugate to a capture line, and a red band appears. No instrument, no power, no cold chain.
- Pregnancy tests since the 1980s; SARS-CoV-2 antigen tests at a scale of billions of units.
- By volume, this is still the dominant nanoparticle product.



Review: Posthuma-Trumpie, Korf & van Amerongen, Anal. Bioanal. Chem. 393, 569 (2009)

Plasmonic ELISA: growing the particle instead

- Standard ELISA ends with an enzyme making a coloured product. Here the enzyme instead controls how gold grows from Au^{3+}.
- Catalase consumes H_2O_2. Lots of analyte → little H_2O_2 left → slow, non-uniform growth → aggregated, blue solution.
- Little analyte → fast nucleation → monodisperse, red.
- The response is **inverse**: less analyte gives a stronger blue. ~10^{-18} g mL^{-1} of PSA and HIV-1 p24, read by eye.

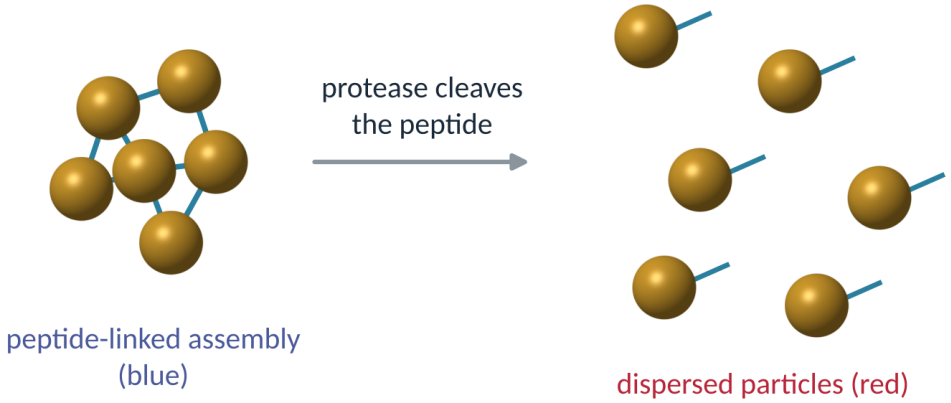


$AuCl_4^-$ + H_2O_2 → Au: the growth rate sets the particle morphology

de la Rica & Stevens, Nature Nanotech. 7, 821 (2012)

Sensing enzyme activity

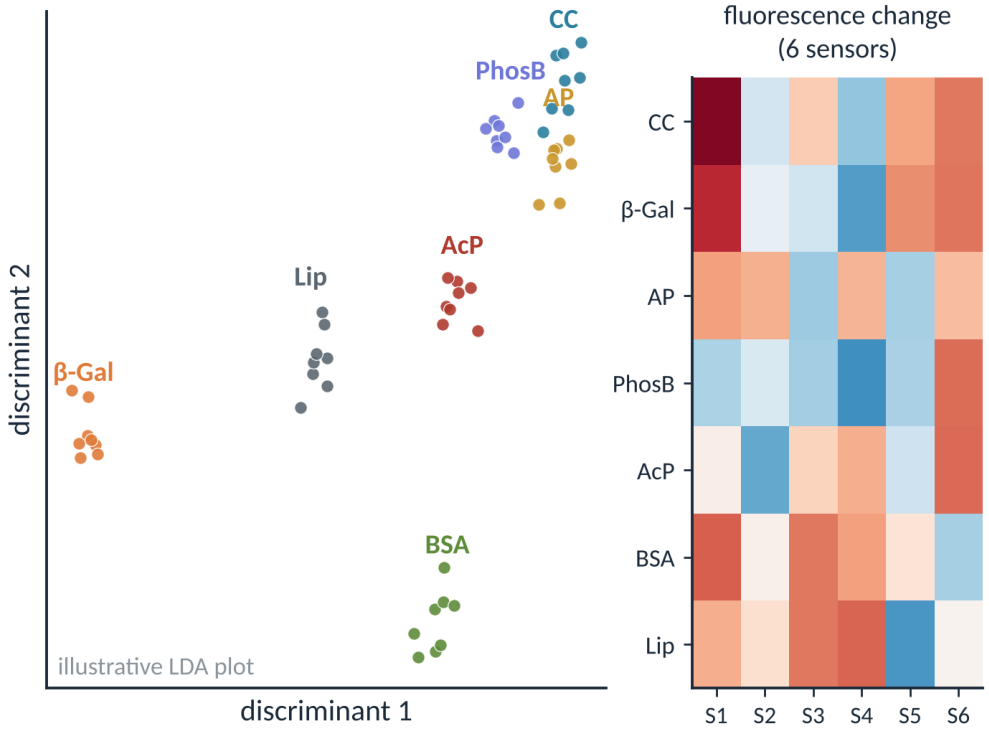
- Coat the particle with a peptide that is the enzyme's substrate.
- Cleavage removes the charged end of the ligand, the balance between repulsion and hydrophobic attraction flips, and the particles aggregate — or, with the opposite design, redisperse.
- Activity, not concentration, is measured: one enzyme molecule turns over many particles' worth of ligands.
- Used for thrombin, MMPs, kinases and phosphatases.



Laromaine, Koh, Murugesan, Ulijn & Stevens, JACS 129, 4156 (2007) · Review: Howes, Chandrawati & Stevens, Science 346, 1247390 (2014)

The chemical nose: patterns, not receptors

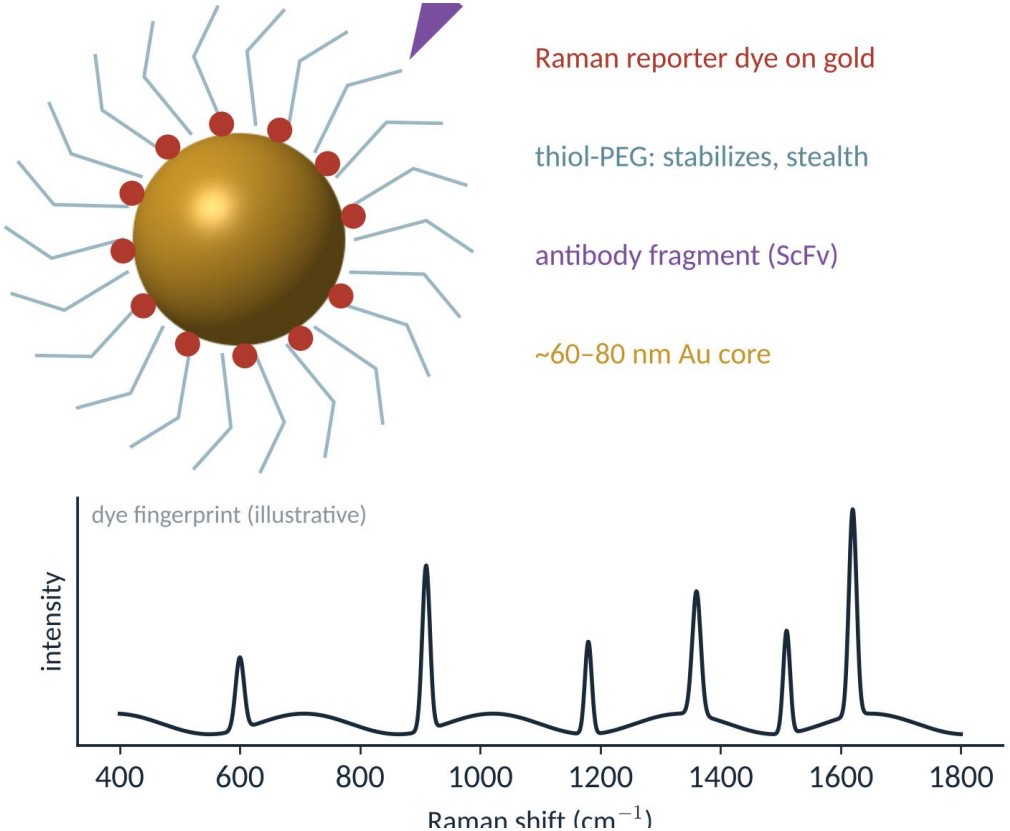
- Instead of a specific receptor for each analyte, use an array of particles with different surface chemistries.
- Each particle quenches a fluorescent polymer; an analyte displaces it to a different extent. The array gives a fingerprint.
- Linear discriminant analysis separates proteins, bacterial species, and normal from cancerous cells — with no biomarker identified in advance.
- Selectivity comes from the pattern across many weak, non-specific interactions.



You et al., Nature Nanotech. 2, 318 (2007) · Bajaj et al., PNAS 106, 10912 (2009)

SERS tags: a narrow fingerprint

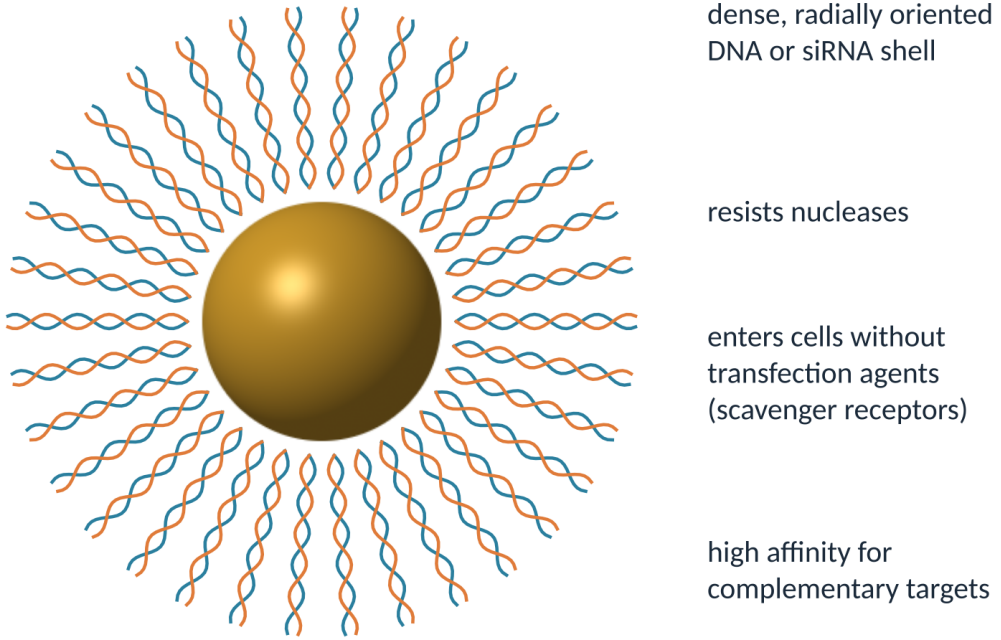
- A Raman reporter adsorbed at the gold surface sits in the enhanced field of the plasmon; the cross-section rises by up to ~10^{14}.
- Raman bands are ~100× narrower than fluorescence, so many tags can be read at once with one laser.
- A PEG shell gives circulation time, an antibody gives targeting, near-infrared excitation gives tissue penetration.
- Demonstrated for tumour detection in live mice.



Qian et al., Nature Biotech. 26, 83 (2008)

Spherical nucleic acids

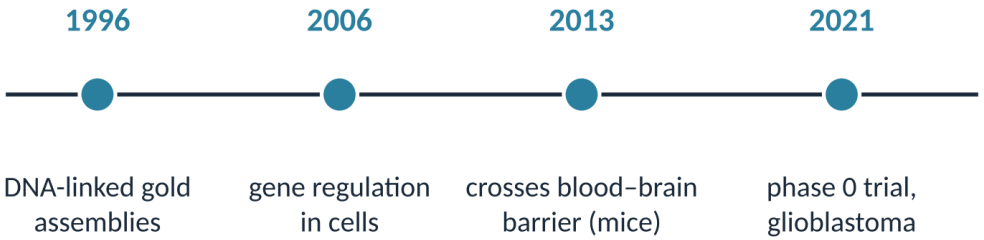
- A dense, radially oriented shell of oligonucleotides. The properties belong to the **arrangement**, not to the gold.
- They enter most cell types without transfection agents, taken up through scavenger receptor A, which recognises the dense polyanion.
- The crowded shell slows nucleases and raises binding affinity through cooperativity.
- The core can later be dissolved away: the shell is the drug.



Rosi et al., Science 312, 1027 (2006) · Choi, Hao, Narayan, Auyeung & Mirkin, PNAS 110, 7625 (2013)

Spherical nucleic acids reach patients

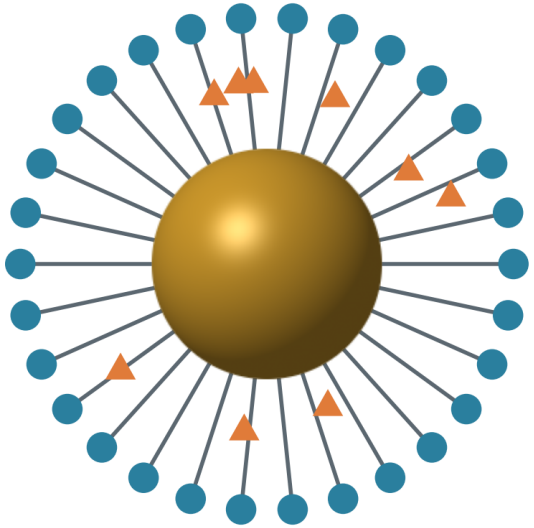
- **NanoFlares**: a reporter strand is displaced by a target mRNA and lights up in a live cell. Widely used — though the quantitative interpretation was later disputed.
- **Psoriasis**: a topical siRNA SNA against TNF, through intact skin.
- **NU-0129**: siRNA against Bcl2L12 for glioblastoma; first-in-human gold-based SNA, crossed the blood–brain barrier, reached the tumour and was well tolerated.



Seferos et al., JACS 129, 15477 (2007) · caveat: Czarnek & Bereta, Sci. Rep. 7, 10396 (2017) · Jensen et al., Sci. Transl. Med. 5, 209ra152 (2013) · Kumthekar et al., Sci. Transl. Med. 13, eabb3945 (2021)

The monolayer as cargo space

- Hydrophobic drugs partition into the alkyl region of the shell and ride there — no covalent chemistry needed.
- Release is triggered in the cytosol: glutathione at ~10 mM displaces the thiols and spills the cargo.
- Cationic shells complex siRNA and protein; engineered shells deliver Cas9 protein and guide RNA together.
- The same shell carries, protects and releases.

