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A silk purse from a sow's ear — bioinspired materials based on α-helical coiled coils

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This past few years have heralded remarkable times for intermediate filaments with new revelations of their structural properties that has included the first crystallographic-based model of vimentin to build on the experimental data of intra-filament interactions determined by chemical cross-linking. Now with these and other advances on their assembly, their biomechanical and their cell biological properties outlined in this review, the exploitation of the biomechanical and structural properties of intermediate filaments, their nanocomposites and biomimetic derivatives in the biomedical and private sectors has started.

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Hard α-keratin — where it all began

It was through the study of α-keratin that the first doyens of Structural Biology coined terms such as 'α-helix' [1] and then 'coiled coil' [2,3] to describe these fundamental features of protein structure. It has taken eight decades to solve most of the crystallographic detail of those first samples of hair and wool [4] and to appreciate the detail of the α-keratin fibre and the precision of its oxidized state that underpins the resilience inherent to wool and hair fibres [5]. The importance of the pseudo-hexagonal packing of the α-keratin fibres and how this contributes to the scaling (nanometre to millimetre) and composite potential of keratocyte α-keratin materials is now realized [6••,7••]. The molecular organization of wool makes it a wonderful textile as it exemplifies phase transition (α-helix to β-sheet [8]) induced elasticity of its component keratin fibres when they are axially stretched [9]. This was first observed and documented by Astbury [4] and subsequently studied in more detail to reveal the importance of coiled-coil sliding and disulphide bonding to the biomechanical properties of hair [10,11]. The ability of hair to undergo a reversible phase transition [12,13] is an important feature to understand and then exploit in nanocomposite biomimetics (Figure 1). The nanocomposite alloy of nickel titanium is called a 'memory metal' because it can return to their original shape once the deforming forces are removed. Both hard α-keratins [9] and cytoplasmic intermediate filaments [14] display such 'memory-like' properties too.

In hair, the biomechanical properties of the component intermediate filaments have been tuned to their local environment. So whilst the α-helix to β-sheet phase transition of individual helices and coiled-coil sliding are key features for hard α-keratins [10], the amorphous matrix into which they are embedded [15••] and the cell matrix complex [16] play their part. The matrix shields the embedded α-keratin fibres from water, which for wool and hair is critical as their α-keratin stretches easier when it is wet than when it is dry [17].

At the other extreme, is hagfish slime. This provides a protective slime coat that is secreted by these animals when threatened or attacked. Intermediate filament-based fibres are the main structural component. The secrets of the assembly, storage and subsequent deployment of the hagfish slime filaments are now under investigation [18••]. Yet more attractive features to incorporate into future intermediate filament-based fibres and nanocomposite materials are being revealed.

It is the inherent biomechanical properties of such α-helical coiled coil fibres and the atomic detail of their α-helix, coiled coil and higher order (e.g. pseudo-hexagonal in hair) packing and organization that provide blueprints for the next generation of bioengineered fibre materials (Figure 1). Whilst the structural determination of some (e.g. keratin) might remain incomplete [19], we can still appreciate the scaling (nm to mm) potential of the fibre–matrix interaction [6••] to generate high tensile strength fibres. Indeed, it is the irregular fibre packing into the macrofibrils found in hard α-keratin materials that has so far resisted the conventional crystallographic interrogation to reveal the detail of this scaling potential and its diversity within keratin-based materials. This tertiary

