Functional Supramolecular Polymers[*]

T. Aida[1,2], **E.W. Meijer**[3], and **S.I. Stupp**[4,5,6,7]

[1]Department of Chemistry and Biotechnology, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-8656, Japan [2]RIKEN Advanced Science Institute, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan [3]Institute for Complex Molecular Systems, Eindhoven University of Technology, Post Office Box 513, 5600 MB Eindhoven, Netherlands [4]Department of Materials Science and Engineering, Northwestern University, 2220 Campus Drive, Evanston, Illinois 60208 [5]Department of Chemistry, Northwestern University, 2220 Campus Drive, Evanston, Illinois 60208 [6]Department of Medicine, Northwestern University, Chicago, Illinois 60611 [7]Institute for BioNanotechnology in Medicine, Northwestern University, 303 E. Superior, Chicago, Illinois 60611

Abstract

Supramolecular polymers can be random and entangled coils with the mechanical properties of plastics and elastomers, but with great capacity for processability, recycling, and self-healing due to their reversible monomer-to-polymer transitions. At the other extreme, supramolecular polymers can be formed by self-assembly among designed subunits to yield shape-persistent and highly ordered filaments. The use of strong and directional interactions among molecular subunits can achieve not only rich dynamic behavior but also high degrees of internal order that are not known in ordinary polymers. They can resemble, for example, the ordered and dynamic one-dimensional supramolecular assemblies of the cell cytoskeleton, and possess useful biological and electronic functions.

Synthetic polymers used extensively in technology and everyday life are macromolecules in which small structural units are connected by covalent bonds. In a supramolecular polymer, building blocks of any size could be connected through non-covalent linkages such as hydrogen bonds or electrostatic interactions to create a coiled chain or ordered filament. Living systems make use of this concept extensively and one example is the cell cytoskeleton in which long ordered filaments of protein monomers form and depolymerize dynamically for vital cell functions. A synthetic platform of functional supramolecular polymers could be an extraordinary source of innovation with impact in areas ranging from energy and medicine to environmental sustainability.

The development of supramolecular chemistry, defined by Lehn as the chemistry beyond the molecule, has offered a framework to design highly interactive molecules (1). This framework has led to a plethora of exciting structures ranging from simple guest-host systems based on molecular recognition to complex self-assembled supramolecular objects (2), crystalline networks (3), and monolayers (4). In polymer chemistry these controlled interactions have been used to create liquid crystalline materials (5) and intriguing architectures in block copolymer assemblies (6). Strong unidirectional interactions among molecules can not only recreate some of the key properties of covalent polymers, but add

functionality based on two basic principles, shape persistence and order within one-dimensional assemblies and the dynamics of non-covalent bonds. Louis Henry in 1878 initially proposed the idea of molecular polymerization by associative interactions (7), but it was Fouquey and coworkers in 1990 who designed and synthesized the first example of a linear supramolecular polymer based on hydrogen bonding among small molecules (8). More recently, strategies were developed to create large and ordered assemblies of molecules in the form of two-dimensional structures and other discrete nanoscale objects (2, 9).

There are at least two distinct types of supramolecular polymers based largely on the mechanism of their formation (10). In one case a random coil is formed without internal order in close analogy to common polymers (random coil supramolecular polymers). Such coils form through an isodesmic supramolecular polymerization similar to stepwise growth of macromolecules and are characterized by high polydispersity. A second type of supramolecular polymer is a shape-persistent nanostructure of molecular units with a high degree of internal order (ordered supramolecular polymers). This type of polymer has no analogy to common covalent polymers and is formed by the cooperative (nucleation-elongation) self-assembly of monomers leading to ordered one-dimensional structures. One example is the assembly of macrocycles into nanofibers (11) as well as rigid nanofibers based on peptides (12). The field of "functional supramolecular polymers" discussed here involves proper design of building blocks to achieve not just one-dimensional assembly of molecules but actual function as well. Fig. 1 shows four molecular units designed to form supramolecular architectures with mechanical (1A and 1B), biological (1C and 1D), and optical (1E and 1F) or electronic functionalities (1G and 1H).