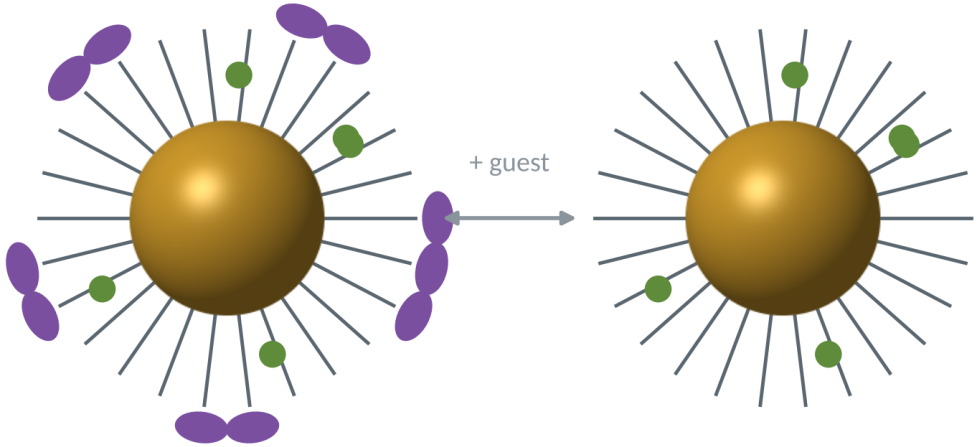


Kim, Ghosh, Han & Rotello, JACS 131, 1360 (2009) · Mout et al., ACS Nano 11, 6416 (2017)

Catalysis in the monolayer

- Scrimin and Pasquato: a monolayer of triazacyclononane–Zn^{2+} cleaves phosphodiesters with Michaelis–Menten kinetics. Neighbouring sites cooperate — the **monolayer** is the enzyme, not the metal centre.
- Rotello: ruthenium catalysts buried in the hydrophobic pocket run bioorthogonal reactions inside living cells; a cucurbituril guest switches them off and on.
- Related: cationic, hydrophobic shells that kill resistant bacteria.

violet: cucurbit[7]uril gate · green: Ru/Pd catalyst in the monolayer



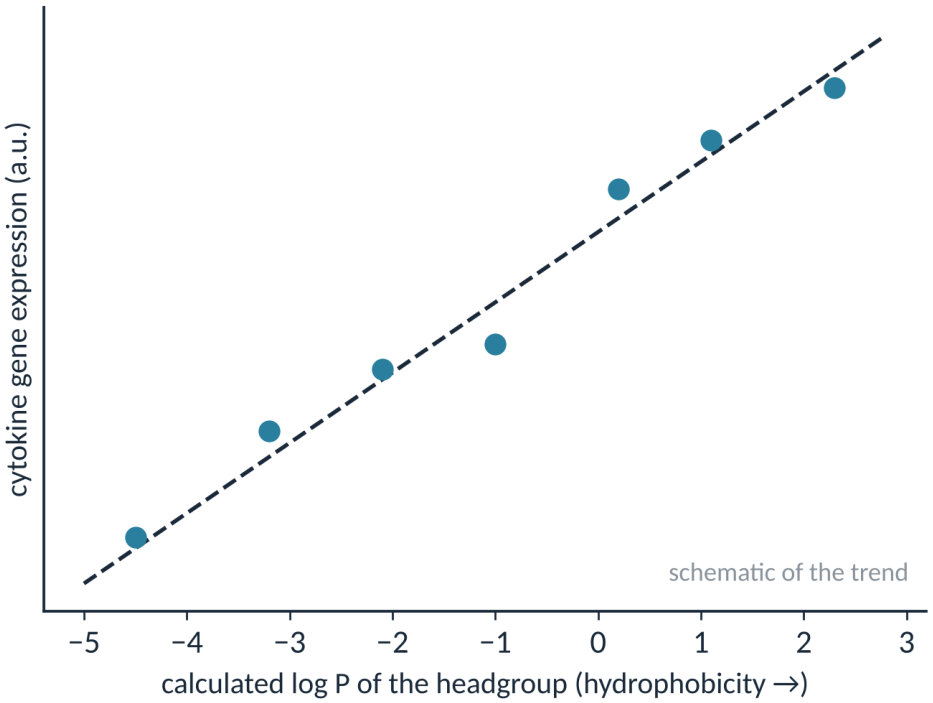
gate on: catalyst blocked

gate removed: catalysis on

Manea, Bodar Houillon, Pasquato & Scrimin, Angew. Chem. Int. Ed. 43, 6165 (2004) · Tonga et al., Nature Chem. 7, 597 (2015)

The bridge: biology reads hydrophobicity

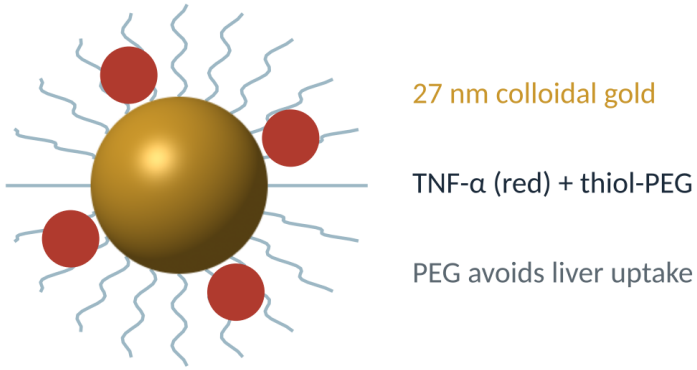
- Same core, same charge, same size. Only the end of the ligand changes, from polar to increasingly greasy.
- The cytokine response of splenocytes — TNF-α, IL-6 and others — rises **monotonically** with the computed logP of the terminal group.
- No receptor for 'nanoparticle' exists. The immune system is reading a physical property of the surface.
- If hydrophobicity is read, it can be designed.

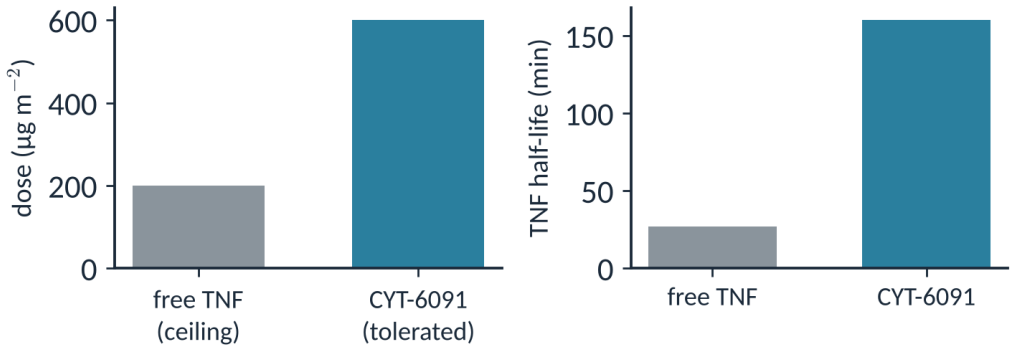


Moyano et al., JACS 134, 3965 (2012)

Gold in the clinic: CYT-6091

- 27 nm citrate gold carrying recombinant TNF-α and thiolated PEG.
- TNF-α is a potent anti-tumour agent whose systemic toxicity blocked its use for thirty years. The particle changes where it goes, not what it does.
- Phase I: maximum tolerated dose 600 µg m^{-2} versus about 200 for free TNF; circulation half-life 27 → 160 min.
- Gold was found in tumour biopsies and not in adjacent healthy tissue.

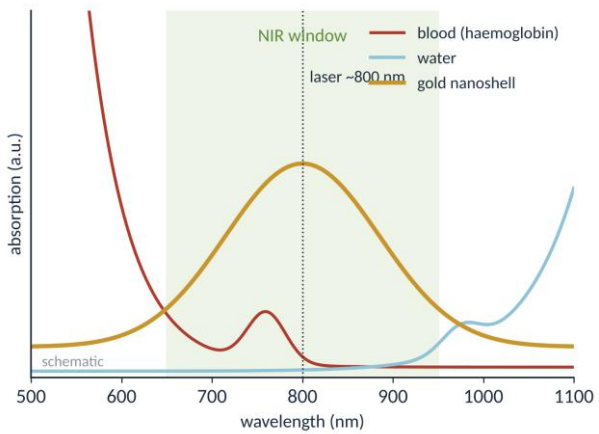


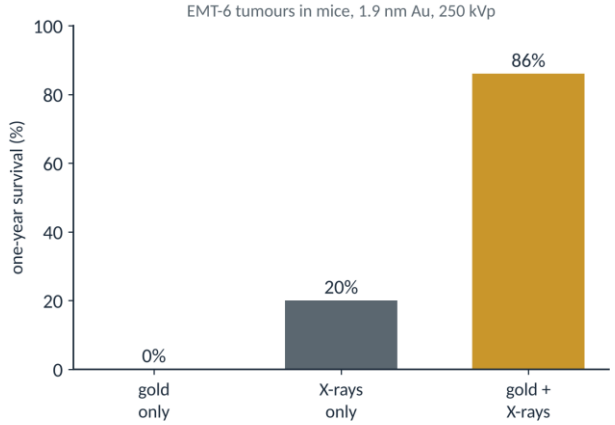


Libutti et al., Clin. Cancer Res. 16, 6139 (2010)

Gold in therapy: heat and X-rays

- **Photothermal.** A silica core with a thin gold shell absorbs at 650–900 nm, where tissue is most transparent. Light in, heat out, tumour ablated. AuroLase has been through a pilot trial in prostate cancer.
- **Radiosensitisation.** Gold's high atomic number means a large photoelectric cross-section at keV energies: dose is deposited locally, sparing surrounding tissue — and the same absorption gives CT contrast.

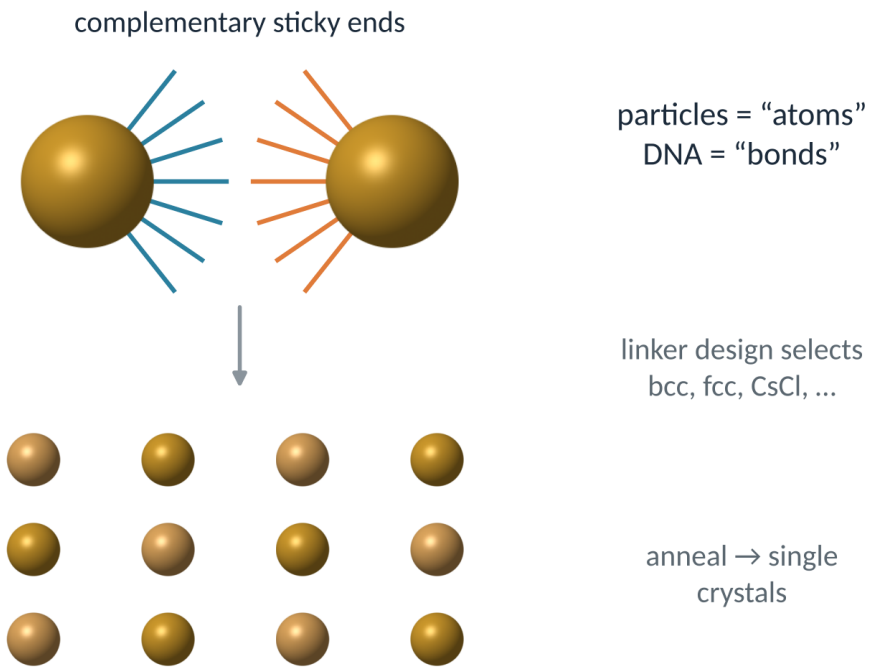




Hirsch et al., PNAS 100, 13549 (2003) · Rastinehad et al., PNAS 116, 18590 (2019) · Hainfeld, Slatkin & Smilowitz, Phys. Med. Biol. 49, N309 (2004)

Programmable matter

- DNA as a designed bond: sequence sets which particles stick, length sets how far apart they sit.
- Two groups showed in the same issue of Nature that gold particles can be crystallised into FCC or BCC lattices by choice of linker.
- Later generalised into design rules — 'nanoparticle superlattice engineering' — and the idea of the particle as an **atom equivalent**.
- The point for us: the shell, not the core, decides the structure.



Park et al., Nature 451, 553 (2008) · Nykypanchuk et al., Nature 451, 549 (2008) · Macfarlane et al., Science 334, 204 (2011)

What made all of those work

1 Optical readout

The plasmon converts a binding event into a colour — DNA detection, lateral flow, plasmonic ELISA, SERS.

2 Surface area

Hundreds of ligands per particle give amplification (bio-barcode) and avidity (sharp melting, SNA uptake).

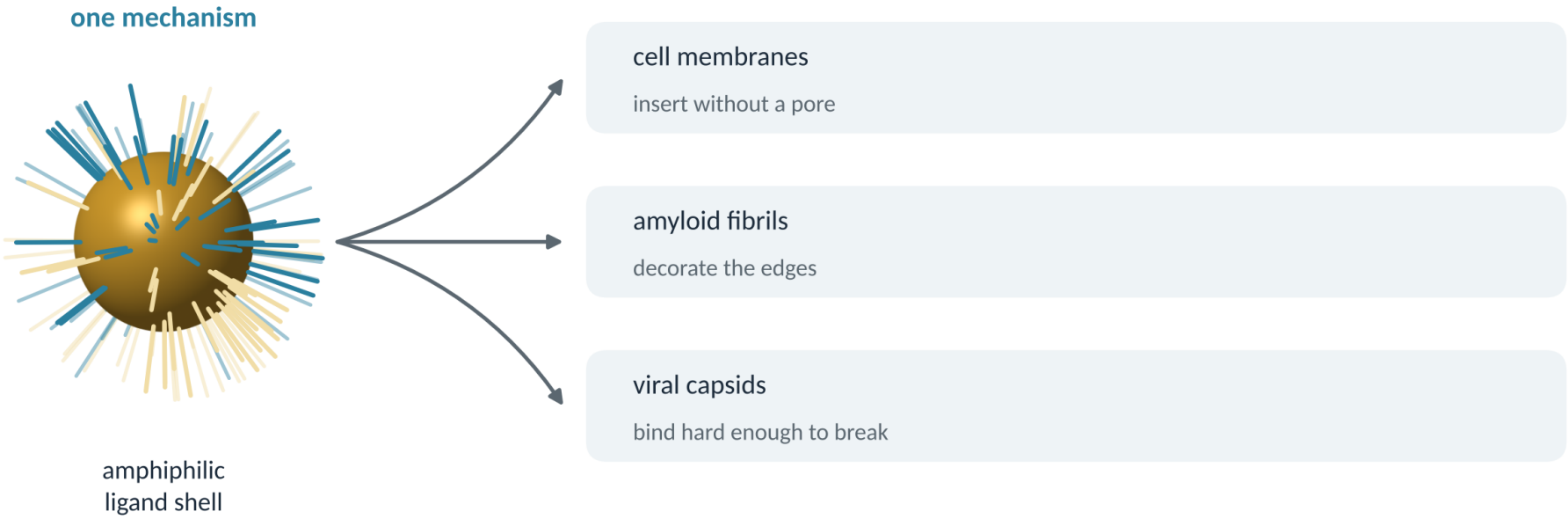
3 The shell is the function

Catalysis, cargo and recognition all live in the monolayer; the gold is a scaffold.