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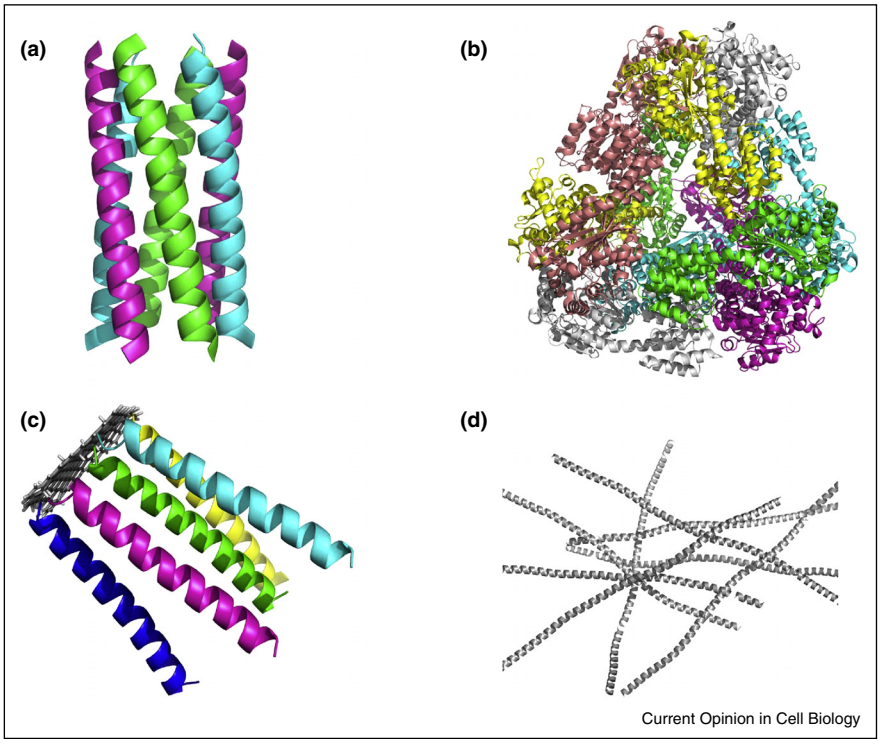
Figure 1



Current and future directions of peptide coils design. **(a)** Crystal structure of the *de novo* designed parallel coiled-coil hexamer (pdb code 3R3K [64]); **(b)** crystal structure of a *de novo* designed 16 nm protein cage (pdb code 4D9J [90]); **(c)** model of designed peptide coils covalently attached to graphene sheet(s) as an example of a potential nanocomposite; **(d)** model of macroscopic structures built from peptide chains.

organization of intermediate filaments is one of the mesoscopic features that we understand the least, but which will be critical to their successful exploitation in future bioengineered nanocomposite materials (Figure 1).

The science of storing coiled coils and weaving threads with the tensile strength of steel

Weight for weight, spider silk is one of the strongest fibres on the planet — stronger even than steel. If intermediate filaments and their biomimetics are to become commercial alternatives, they will need to be similarly strong. Some coiled-coil protein fibres can accommodate very high elastic strains (e.g. hagfish slime fibres [20]) and when confronted with high deforming forces, transform from α-helical rich structures into rigid β-sheets that are then locked to exhibit failure stresses approaching that of natural silk [20]. The recent analysis of silk proteins from bees, ants and hornets has found them to be coiled-coil based. They illustrate that we have still much to learn about coiled coil and their potential as materials of the future [21]. These silks are woven on demand by the insects forming either fibres or sheets [22]. Making threads from recombinant intermediate filament proteins is more challenging [23,24••]. Generating recombinant silks [25] is already a multibillion pound, global industry because of the wide range of desirable properties associated with such fibres and a shortage of spiders with a strong work ethic!

A bioelastomeric fibre made recombinantly and to specific mechanical, dye uptake, hydration compatible properties are highly desirable features for the textile industry. If such properties could then also be coupled to the storage and weaving of these materials as observed in nature then this would revolutionize yarn production and storage. Imagine being able to form *de novo* fibres on demand from a pool of 40 μm tactoids or 1 μm birefringent rods as seen for the silks of different *Apoidea* and *Vespoidea* species (see [22] and references therein). Imagine storing pre-woven, untangled skeins as in the hagfish slime thread gland [18••]. The storage, spinning and curing of the coiled-coil fibres achieved in the natural world is a reality far beyond the structural biologist's panacea for dealing with intermediate filament coiled coils — urea and then more urea and guanidinium hydrochloride! To understand the extent of the universe for natural intermediate filaments, we need

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to understand how fibres are 'cured' during their assembly, the mechanisms of their strain-induced conformational changes at the molecular scale and the origin of the internal energy dissipation. Armed with such properties, the future textile, medical and defense industries will be unrecognizable!