Tuning the strength and directionality of interactions among molecular units is the key feature that defines the field of supramolecular polymer materials. When the lifetime of these bonds is too short ($\tau < \mu s$) a robust one-dimensional assembly that resembles a polymer does not exist, whereas too long a lifetime ($\tau > min$) yields materials without interesting dynamic behavior. In an intermediate range of bond lifetimes lies the opportunity to create materials with properties such as adaptability, responsiveness, self-repair and unique processing options. Highly ordered supramolecular polymers also have the possibility of undergoing well-defined transitions between states of short and long bond lifetimes due to the self-assembly mechanism involved in their formation.

Supramolecular Forms of Contemporary Polymeric Materials

Interest in coil-like supramolecular polymers was triggered by the discovery that small molecules assembled by secondary interactions into long chains can yield materials with mechanical properties that were until then exclusively connected to covalent macromolecules (13). The first of these polymers are based on self-complementary quadruple hydrogen bonding units with lifetimes on the order of 0.1–1 sec in solution at room temperature. This approach was used by Meijer and coworkers to prepare these small molecules with two ureidopyrimidinone (UPy) termini separated by a spacer (Fig. 1). These small molecules behave like macromolecules in dilute and concentrated solution as well as in the bulk (Figs. 2A, 2B, and 2C). In solution, they obey the classical theories of polymer physics and possess an interesting equilibrium between cyclic and linear polymers. Virtual molecular weights of over 500,000 Daltons were reached at room temperature, combining excellent mechanical properties in the solid state with low viscosities at elevated temperatures where hydrogen bond lifetimes shorten considerably. The molecular explanation for this interesting combination is rooted in the possibility of supramolecular chains moving like a reptile (reptation) as conceived by De Gennes (14), but also breaking and reforming their bonds with other partners at elevated temperature. Copolymers can be

easily formed in these coil-like supramolecular polymers by adding other molecules, and this approach has been illustrated in systems that optimize composition for energy transfer in materials designed to serve as white-light emitting diodes (Fig. 2D) (15). Also the length distribution of chains generated by supramolecular polymers and therefore their physical properties can be modified through changes in designed interactions among the monomers. Systems based on UPy monomers have been found to obey predictions by Flory for covalent condensation polymers yielding a polydispersity index, Mw/Mn, equal to 2 under thermodynamic equilibrium (16).

The fascinating elasticity of rubbery materials proved to be an extremely interesting platform for the supramolecular approach (17). A rubbery matrix can be held together by intermolecular interactions along two orthogonal directions, that of the main chain and that of the side chains leading to crosslinks. These types of supramolecular elastomers exhibit self-healing behavior as first reported by Leibler et al. (18). In this work the chemical system involved biologically derived monomers polymerized through multiple hydrogen bonds. These crosslinked supramolecular polymers showed full strain recovery after extension under load, but in contrast to conventional covalent rubbery materials exhibited self-healing behavior toward their original strength and elasticity after two fracture surfaces of a sample were brought into contact for a given period of time. In other systems UV light absorption was shown to result in mechanical healing behavior in supramolecular polymers formed through metal-ligand interactions (19). If polymer backbone formation and crosslinks were to be based on very different intermolecular interactions, it would be possible to modulate elasticity or to switch it on or off through temperature changes or other external forces.

The reversible nature of chain-forming interactions in supramolecular polymers also offers unique opportunities in recycling of materials. In principle, these materials could be recycled by simply purifying their monomers without requiring depolymerization. The chemical structure difference between repeating unit and polymer indeed vanishes, and it is only the changes in lifetime of non-covalent bonds as a result of changes in temperature or other external stimuli that determines the state of matter. This will be specially possible and important in materials designed mostly for mechanical functions and utilized in large scale. In the ordered supramolecular polymers discussed below for biological and electronic functions, bond reversibility will be more complex since large monomers and strong interactions are likely to be involved.