4 Biology reads the surface

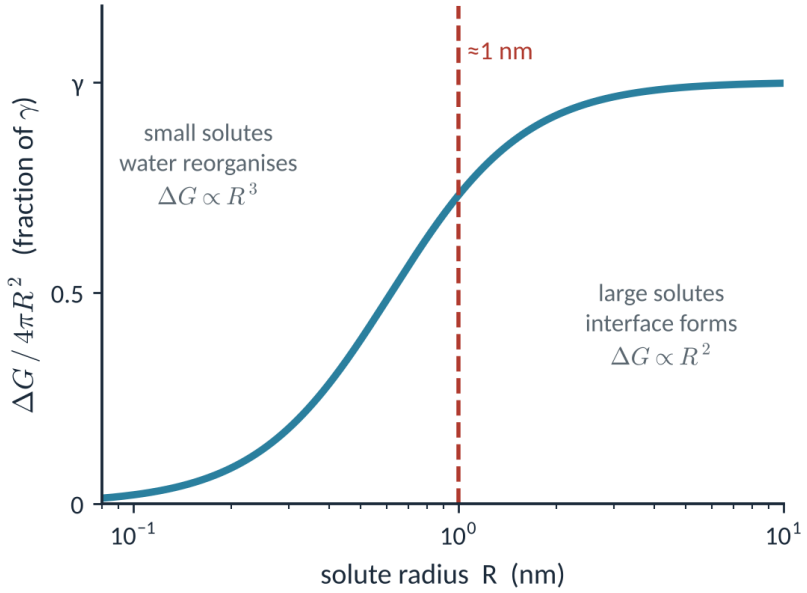
Charge, density and **hydrophobicity** — not the identity of the core — set uptake, clearance and immune response.

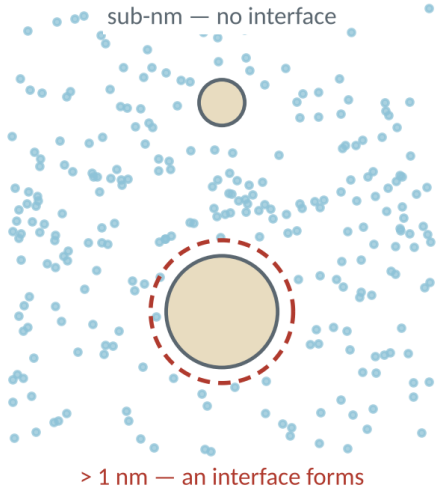
One variable, three problems



The ligand shell of our particles is amphiphilic: a charged sulfonate head on a long alkyl chain, often mixed with a purely hydrophobic ligand. That combination keeps the particle water-soluble while presenting hydrophobic surface — and hydrophobic surface is what biology is made of inside.

Hydrophobicity has a length scale

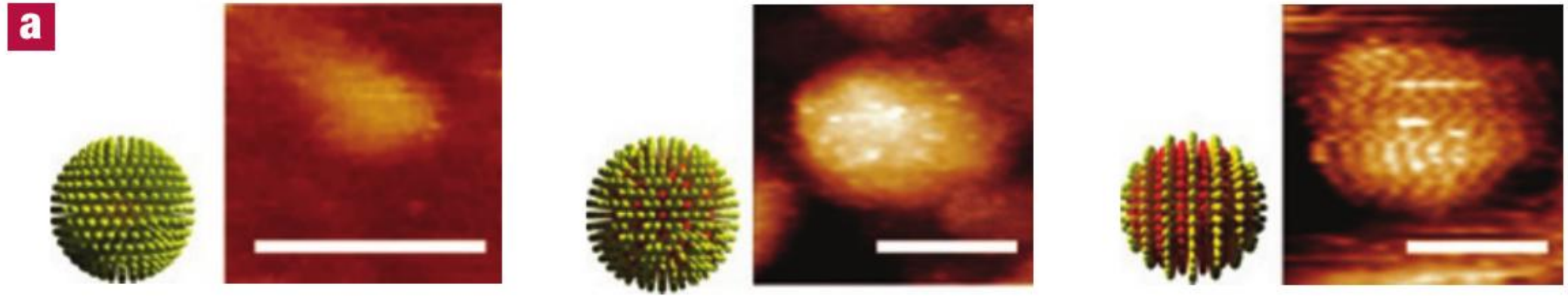




- Below ~1 nm, water reorganises around the solute: the cost grows with **volume**.
- Above ~1 nm, an interface forms: the cost grows with **area**, with the coefficient γ.
- Our particles sit just above the crossover — they behave as pieces of hydrophobic **surface**.

D. Chandler, Nature 437, 640 (2005) · Lum, Chandler & Weeks, J. Phys. Chem. B 103, 4570 (1999)

Designing the shell: ordered mixed monolayers

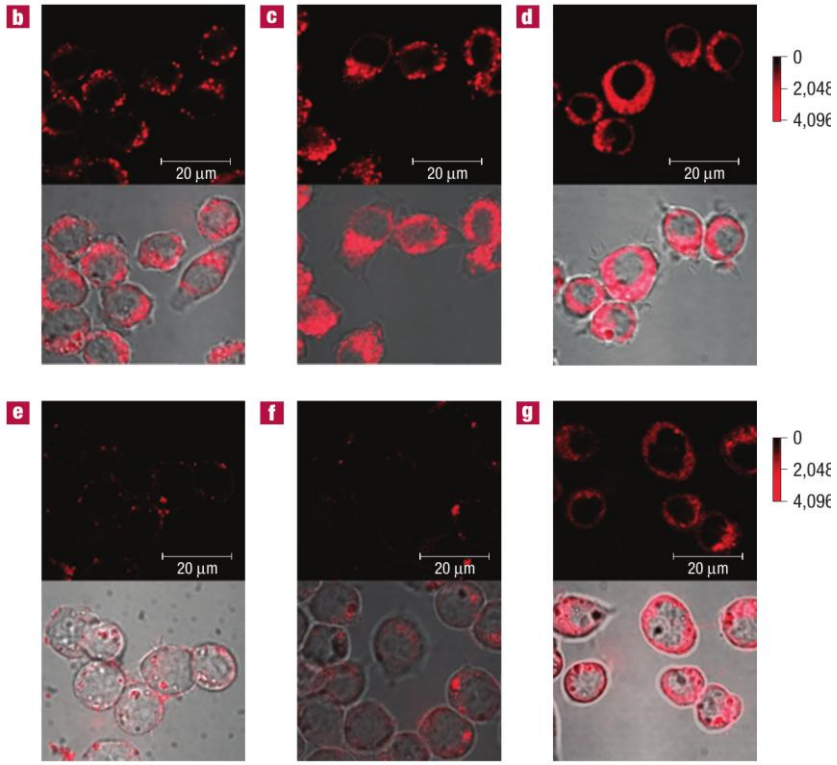


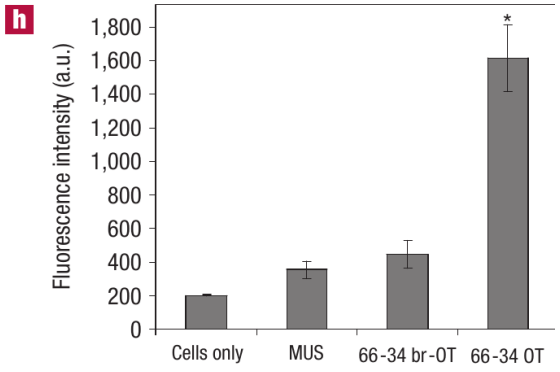
all-MUS · 66-34 branched-OT (disordered) · 66-34 OT ('striped') — scale bars 5 nm

- Ribbon-like domains below 1 nm wide form on a curved surface.
- Branched ligands of the same ratio give a **disordered** shell — the control.
- Same size, same ζ-potential, same hydrophobic fraction.
- Only the **arrangement** of hydrophobic groups differs.

Verma et al., Nature Materials 7, 588 (2008) · Centrone et al., PNAS 105, 9886 (2008) · Kuna et al., Nature Materials 8, 837 (2009)

Entering cells without making a hole

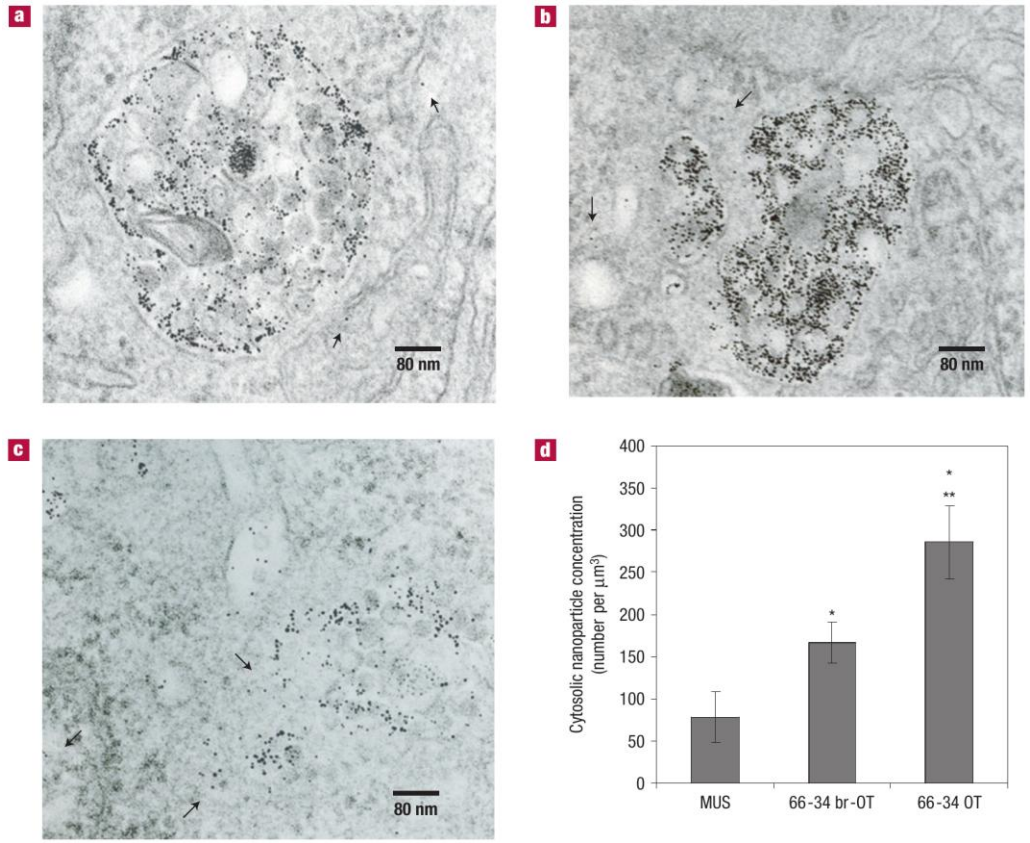


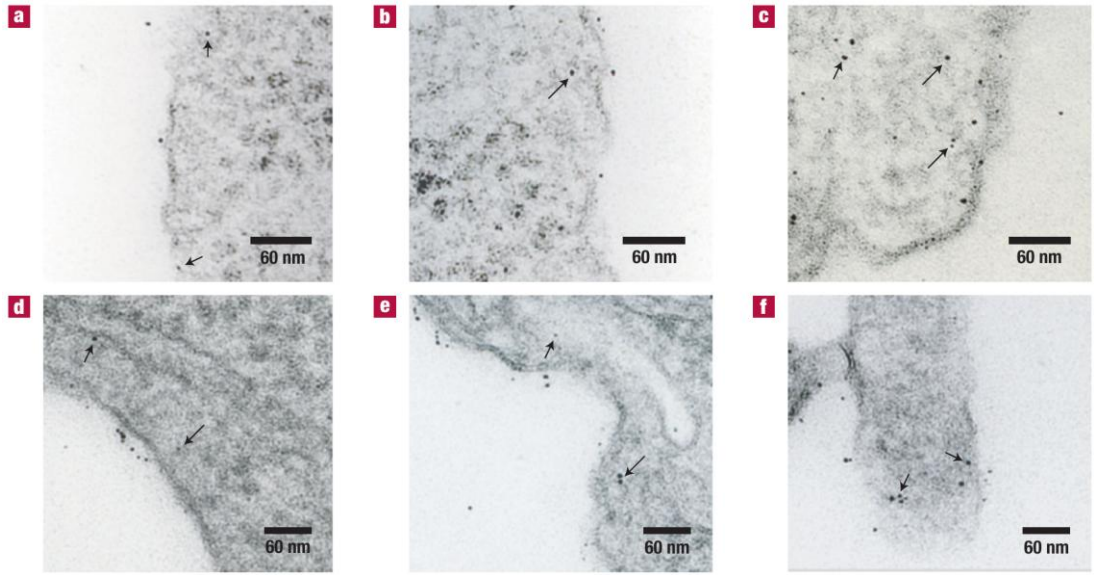


- At 4 °C with ATP depletion, striped particles still enter — **8× background**.
- MUS and branched-OT stay at background: they need endocytosis.
- No calcein entry and no calcein leakage → **no pore**.
- Detected inside cells within 5 minutes; excluded from the nucleus.