Human hair — a shape memory material with ancient origins

For each of us, hair is a daily reminder of the importance of α-keratin-based fibres and it is also a signature for future archaeologists [26•]. The interconversion of straight and curly hair is a cosmetic decision for which the mechanistic and cell biological details are now becoming clearer. The matrix proteins that embed the α-keratin fibres are critical for such cosmetic changes [27] with the inter-matrix S–S oxidation of these proteins and not the keratins determining the degree of curl. Curly hair is independent of ethnicity and due to the asymmetric differentiation of the precortex in the human hair shaft as a result of differences in cell proliferation, but the extent of the curliness seems to be due to the α-keratin content [28]. We can perhaps add 'memory material' as a feature to the dynamic nanocomposite property of human hair.

There are 24 different keratins expressed in those cells making the human beard [29••] and, considering the functional unit of both epidermal and hard α-keratins are tetramers [30,31], we have yet to determine whether fidelity or promiscuity [32] in α-keratin pairing are mutual exclusive or tolerated within the hair fibres [29••]. Hair α-keratins themselves have ancient origins as revealed by analysis of the Neanderthal genome and its relationship to present day humans [33•,34•]. Four hair α-keratin genes with an unusually high frequency of introgression were found in East Asians (KRT83, KRT84, KRT85, KRT86) whilst those with high frequency in Europeans (KRT5, KRT71, KRT74) were three completely different genes of epithelial keratin (KRT5) or without annotated function [34•]. From these studies on humanoid evolution, it is the thermoregulatory and protective properties of hair that is considered to be an important property. It is also clear the resilience of hair and its proteins are critical, a point illustrated by the fact that storage for 30 000 years in the Siberian permafrost did nothing to dent the *in vitro* assembly potential of mammoth hair α-keratins [35]. This resilience affords hard α-keratins a role as a forensic/drug abuse/diet sensor (e.g. [36•,37]). Tracking modern carbon in tusks [38] and verifying shahtoosh products [39] absolutely depends upon the resilience of hair.

Intermediate filament coiled coils and their current applications in biomedicine

Our discussion has so far focused our attention onto the materials industry, but the application of the underlying knowledge of intermediate filament, coiled coil assembly has already been exploited in biomedicine as a self-assembly nanoparticle delivery platform. These applications would not have been realized without the following intellectual framework. Crystallographic data for vimentin, keratin and lamin proteins [19,40••,41], combined with chemical cross-linking [42,43] and biophysical characterization of the assembly units [31,44], the importance of trigger sequences [45] and the design of stable coiled coil peptides [46] were the knowledge base needed to design trimeric and pentameric coiled coil nanoparticles [47]. Such particles now function as a vaccine scaffold [48]. The self-assembly polypeptide nanoparticle (SAPN) strategy has other guises (e.g. synthetic virus-like particle; SVLP) and derivations such as lipoprotein virus-like particles [49] and coiled coil based vesicles with membrane fusion properties [50••]. Using such technologies, vaccines to malaria [51,52], toxoplasma [53] and HIV [54] are being developed, but the technology is also a useful scientific tool to target specific epitopes in any protein of interest e.g. Schroeder et al. [55]. It is also clear though that such virus-like structures can be used to target specific cells [56••] and also deliver cargo, as evidenced by the proof principle experiment of encapsulating gold particles within these structures [57] to expand their biomedical application [58].

It is the potential of the coiled coil and its ordered oligomerisation that is inspirational to bioengineers as evidenced by the analysis of the GCN4 coiled coil [59•,60]. There are several aspects to the oligomerization that might be controlled including the binding affinity, oligomerization state (dimer, trimer, tetramer, etc.), the direction of association of sequences (parallel versus anti-parallel) and the partnering specificity. Control of binding affinity can be achieved via sequence length and has been explicitly demonstrated in dimeric coiled coils [61]. Dimer, trimer or tetramer coiled coils can be designed [62••], but their ability to sort within a mixture is still missing. Design of α-barrels with central channels formed from (parallel) coiled coils extent the potential applications [63] on the back of the discovery of the CC-hex state for a synthetic coiled coil [64]. Anti-parallel coiled coils have also been investigated [65], culminating in a tetrahedron built from a single polypeptide chain because the designed peptide specified both parallel and anti-parallel coiled coils [66]. Finally the analysis of partner specificity of parallel dimeric coiled coils [67,68] resulted in algorithms to predict the interaction strength of *de novo* sequences [69,70]. Now sequences that assemble in defined partnerships [71] to produce specified small nanostructures are available [72].