Biomedical and Biomimetic Opportunities with Ordered Supramolecular Polymers

Signaling cells with bioactive filaments

Signaling of cells with biocompatible artificial structures will provide many opportunities to cure disease and improve quality of life for the world's population through regenerative medicine. If these artificial structures are to be placed in the human body, they should signal and then biodegrade into nutrients or be safely eliminated. A supramolecular polymer could be a rigid assembly of molecules displaying multiple signals to receptors in high density and highly directed geometry, but composed of water soluble monomers. Furthermore, the supramolecular polymer could also be reconstructed by the cell to fit the necessary geometry by easily rupturing and reforming in situ its noncovalent bonds, an opportunity obviously not accessible with covalent chains (see Fig. 3A and 3B).

Fig. 3A depicts schematically a rigid filamentous supramolecular polymer that displays signals spatially to receptors over long distances on the cell surface. These rigid assemblies of small molecules could also recruit the multiple receptors necessary in the raft structures of cell membranes. Fig. 3B depicts schematically how the rupture of non-covalent bonds in

the supramolecular polymer could adapt its architecture to the high binding affinities of receptors for the signals displayed on the artificial nanostructure. In order to create a vast number of such supramolecular polymers, we need self-assembly codes that lead to rigid filaments. The functional form of peptide-based supramolecular polymers has been extensively developed by Stupp and co-workers in peptide amphiphiles, molecules containing peptide segments covalently bonded to lipid-like hydrophobic segments (see Figs. 3C–E) (20, 21). These supramolecular polymers have been shown to be highly bioactive *in vivo* when designed to promote biological events such as regeneration of axons in the injured spinal cord (22), the growth of blood vessels (23), the regeneration of bone and cartilage (24–26). In other work by Hartgerink and co-workers (27) peptide amphiphile supramolecular polymers have been engineered as cell scaffolds that integrate substrates for enzymes that can degrade the matrix with biological adhesion signals in order to promote cell viability, migration, and proliferation.

An example of complex function in ordered supramolecular polymers was their use to promote the rapid and selective differentiation of neural stem cells into neurons without the development of astrocytes (28). This selective differentiation was achieved in a supramolecular polymer capable of displaying up to 10^{15} signals per cm^2 of the pentapeptide laminin signal IKVAV. The actual signal density is of course dependent on the internal level of hydration and bundling of the filamentous assemblies. The observed differentiation required assemblies in which nearly 50% of the peptide amphiphile monomers used to create a filamentous network contained the biological signal (see Fig. 3D). In another example the supramolecular filaments have been used to promote blood vessel formation utilized heparin displaying nanofibers that bind the proteins vascular endothelial growth factor and fibroblast growth factor (23). The regeneration of cartilage was triggered by nanofibers that displayed peptides discovered by phage display that can bind the protein transforming growth factor β1 (25). In approaches using proteins bound to the supramolecular polymer the large real state on the rigid assembly can accommodate the nanoscale footprint of a growth factor or antibody to trigger a specific signal transduction pathway or target a specific cell for therapeutic purposes. It is also important that supramolecular polymers put together through noncovalent interactions will not only be likely to biodegrade at faster rates than covalent polymers but monomer design will allow fine tuning of their half life.

Biomimetic Dynamic Structures

The potential in supramolecular systems to achieve dynamic functions derives inspiration from the cell cytoskeleton. The reversible association of protein monomers to dynamically create and dissolve a skeleton of stiff filaments inside microscopic gels suggests many ideas for synthetic systems. In cells this fascinating process in which supramolecular polymers form and depolymerize rapidly not only controls cell migration, attachment, and division, but also serves as a highway for internal transport of molecules to specific compartments (29). If suitable chemistry could be developed to create biomimetic analogues, one could imagine many possibilities for novel functions. One example would be soft materials that stiffen or deliver chemicals reversibly with chemical or photonic stimuli.