Verma et al., Nature Materials 7, 588 (2008)

Where they end up

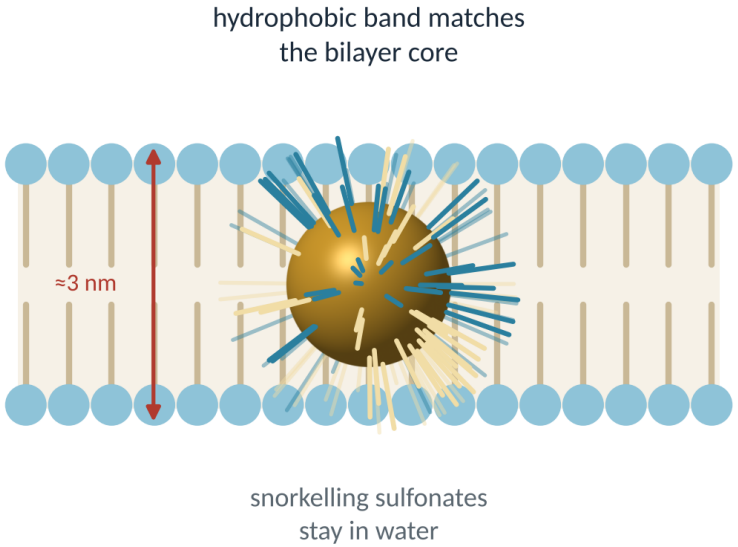


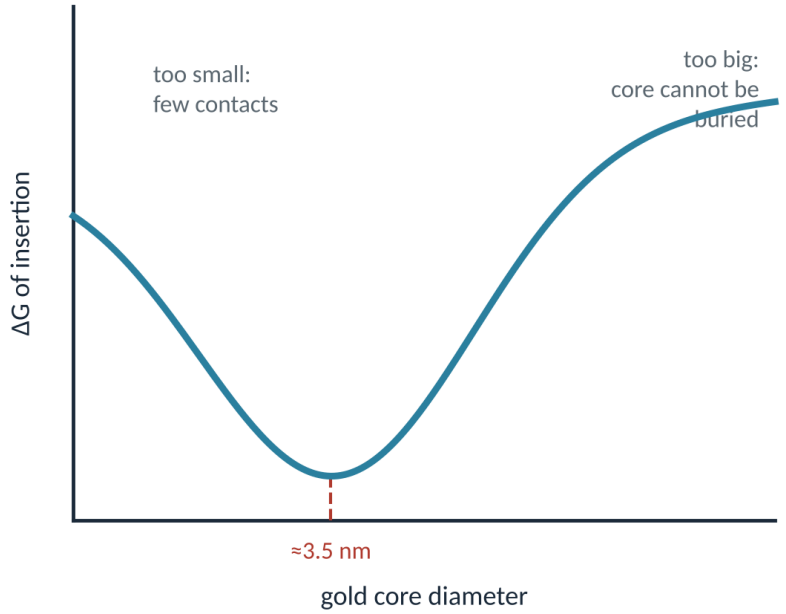


- Cytosolic particles per µm³: MUS ≈ 80, branched-OT ≈ 165, striped OT ≈ 285.
- Same trends in serum-containing medium — not a protein-corona artefact.

Verma et al., Nature Materials 7, 588 (2008)

Why: hydrophobic matching

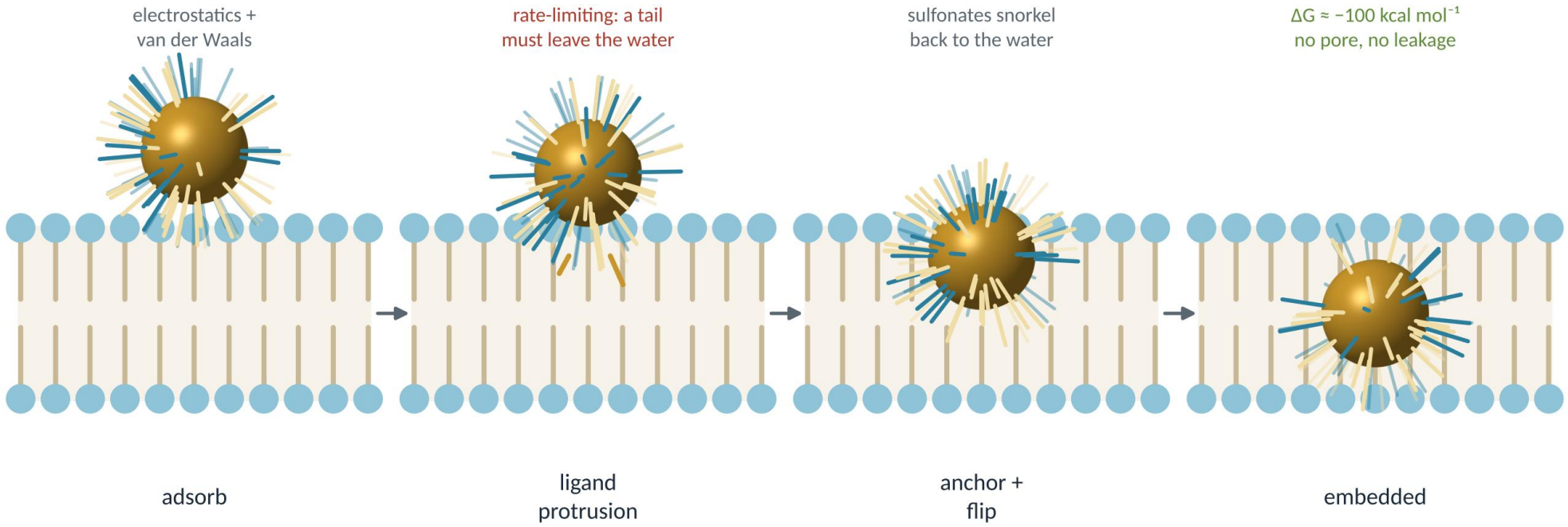




- The embedded state is a free-energy **minimum**, not a trapped state.
- Ligands rearrange so that the hydrophobic band matches the bilayer core.
- Too large a core cannot be buried; too small gives too few contacts.
- Optimum around 3–5 nm — the sizes we actually make.

Van Lehn et al., Nano Lett. 13, 4060 (2013) · Van Lehn & Alexander-Katz, with Carney et al., ACS Nano (bilayer experiments)

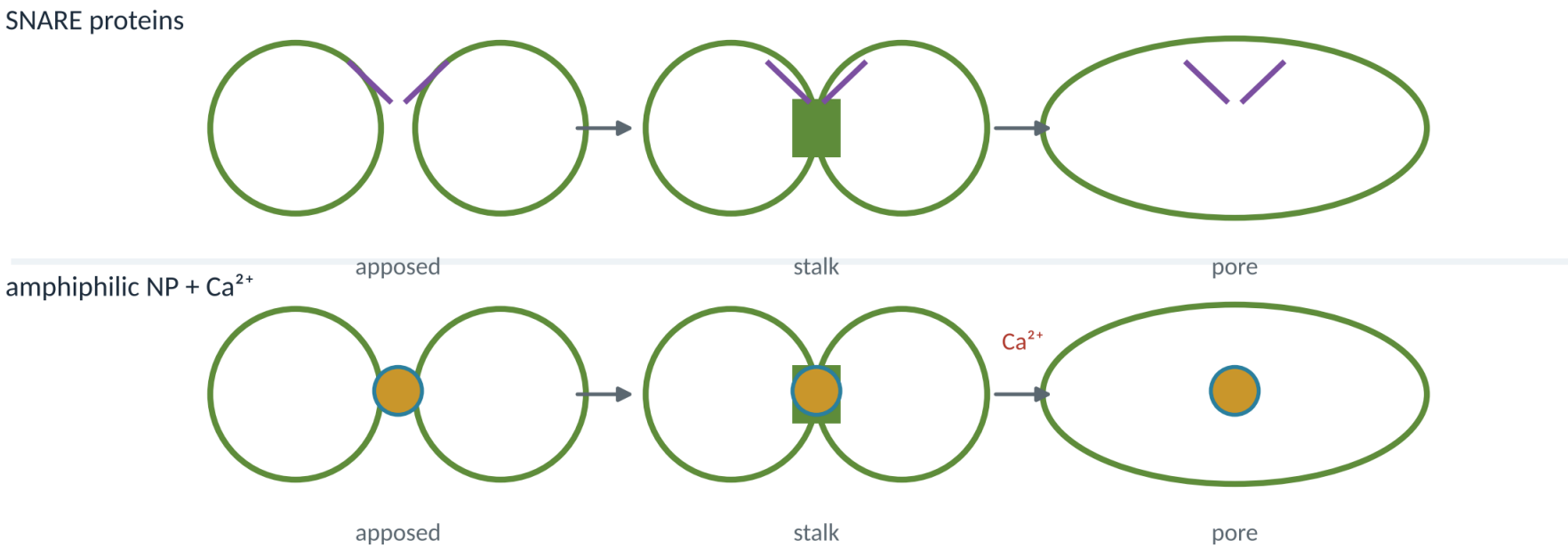
The pathway, and what limits it



The whole process is a sequence of hydrophobic contacts being made one at a time. That is why ligand length, flexibility and the ratio of hydrophobic to charged ligands control it — and why a disordered shell of the same composition behaves differently.

Van Lehn et al., Nature Commun. 5, 4482 (2014) · Van Lehn & Alexander-Katz, PLoS ONE (free-energy landscape)

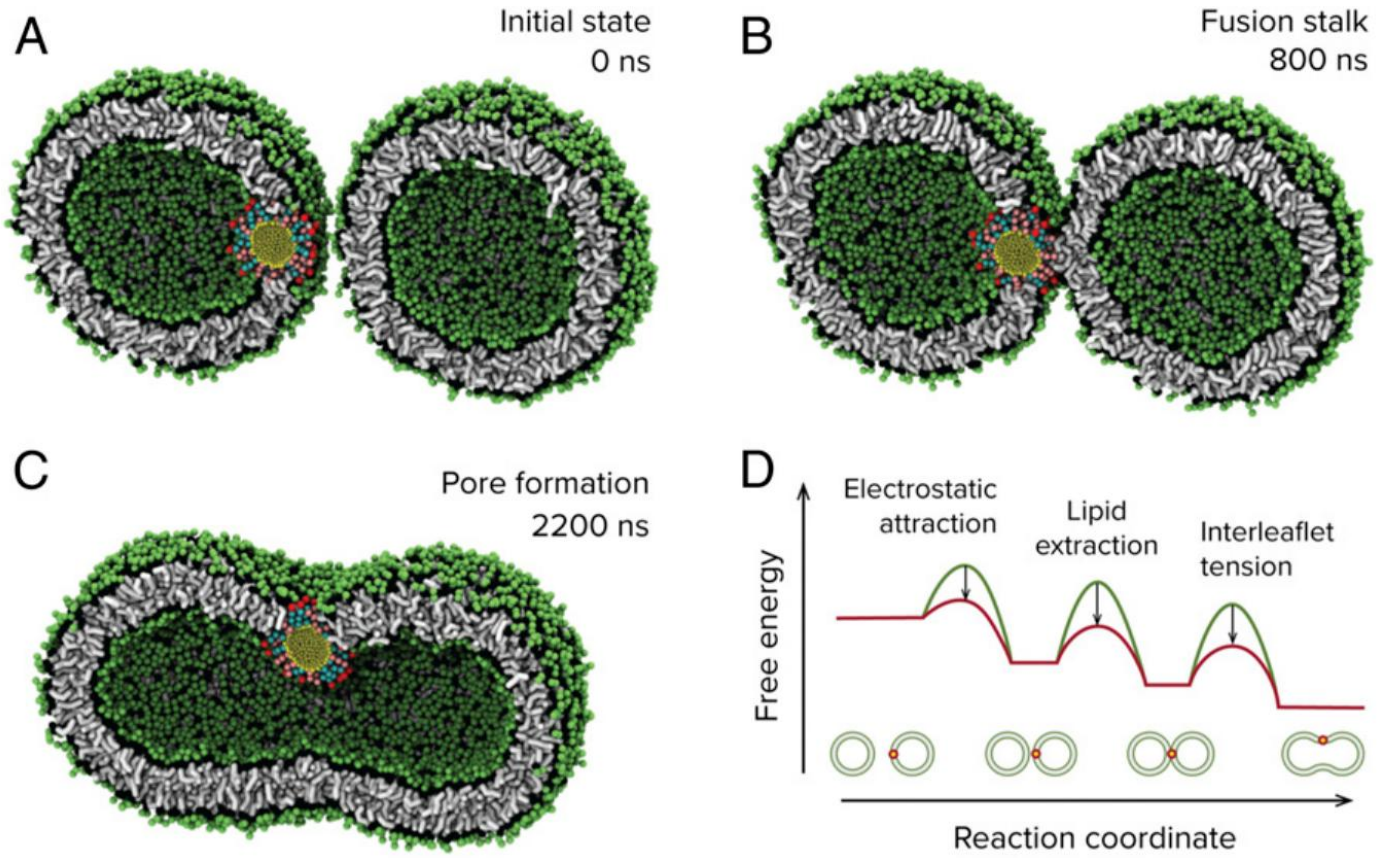
From entering one membrane to fusing two



The particle embedded in one vesicle holds the second vesicle close through its sulfonates, then extracts a lipid from the opposing bilayer — the transition state — and bridges the two hydrophobic cores. The stalk then sits there, stable, until something stresses the outer leaflet.

Tahir et al., PNAS 117, 18470 (2020)

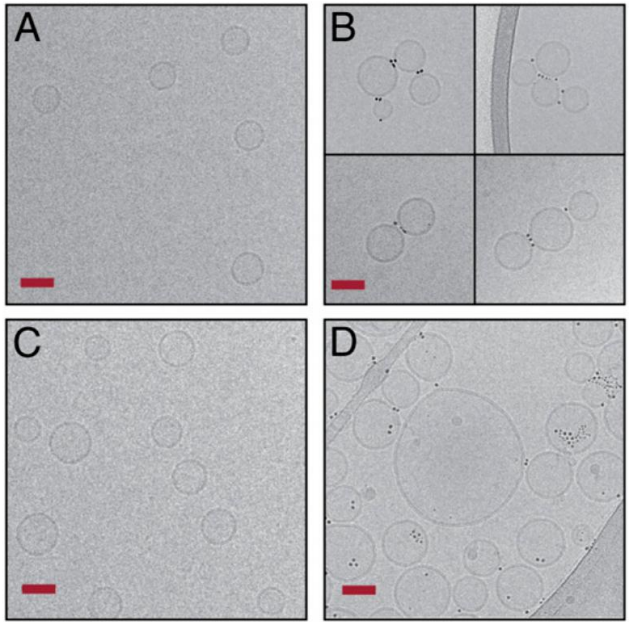
Simulation: a stalk, then a calcium-triggered pore

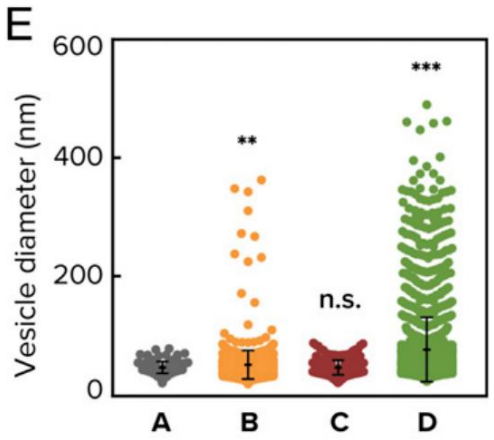


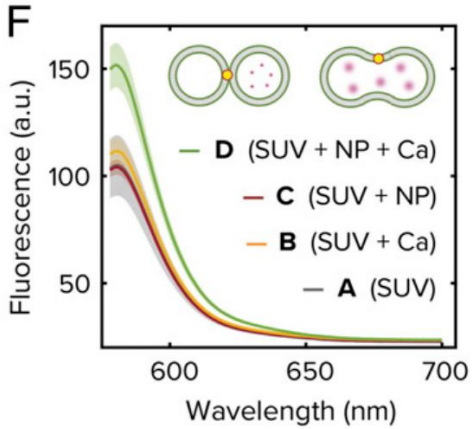
- No particle → no fusion over microseconds.
- Particle → stalk in ~1 µs, then **arrested**.
- Transition state: extraction of one lipid.
- Ca^{2+} condenses the outer leaflet by ~9 %; the resulting interleaflet tension opens the pore.