Bioinspired filaments based on coiled coils — deciphering the scaling features of intermediate filaments for application in the materials of the future

The complex mechanical properties of intermediate filaments [14], including their ability to form filaments of

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defined width, their ability to exhibit visco-elasticity and strain hardening and their ability to respond to deformation in a dynamic and environmentally sensitive fashion are a challenge to replicate in bioengineered mimetics. Knowledge of the coiled coil building block, the heptad repeat with its hydrophobic seam and knobs-into-holes packing [3] and the surface charge repeat that drives oligomerization [59•,60] have allowed the first attempts at the manufacture of bioinspired filaments. These attempts included the Self-Assembly Filaments (SAFs) that utilize the keratin heterodimer principle [73], and helped identify the importance of the scaling problem [74]. The synthetic filaments formed were rigid with variable width and length, a far cry from the uniformity of the cytoplasmic intermediate filament. Progress is being made and the recent iteration illustrates that refinement of the original 28mer polypeptide can deliver 80 nm wide 40 μm long fibres [75]. For these engineered filaments and the intermediate filament proteins themselves [40••], it is atomic level structural information of the coiled coil packing within the polymer that is required to understand the self-assembly features. Using coiled coil domains from other structural proteins (coiled-coil domain of cartilage oligomeric matrix protein [76] or by design [77] pH or small molecule induced fibre assemblies are possible and seem capable of forming microfibres [76] therefore demonstrating the nano-scaling to meso-scaling property required for future biomimetics of, for instance, wool or silk.

Conclusions

The current state of the art regarding designed coiled coil filament assembles can be summarized as follows. Successful programming of the behavior of individual building blocks permits controlled self-assembly at the nanometre scale. Width and radius can be controlled by the length of the assembly subunit, but subsequent hierarchical assembly for example [74–76] remains an emergent property that is poorly understood and, as length scales increase, the synthesis of specific microstructures is unpredictable. This matches the information known from natural systems in which the specifics at the nano-scale are often well characterized by the connection to the primary sequence whilst the detail of the metre-scale microstructure is not. The challenge therefore, for structural cell biologists and bioengineers is to understand the principles that afford the width, length and subcellular organisation of intermediate filaments.

It is the length scale spanning nanocomposite nature of intermediate filament-based materials [6••,7••] that is responsible for their remarkable mechanical properties [9]. In living cells too intermediate filaments are key determinants of the cellular mechanical properties for example [78] and their networks proposed to be flaw tolerant [79], but they are also integral to the cellular stress response [80,81]. The dynamic nature of intermediate filaments and the role of post-translational modifications in facilitating their subcellular organization and their different functions underline the importance of their assembly and subunit dynamics to their cellular functions [82]. We must also appreciate their links to membranes and other cellular structures, whether it is the attachment of the nuclear lamina to the inner nuclear membrane for example [83] or the attachment of cytoplasmic filaments to the outer nuclear membrane for example [84] or to the plasma membrane and other membrane compartments within the cell for example [85,86], all are crucial to their biomechanical function and are further examples of their nanocomposite potential. These properties are conserved throughout evolution, with bacteria such as *Streptomyces* also utilizing intermediate filament-like proteins to strengthen hyphael membranes. The bacterial intermediate filament-like protein FlIP forms a fibrous mesh to support vulnerable points on the plasma membrane [87], electron microscope images that fire the imagination and resonate with those iconic pictures of the oocyte nuclear lamina [88]. Whilst there is currently a large gap between the functionality of synthetic and natural fibres, bioengineered nanocomposites [89] that can sense and transduce mechanical and environmental cues to produce transcriptional and translational responses [82] is a technological prize awaiting our full appreciation and application as a result of exploiting fully the meso-scale properties of intermediate filaments and their bioengineered mimics.

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