Hierarchical Structures

The use of noncovalent interactions to design functional materials will be greatly enhanced if the supramolecular structure codes can be extended beyond a single assembly of molecules defined as the polymer. A number of examples of supramolecular hierarchical structures have been reported recently. Cylindrical assemblies of peptide amphiphiles were found to crystallize spontaneously or triggered to do so reversibly by x-ray photons that create charge on surfaces of the supramolecular filaments (30). In this case the hexagonal

crystal formed as a result of repulsive electrostatic forces among the supramolecular polymers trapped mechanically by the networks they formed. In another example, bundles of dozens of peptide amphiphile cylindrical nanofibers were observed to form through a mechanism analogous to a two-dimensional Rayleigh instability and to consequently self-order into an aqueous liquid crystal at exceedingly low concentrations in the range of 0.5% by weight (31). These solutions of bundled supramolecular polymers can be sheared by a human hand into orientational monodomains of arbitrary macroscopic length. Their potential functions in aligning large populations of cells or promoting electrical connections among cardiac cells has been demonstrated. These hierarchical systems may serve as scaffolds for wires to repair parts of the brain, the heart, and the spinal cord. As recently shown, hierarchical supramolecular polymers could also incorporate in their building blocks the multimeric association of molecules observed in biological systems such as the collagen triple helix (32).

In a final example of hierarchical structure, positively charged supramolecular peptide filaments in dilute aqueous solution come into contact with dilute solutions of oppositely charged biopolymers with an average molar mass in the range of millions of Daltons, and assemble into a membrane with speeds in the range of milliseconds (33). The supramolecular rigid filaments screened by polymer chains bearing opposite charge assemble into a dense layer which serves as a diffusion barrier to prevent the chaotic mixing of both solutions. This remarkably ordered structure formed by a hierarchical structure of supramolecular polymers is permeable to large molecules such as proteins. The miniaturization of this process to scales of microns is a potential platform demonstrated recently to create the scaffold of synthetic cells with filamentous surfaces (34).

Electronic Functions in Ordered Supramolecular Polymers

Semiconducting Nanofibers

π-Conjugated molecules that self-assemble by stacking have the potential for developing semiconducting nanowires that transport charge carriers unidirectionally over long distances (35, 36). Nearly a decade ago, several pioneering examples of such electroactive nanowires (37–41) were reported, many of which utilized π-conjugated aromatic units in conjunction with hydrogen-bonding motifs. For example, mono- and bithiophene derivatives carrying urea functionalities self-assemble into nanofibers, which display highly mobile charge carriers on pulse radiolysis (37). The self-complementary quadruple hydrogen-bonding motifs (13) when coupled with oligo(*p*-phenylenevinylene) derivatives (Fig. 1) are useful for supramolecular electronics (38). Meanwhile, a different strategy to create electroactive one-dimensional nanostructures has been reported by making use of molecules with architectures that include rod-like, coil-like, and dendritic segments (dendron rodcoils) (39, 40). These molecules polymerize into ribbons through hydrogen bonding and π-stacking interactions.

More recent studies have focused on ordered supramolecular polymers based on very large monomeric units with extended π-conjugated motifs in order to attain high charge mobilities (42, 43). In this context, Müllen et al. initiated work on coronene derivatives which have attracted attention as monomers for functional supramolecular polymers (44). Nuckolls and coworkers reported that contorted hexabenzocoronene (HBC) (molecular graphene) derivatives with eight long paraffinic side chains self-assemble into one-dimensional, single-crystalline nanofibers that can be used to create field effect transistors (42). Because of strong π-stacking interactions among the molecular units these one-dimensional nanostructures form without the involvement of any other interactions.