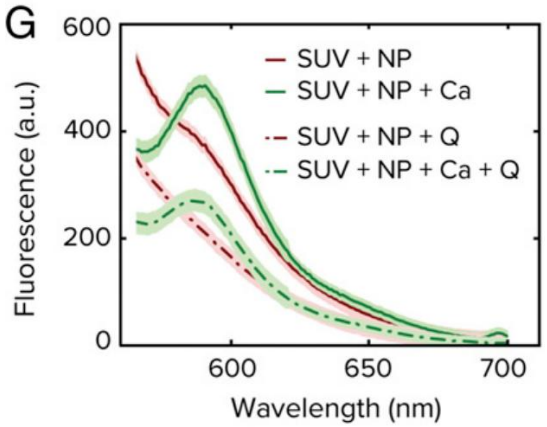
Tahir et al., PNAS 117, 18470 (2020) — figure from the paper

And it happens in the flask





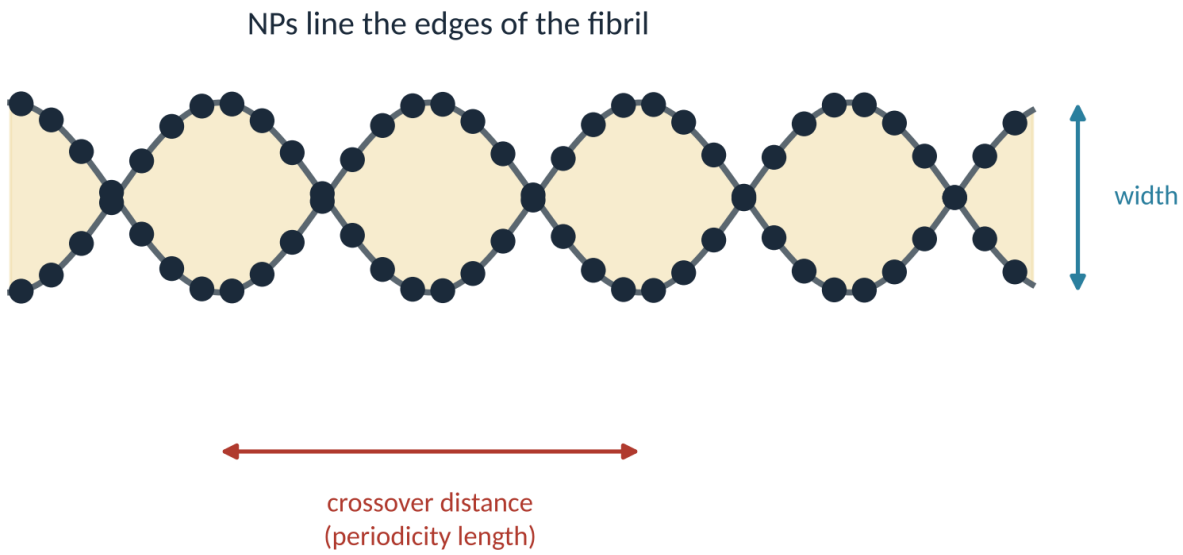




- **A** vesicles · **B** +Ca^{2+} · **C** +NP · **D** +NP then Ca^{2+}. Only D grows.

Tahir et al., PNAS 117, 18470 (2020) — figures from the paper

Amyloids: the same protein, many fibrils



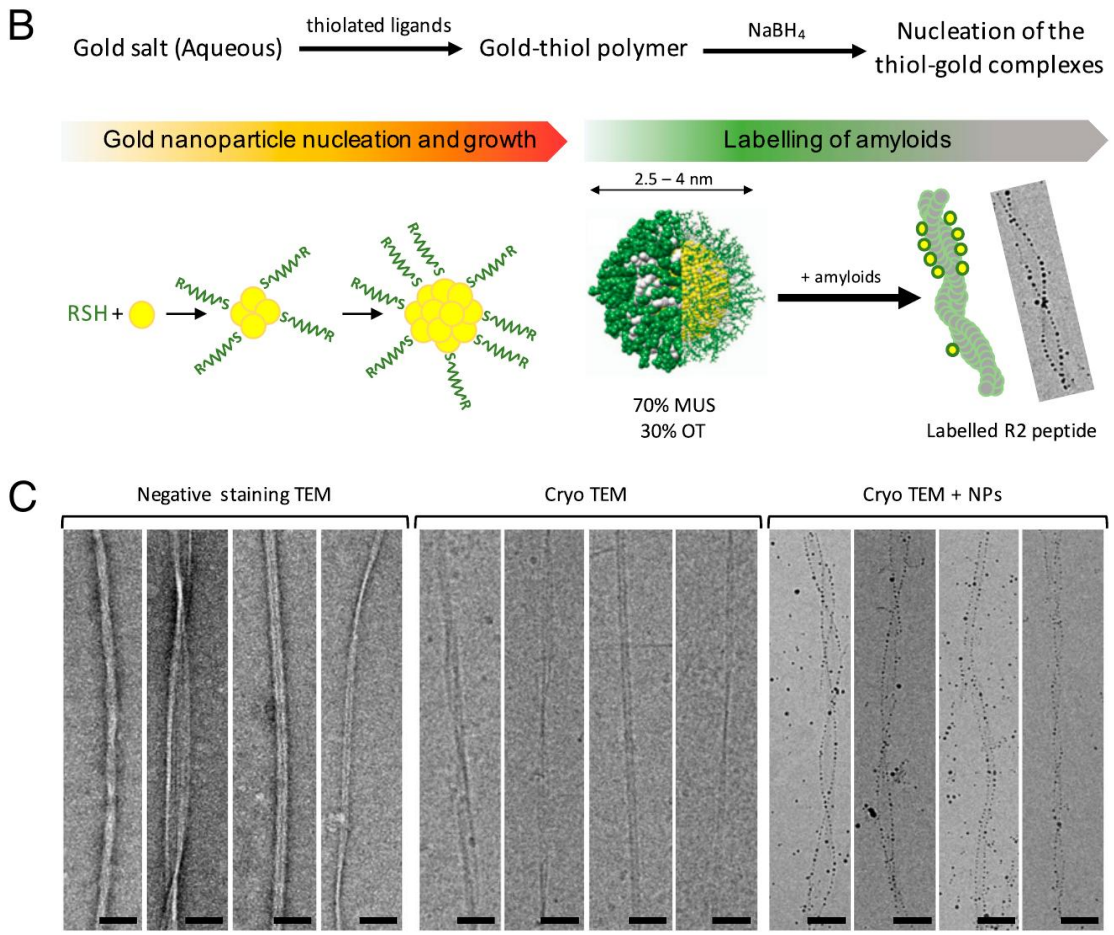
two-fold
twisted ribbon

contrast in cryo-EM
without stain or
antibody

The idea: add something small, electron-dense and selective for the fibril surface. Gold gives contrast with no stain and no antibody — and at 3 nm the particle is small enough not to hide the morphology it is reporting.

Cendrowska, Jacob Silva et al., PNAS 117, 6866 (2020)

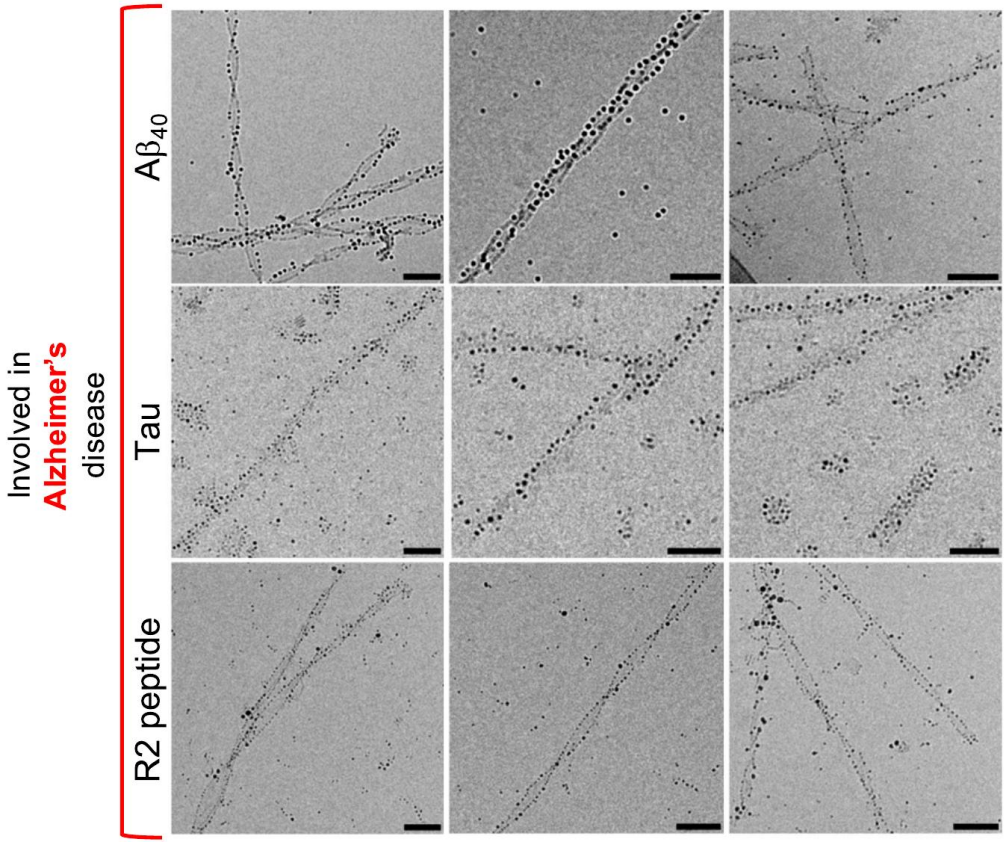
Nanoparticles line the edges of the fibril

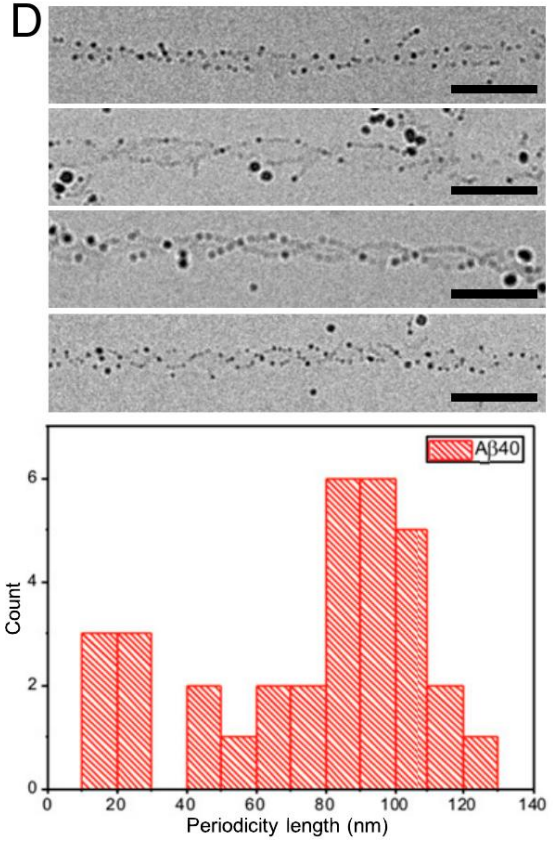


- Only the **mixed** MUS:OT shells label well — MUS, MUP, TMA and zwitterionic shells do not.
- Higher OT fraction binds better but costs solubility.
- Simulations attribute binding to **hydrophobic contacts** with exposed residues.
- The twist becomes visible without stain, without antibody and without image processing.

