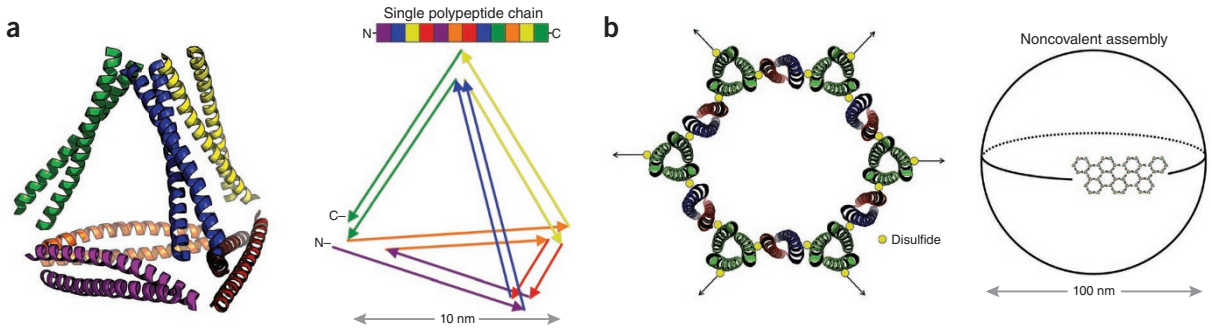

Figure 1 Protein nanocages engineered from coiled coils. (**a**) Gradisar *et al.*[1] linked 12 coiled-coil segments in a single polypeptide chain to build a regular tetrahedron (TET12). (**b**) Fletcher *et al.*[2] linked a coiled-coil homotrimer and a coiled-coil heterodimer with disulfides to build a hexagonal lattice, which spontaneously curved into closed spherical objects (SAGE particle).

regarding the 'designability' of protein cages. Namely, although protein cages have striking and seemingly sophisticated structures, they might actually represent a friendly design goal. Spheres have the minimal surface area–to-volume ratio, which may result in a natural propensity for enclosed sphere-like structures to represent the lowest-energy state for molecular assemblies.

The 100-nm SAGE particle and 10-nm TET12 particle were both built from coiled coils, but they are very different assemblies that will likely be suited for different applications. One application for the large, porous and hollow SAGE particle would be encapsulation of an enzyme cascade for metabolic engineering or enhanced biocatalysis. The inward-facing termini of the three different coiled coils could be fused to three different enzymatic domains, and the 5-nm pores of the SAGE particle would allow entry and exit of metabolic substrates and products. As an alternative to the challenge of repurposing natural bacterial microcompartments[10], the SAGE particle is similar in size and could provide the first example of an engineered spherical protein cage used for enzyme encapsulation. As a second example, rather than decorating the interior of the SAGE particle with enzymes, the exterior could be decorated with antigens to improve vaccination. Monomeric peptides and proteins may not provide robust immunoprotection, so a large protein cage could carry the antigen sequences to slow renal clearance and boost the local antigen concentration for improved multivalent recognition by immune cells[11,12].

The small size of the TET12 tetrahedron will not permit encapsulation of enzymes, but it could carry small-molecule drugs or other small cargo. In contrast to other small, engineered cages (**Table 1**), the TET12 cage is a single, folded polypeptide and does not assemble from repeating symmetric components. This feature would facilitate encapsulation of a single payload, rather than a symmetrically repeated payload. If the interior could be loaded with a cancer drug, and if the exterior could be tagged with cancer cell–recognition domains, the TET12 tetrahedron could serve as the scaffold for a targeted anticancer drug delivery system. In contrast to the stochastically assembled SAGE particle, the deterministic structure and monodispersity of the TET12 tetrahedron may be better suited for drug development pipelines owing to reduced sample heterogeneity.

Gradisar *et al.*[1] and Fletcher *et al.*[2] report relatively simple, rational approaches to construct artificial protein cages 10 nm and 100 nm in diameter. Furthermore, the dissimilar structures that resulted from similar coiled-coil building blocks demonstrate the potential diversity that can be achieved by rational assembly of a limited subset of protein parts. These early efforts in nanocage engineering have not yet reached the sophistication of the cage-like protein assemblies found in nature, such as proteasomes (15 nm), folding chaperones (15 nm), ferritin complexes (12 nm), carboxysomes (80–150 nm) and virus capsids (20–120 nm). However, these artificial nanocages show that modular design strategies can be used for complicated design goals, with the potential to address current and future needs in biotechnology and medicine.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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