Semiconducting Nanotubes

The design strategy to create supramolecular nanotubes can be very different from that used for nanofibers since they derive from the polymerization of units into sheet-like objects. Aida and coworkers reported that an amphiphilic HBC, carrying triethylene glycol (TEG)-appended phenyl groups on one side and dodecyl side chains on the other, self-assembles into several tens-to-hundreds of micrometer-long graphite-like nanotubes with a wall thickness of 3 nm (45) (Fig. 1). These supramolecular nanotubes are thus characterized by a very large aspect ratio and have a uniform, 14-nm-wide, open-ended hollow space. The oxidized nanotube across a 180-nm-gap electrode displays an electrical conductivity of 2.5 MΩ at 285 K (45). From a suspension of long nanotubes, it is possible to obtain a macroscopic fiber a few centimeters in length, consisting of unidirectionally oriented nanotubes. Because of this alignment, the doped macroscopic fiber displays a clear anisotropy in electrical conductivity (46). Graphite-like supramolecular nanotubes with a variety of surface functional groups in their TEG termini can be fabricated through this strategy (e.g., chemically reactive groups, metal-binding functions, and chromophores) (47). When an asymmetric center is incorporated into the ether side chains, nanotubes (48) and even nanocoils with one-handed helical chirality are formed. Knoester and coworkers reported the polymerization of a supramolecular nanotube with a bilayer wall based on a *J*-aggregated amphiphilic cyanine dye (49). By means of polarization-resolved near-field scanning optical microscopy, such a red-shifted exciton emission can be detected directly from a single piece of the supramolecular nanotube (50).

Photoconductive Nanowires and Device Applications

One of the interesting functions for ordered electronically active supramolecular polymers would be photovoltaic activity. Although examples of such functional systems are still limited, work reported so far is creating a foundation and vision for this field (Fig. 4A). The nanowire polymers required must contain electron-donating (D) and accepting (A) components, either properly located in a single one-dimensional object or in different ones within a suitable electron transfer distance for exciton splitting after light absorption. The D- and A-components must assemble into individual *p*- and *n*-type semiconducting arrays (*p/n*-heterojunction) in such a way that the photogenerated holes and electrons can efficiently move toward opposite electrodes. Ordered supramolecular polymers would offer the possibility to more precisely design the heterojunctions in contrast to the common approach that relies on phase separation. One of the challenges is to avoid unfavorable charge-transfer (CT) D/A interactions at distances on the scale of molecular dimensions. In pioneering work, a D-A-D supramolecular triad, consisting of oligo(*p*-phenylenevinylene) (D) and perylene bisimide (A), was found to self-assemble into nanofibers that presumably consist of segregated D- and A-arrays (51, 52). Although radical anion and cation could be generated photochemically in the nanofiber, they recombined within 60 ps (51).

Recently, a design strategy for photoconductive nanotubes with a coaxial *p/n*-heterojunction based on HBC units was successfully elaborated (53). In this supramolecular structure, a molecular layer of the electron acceptor trinitrofluorenone laminates a graphite-like tubular wall of HBC units which are electron donors (Fig. 4B). This coaxial *p/n*-heterojunction structure enables photocurrent generation with a large on/off ratio greater than 10^4 (Fig. 4C). It is interesting to note that at high concentrations of the building blocks, the anticipated charge transfer interactions prevail and only ill-defined microfibers form that hardly display a photocurrent (53). When a fullerene is utilized in these structures as the acceptor, the resultant carbon-rich coaxial nanotube shows upon light illumination an ambipolar charge carrier transport profile, where the intratubular mobility is as large as the intersheet mobility in graphite. Furthermore, the nanotube shows a photovoltaic response (54) although the overall device performance is not satisfactory for practical use. More recently, this

assembling strategy was extended to the formation of a graphite-like nanotube with a linear D/A-heterojunction using a surface-crosslinked HBC nanotube as the seed and a fluorinated HBC as the monomer (55). Matile and coworkers proposed a zipper-type supramolecular copolymerization of positively and negatively charged D-A dyads from initiating groups immobilized on a gold substrate (56, 57). This approach has the potential to yield aligned systems on electrode surfaces with many tunable properties. Generally speaking, a key issue to consider is the essential difficulty in aligning ordered supramolecular polymers unidirectionally over macroscopic length scales to create devices, and here is where approaches to hierarchical supramolecular structures described in the previous section could become useful.