Cendrowska, Jacob Silva et al., PNAS 117, 6866 (2020) — figures from the paper

It works for every amyloid we tried

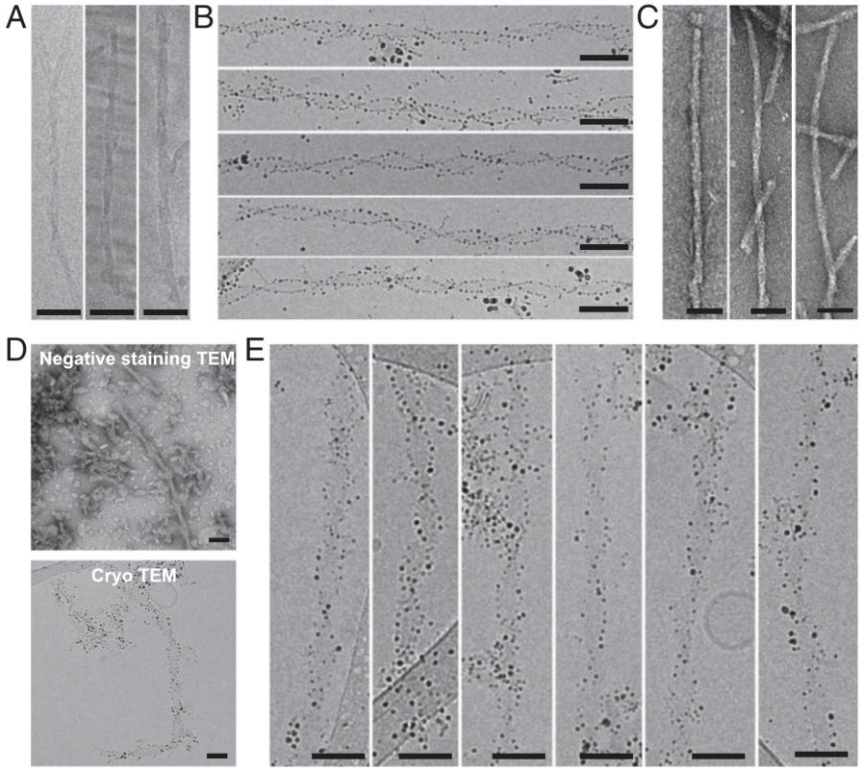


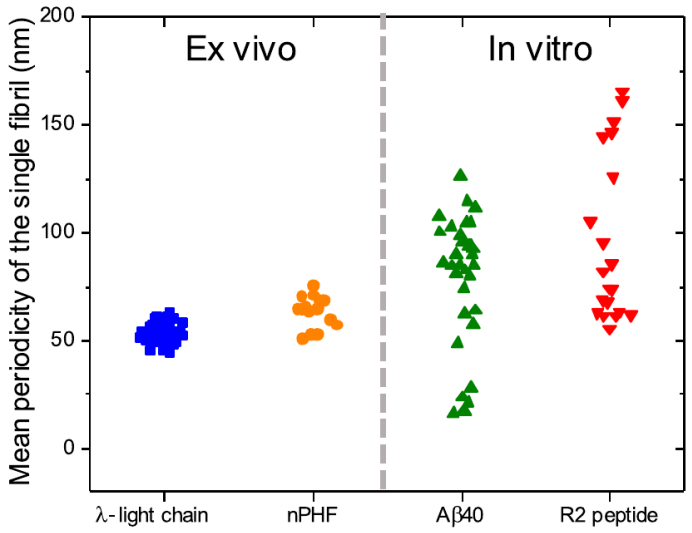


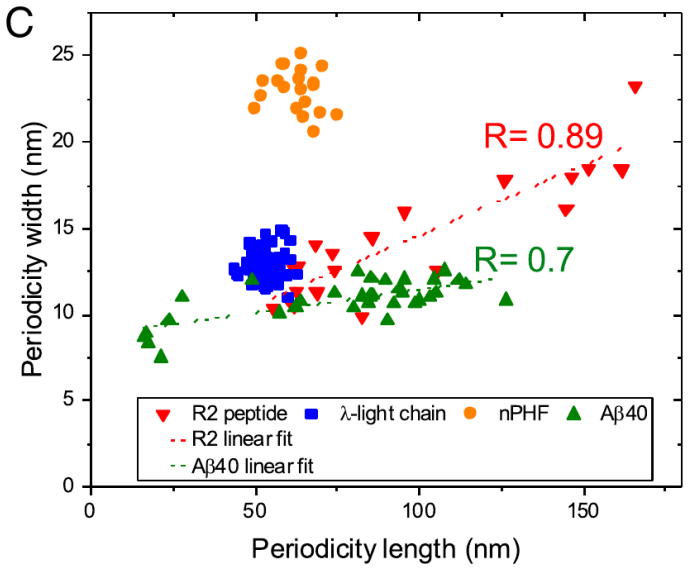
- Aβ40 in one sample: both two-fold and three-fold symmetric fibrils.
- Quiescent growth → long, twisted. Agitated → short, straight ribbons.
- Thin R2 fibrils (<10 nm) stay **undecorated** — a different surface.

Cendrowska, Jacob Silva et al., PNAS 117, 6866 (2020) — figures from the paper

Fibrils from patients are remarkably uniform



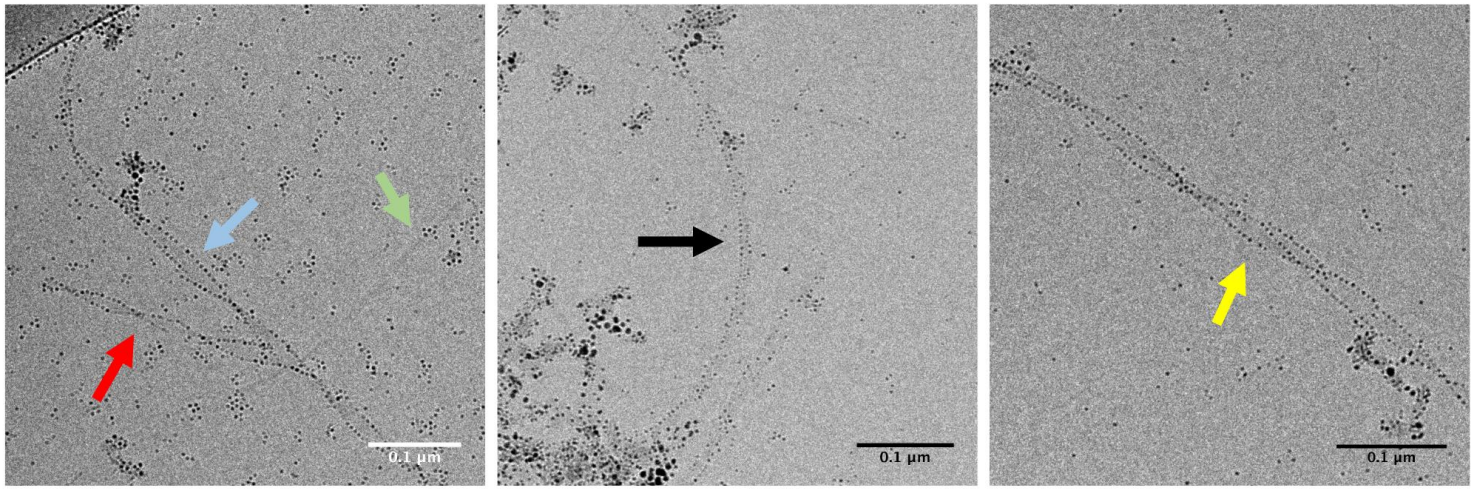




In vitro fibrils fall on a line of width against periodicity — more protofilaments, longer pitch. The tissue-derived fibrils cluster at one point instead: the physiological milieu selects a single polymorph. That supports the strain hypothesis, and it is a caution about what we learn from fibrils grown in a tube.

Cendrowska, Jacob Silva et al., PNAS 117, 6866 (2020) — figures from the paper

Reading polymorphism directly

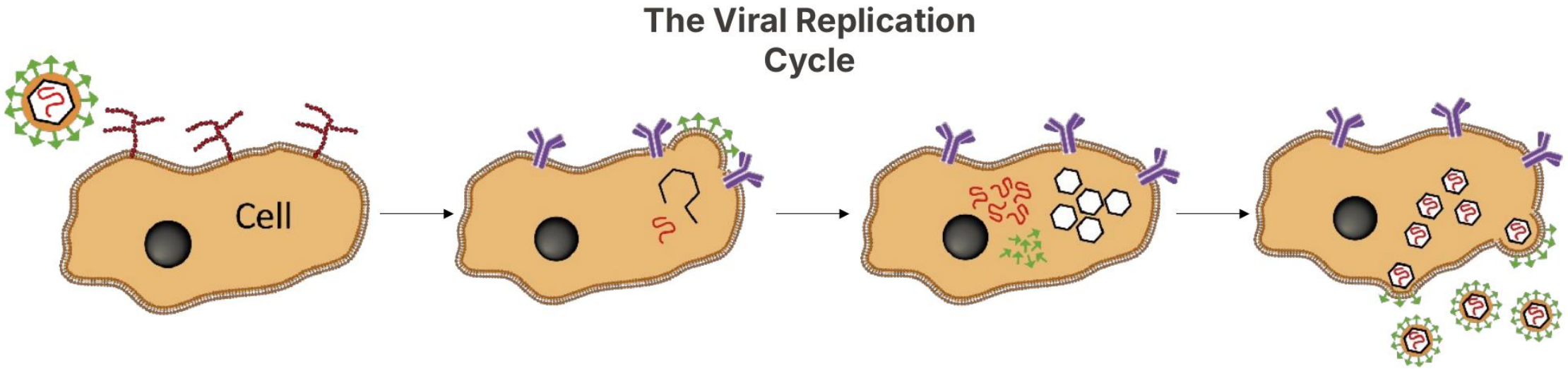


The same sample (allMUS AuFe), different structures:

- Big twists
- Small twists
- Straight
- Not decorated
- Three fold

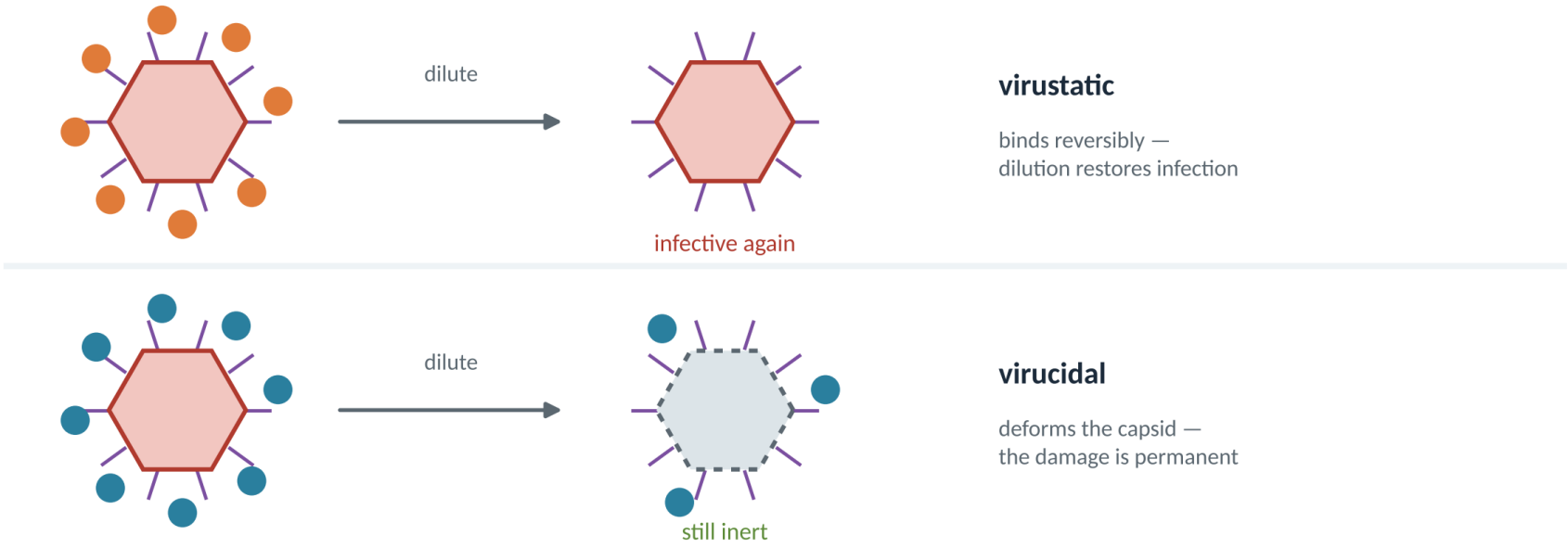
Cendrowska, Jacob Silva, …, Stellacci & Lashuel, PNAS 117, 6866 (2020)

Viruses: why we want a broad-spectrum drug



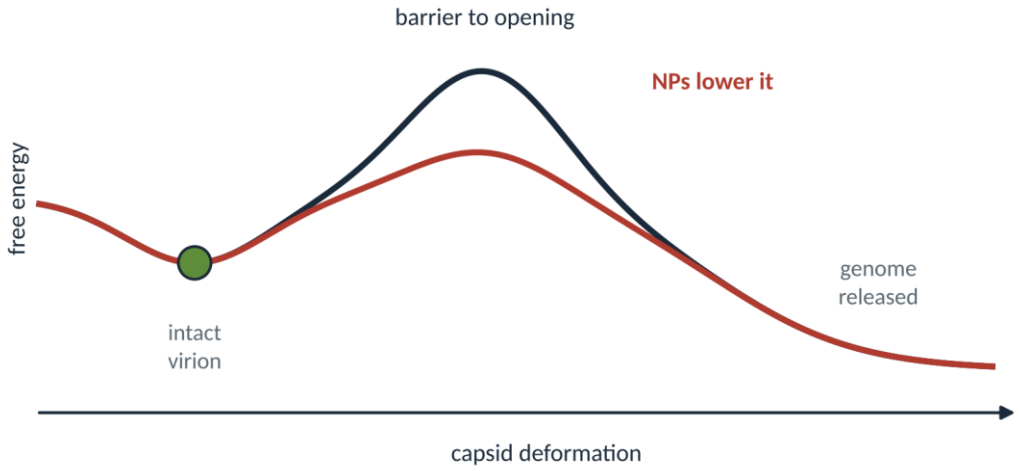
- Attachment is the first and most shared step of infection.
- Many families bind heparan sulfate proteoglycans (HSPG) or sialic acid.
- Target the virus, not the host cell, and one drug can cover many viruses.
- The hard part is making the effect **last**.

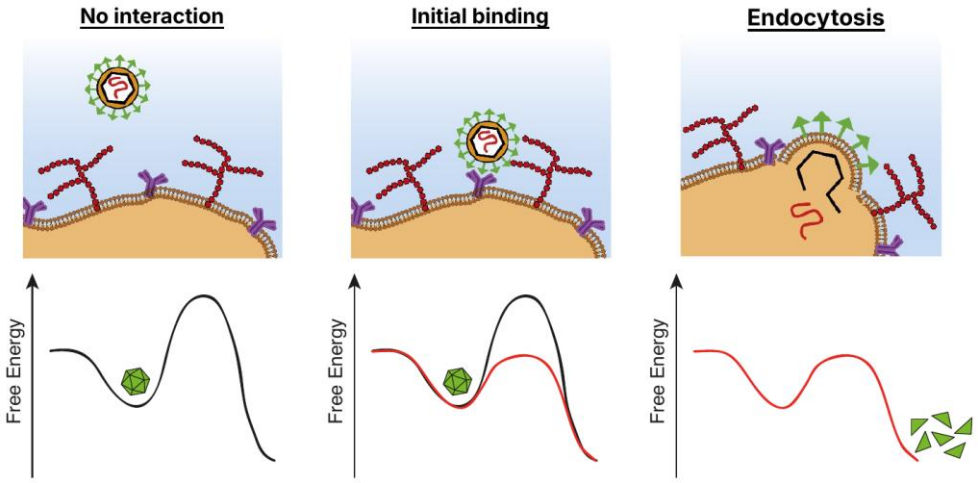
Virustatic is not good enough



Heparin, dextran sulfate, cellulose sulfate, and our own MES particles are all virustatic: strong inhibition in the assay, full recovery on dilution. A virucidal agent must do irreversible damage, which means delivering mechanical work, not just binding energy.

The thermodynamic idea





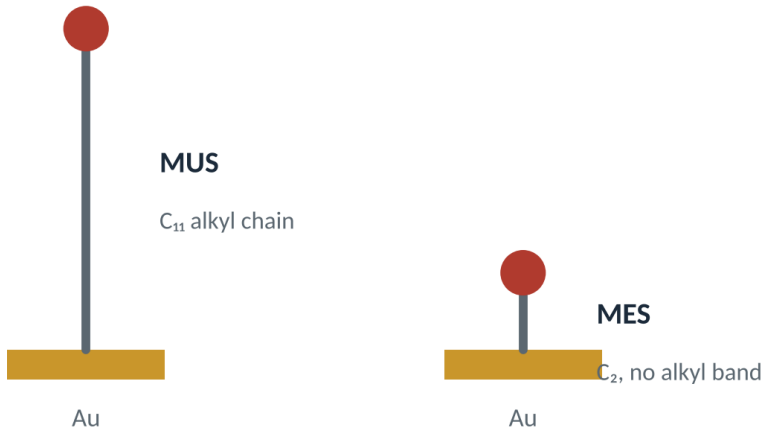
$$\tau \approx \tau_0 \, e^{\Delta E / k_B T}$$

lifetime is exponential in the barrier

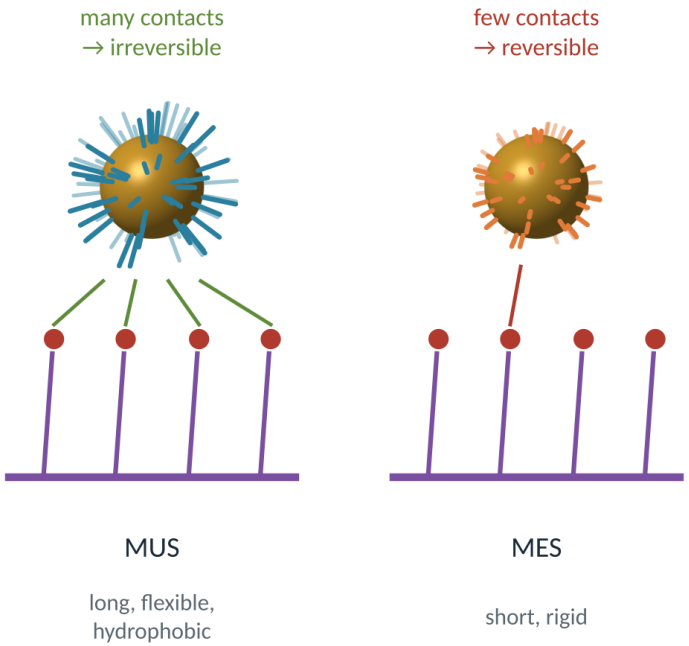
Pelliccia et al., Nature Commun. 7, 13520 (2016) · fluctuating-shell picture after Fejer et al., PNAS 109, 19551 (2012)

The design: it is the linker

same head group, different linker



binding to the attachment ligand



- Same head group, same charge density.
- MUS: multivalent, long-lived contact.
- MES: monovalent, reversible — a conventional polyanion mimic.
- The hydrophobic linker is the design variable.

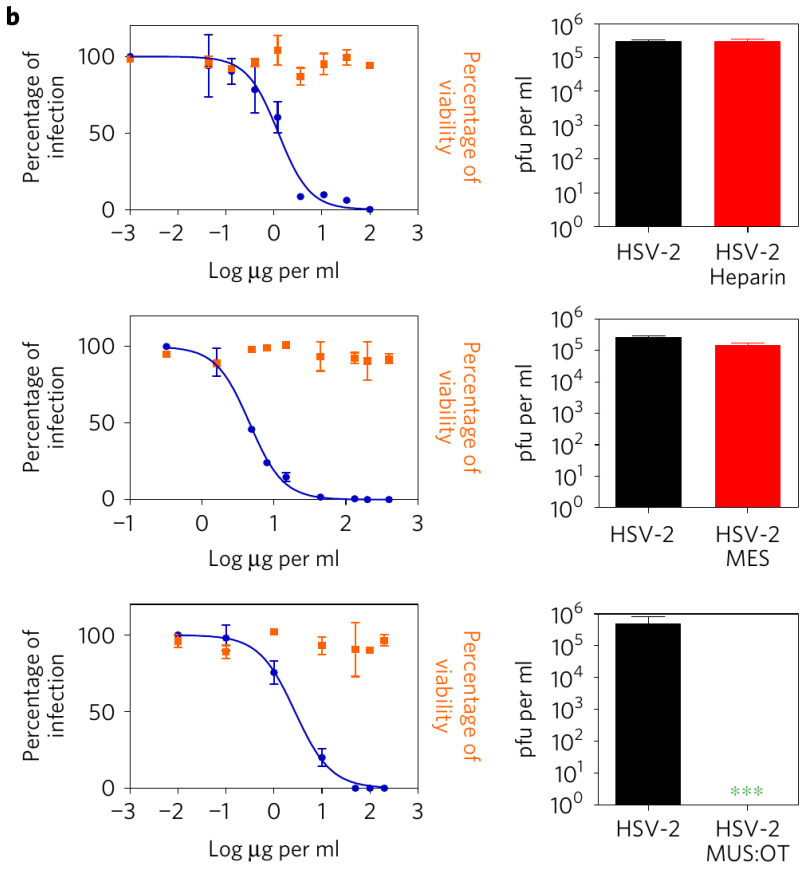
Cagno et al., Nature Materials 17, 195 (2018)

Broad-spectrum, nanomolar, non-toxic

Virus	MUS:OT EC_{50}	MUS EC_{50}
HSV-1	10.9 (36.3 nM)	31.3 (104 nM)
HSV-2	1.61 (5.3 nM)	4.10 (13.7 nM)
HPV-16	4.07 (13.6 nM)	2.2 (7.33 nM)
RSV	9.17 (30.6 nM)	41.1 (139 nM)
Lenti (VSV-G)	10.35 (34.5 nM)	24.6 (81.9 nM)

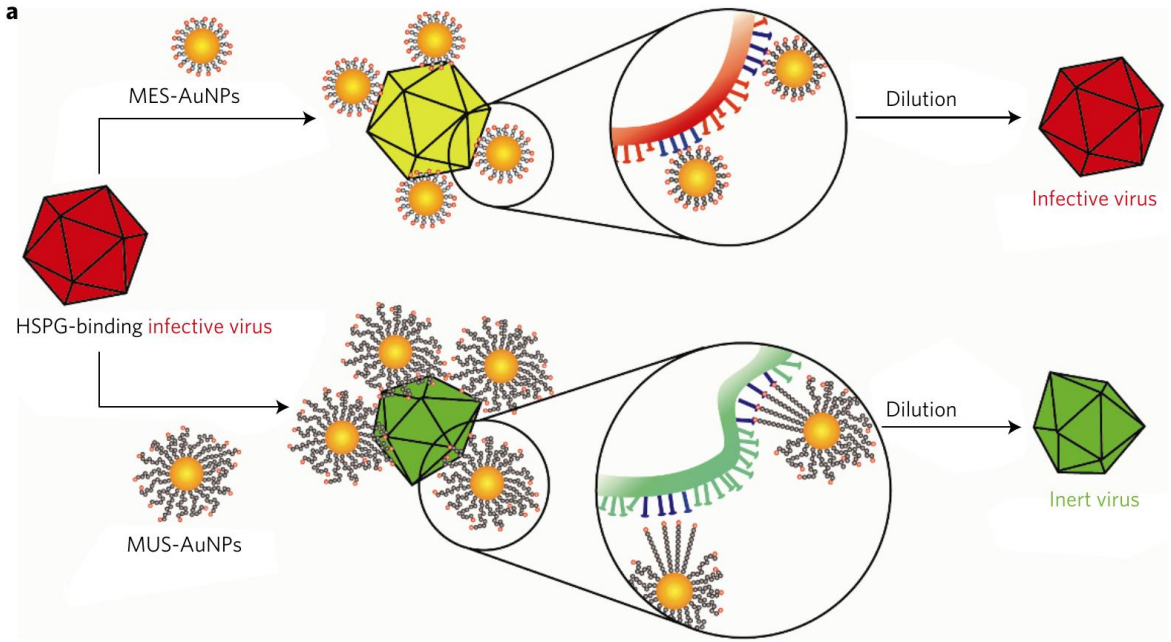
EC_{50} in μg ml^{-1} · CC_{50} > 300 μg ml^{-1} for all · dengue also inhibited

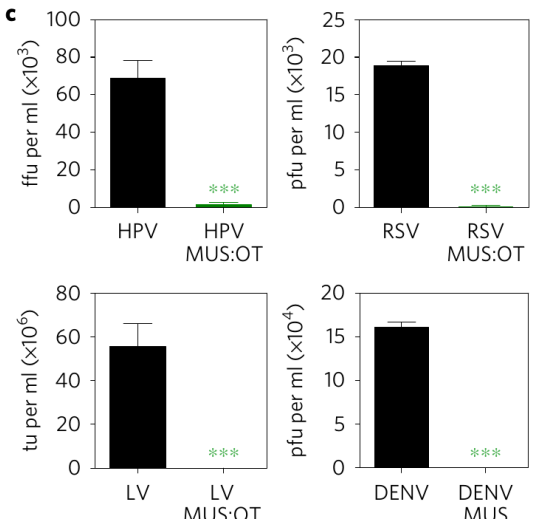
- Inactive controls: free MUS ligand, pre-formed MUS polymer, 15 nm citrate gold.
- Also active: MUS-coated **iron oxide** — the effect is not about gold.

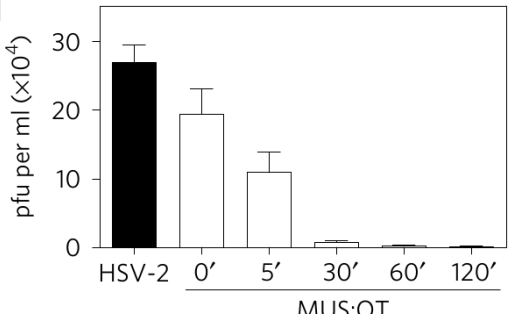


Cagno et al., Nature Materials 17, 195 (2018) — figure from the paper

Irreversible: the virucidal assay



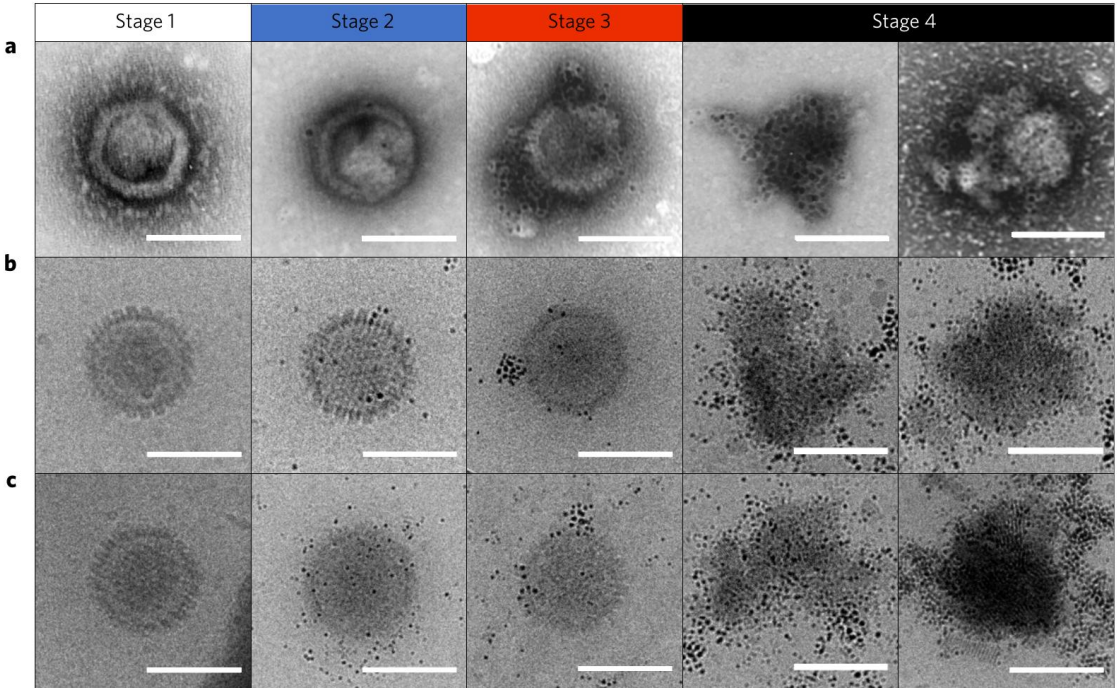


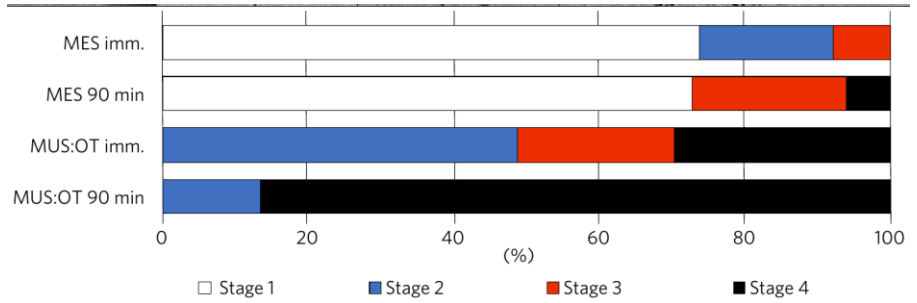


Green asterisks: no detectable plaques after dilution. The time course on the right is the signature of a mechanism that needs the particles to accumulate and act, not merely to bind.