Future Outlook

Functional supramolecular polymers offer a great platform for materials that integrate order and dynamics to achieve functions such as high responsivity to stimuli, environmental adaptation, and self-repair capacity. It is also clear that an important direction in this platform is to explore novel functionality in hybrid systems with nanoscale structures of both supramolecular and covalent polymers. Similarly, materials that couple supramolecular and inorganic structures remain largely unknown but have potential as evidenced by a recent report on semiconducting systems (58). Finally, the platform for supramolecular polymers could also transition into 2D and even 3D complex systems (34, 59) to craft novel functions of interest in sustainability, electronics, and health.

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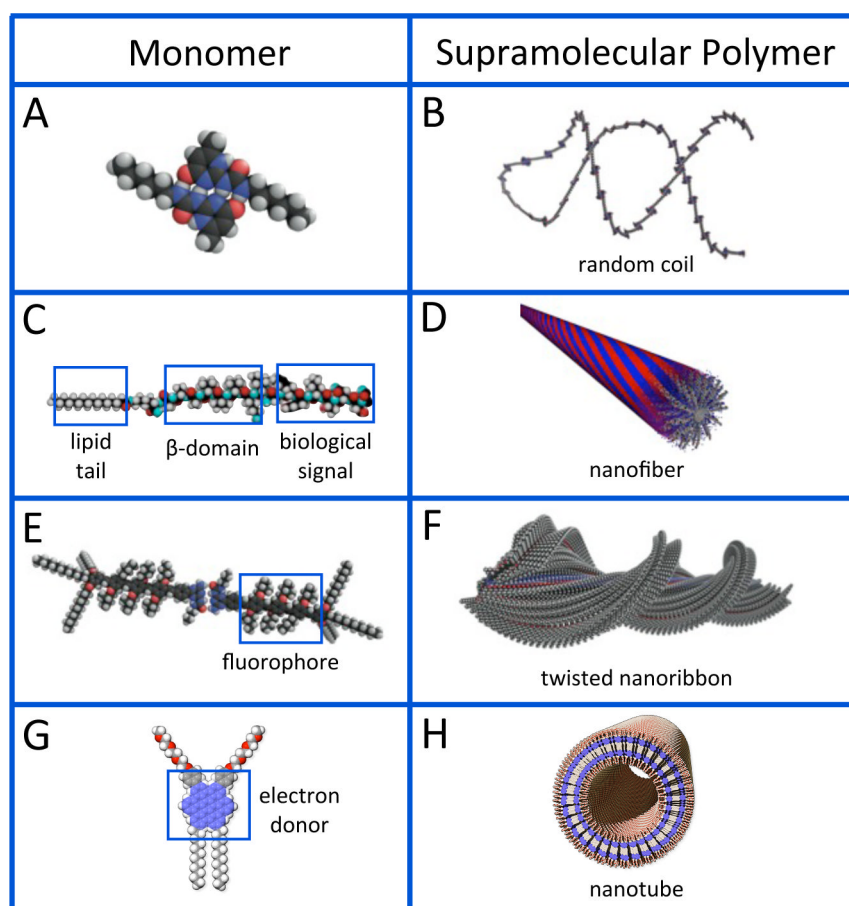
Figure 1.
Molecular representation of four different monomers and the corresponding supramolecular polymers formed after their aggregation through specific interactions. The first pair (A and B) is a ureidopyrimidinone monomer capable of forming quadruple hydrogen bonds to assemble a random coil supramolecular polymer. The second pair (C and D) is a peptide amphiphile monomer composed of three segmental domains, a sequence bearing a biological signal, a domain containing amino acids with a strong tendency to form β sheets, and a hydrophobic alkyl tail. The idealized structure of this ordered supramolecular polymer formed by these monomers is a cylindrical aggregate in which twisted β sheets (red) collapse through hydrophobic interactions among alkyl chains, thus displaying high densities of the biological signal. The blue regions represent water domains present in the interior of the supramolecular assembly (in real dynamic