Cagno et al., Nature Materials 17, 195 (2018) — figures from the paper

What the virus actually looks like

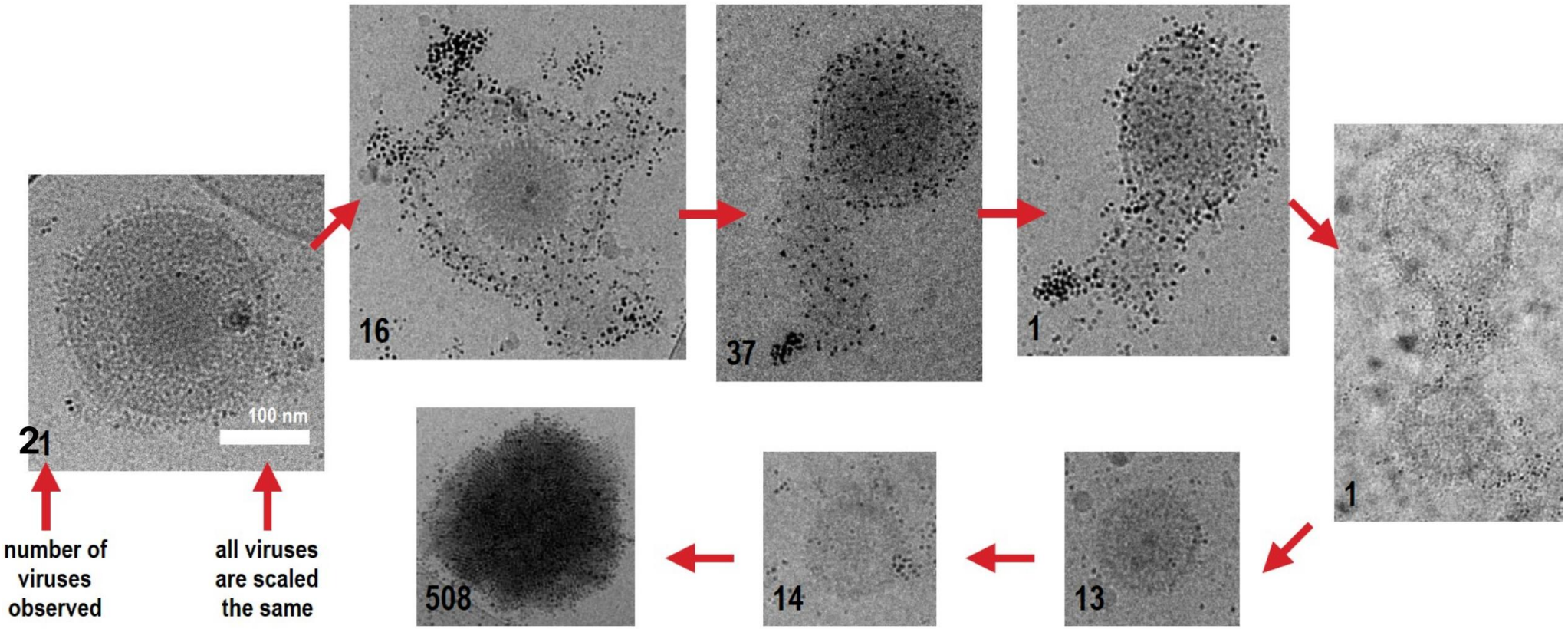




- MES, 90 min: 13 % stage 2, **5 %** stage 4.
- MUS:OT, 90 min: **87 %** deformed and fully coated.
- The progression with time matches the virucidal assay.

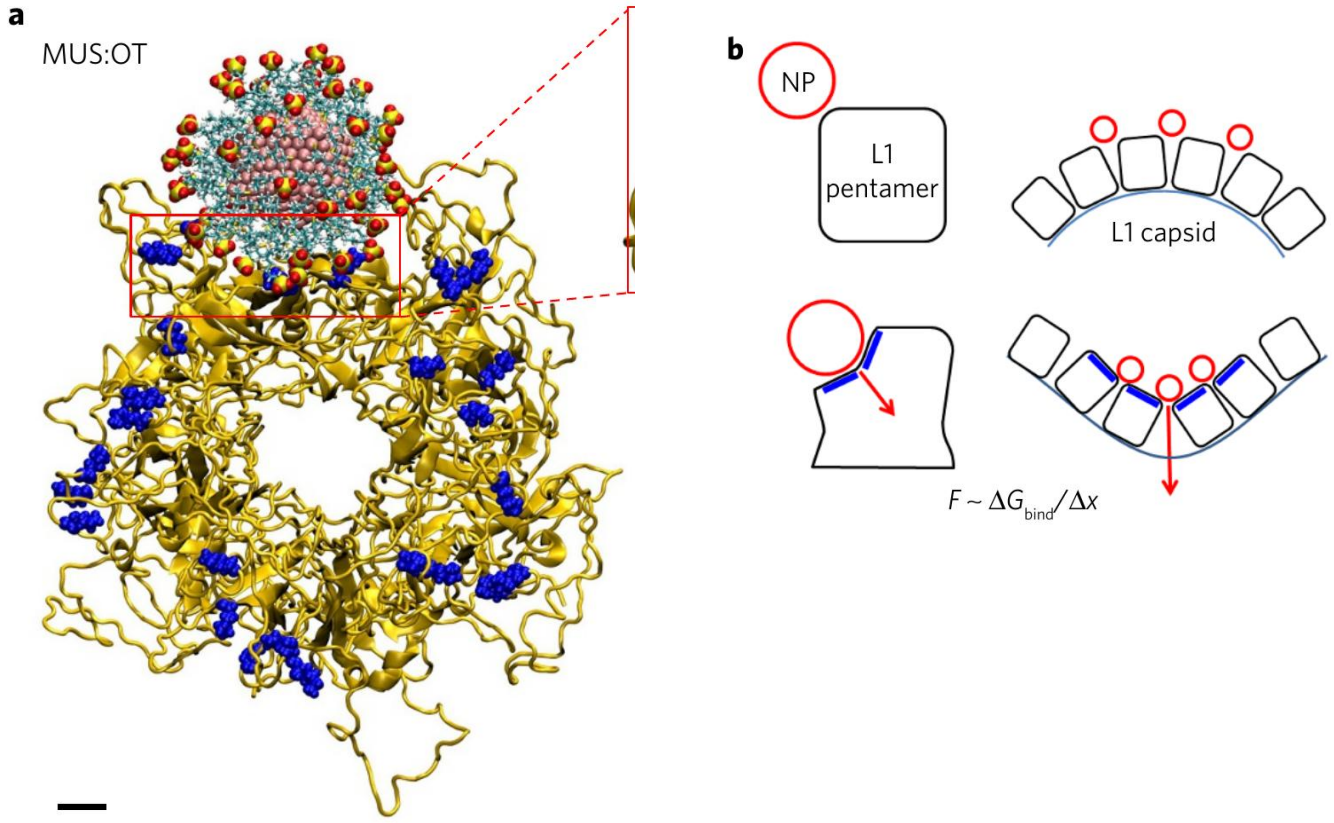
Cagno et al., Nature Materials 17, 195 (2018) — figures from the paper

The sequence, virus by virus



M. Müller, doctoral thesis, EPFL — cryo-TEM of HSV with MUS:OT nanoparticles

How hard do the particles pull?



$$\Delta G_{\text{bind}} \approx \underbrace{n\,\Delta G_1}_{\sim -34\ \text{kcal mol}^{-1}} + \underbrace{\Delta G_{\text{non-polar}}}_{\sim -21\ \text{kcal mol}^{-1}}$$

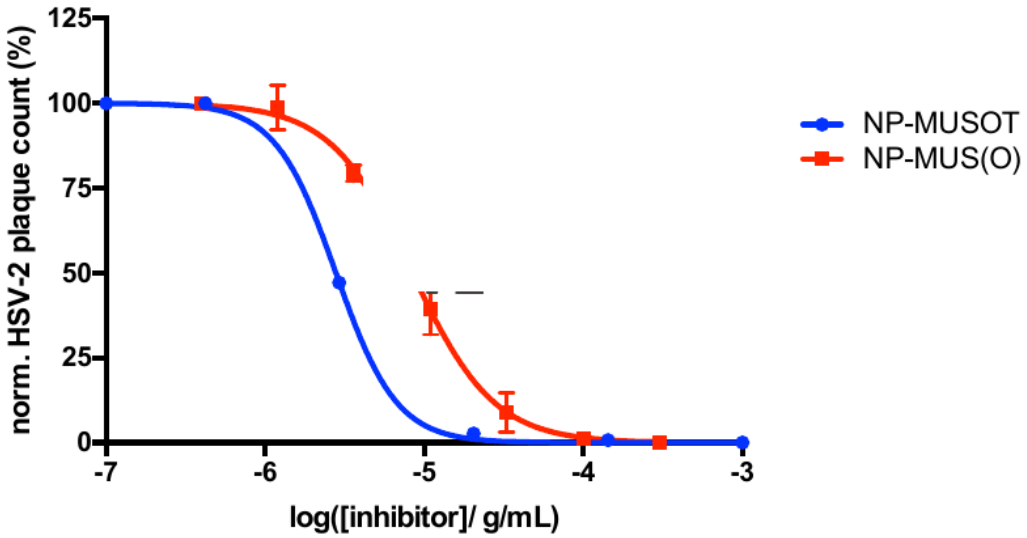
$$F \sim -\frac{\Delta G_{\text{bind}}}{\Delta x}$$

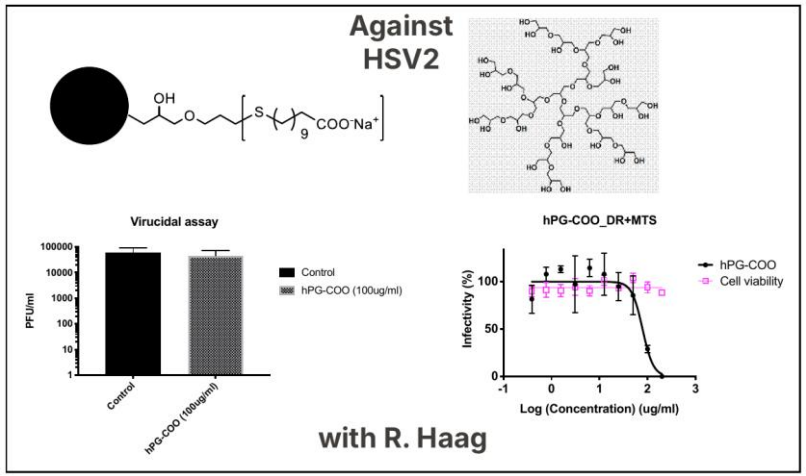
$$F \sim \frac{28\ \text{kcal mol}^{-1}}{10.4\ \text{Å}} \approx 189\ \text{pN}$$

- Comparable to the forces that unfold a protein domain — and it is delivered by binding alone.

Cagno et al., Nature Materials 17, 195 (2018) — figure from the paper

Beyond gold: the linker is what matters

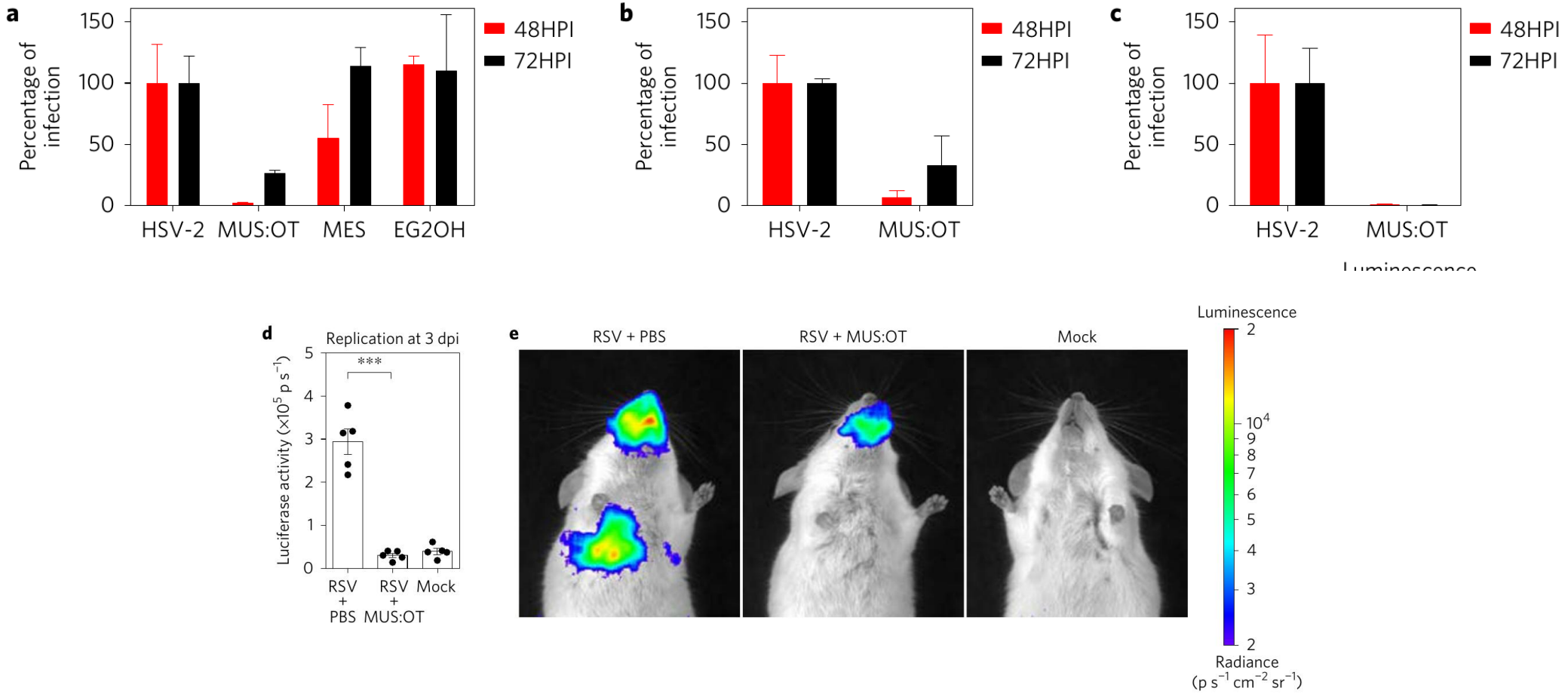




- Same charge, same length, hydrophilic linker → **not** virucidal.
- No gold needed: a dendritic polymer with hydrophobic linkers works.
- Also virucidal: MUS on **iron oxide**.

Gasbarri et al., manuscript in preparation · polyglycerol work with R. Haag (FU Berlin)

Does it work in tissue, and in an animal?



Cagno et al., Nature Materials 17, 195 (2018) — figures from the paper

Take-home

1. **the ligand shell is the particle**

   size, charge and hydrophobic pattern set the biology

2. **hydrophobicity is a design variable**

   chain length and ratio tune insertion and binding

3. **multivalency turns binding into damage**

   many weak contacts → ~190 pN → irreversible

Open questions: can we separate amyloid polymorphs rather than only count them? How far can the virucidal idea be pushed towards a biodegradable, manufacturable drug? And how general is hydrophobic matching across membranes of different composition?

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