structures the peptide amphiphile and water domains are not expected to have a characteristic periodicity). The third monomer is based on the fluorophore oligo(phenylene vinylene), substituted by alkyl groups for solubility and also chiral centers. One terminus of the monomer is capable of forming quadruple hydrogen bonds to create stable dyads. The ordered supramolecular polymer takes the form of a twisted ribbon with defined chirality (E and F). The last monomer is based on a hexabenzocoronene core which can behave as an electron donor, substituted by phenyl triethylene glycol and dodecyl chains (G and H). The ordered supramolecular polymer formed from this monomer is a nanotube with a wall thickness defined by the dimension of monomeric units.
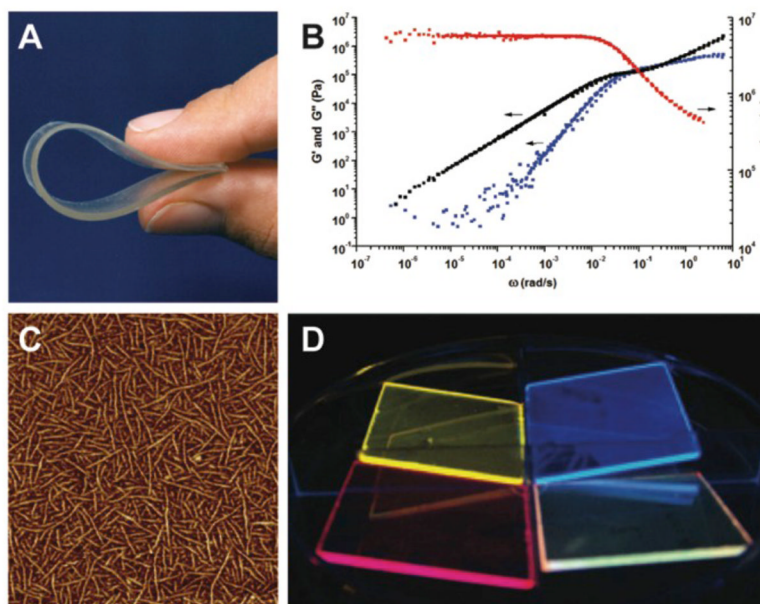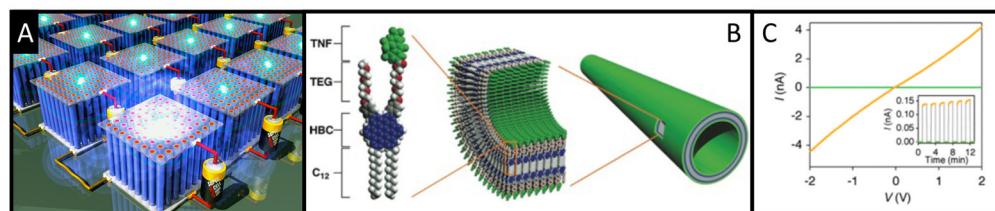
Figure 2.
Supramolecular polymers based on random coil chains with excellent mechanical properties.
A. Rubbery material of a small molecule based on two ureidopyrimidinone moieties
separated by a flexible spacer. B. Plots of storage modulus (G′) and loss modulus (G″) as a
function of frequency for a material similar to that shown in A. but containing a stiff and
short spacer between ureidopyrimidinone units. C. Atomic force micrograph of
supramolecular polymers that form nanofibers due to lateral hydrogen bonding of a urea
group adjacent to a ureidopyrimidinone unit; these materials behave mechanically as
thermoplastic elastomers. D. Light-emitting films based on supramolecular copolymers
formed by monomers with molecular segments having different fluorescent properties. A
large variety of films can be obtained and even white light emission is possible in these
systems when a specific ratio of three different components leads to association of
monomers into a random terpolymer.
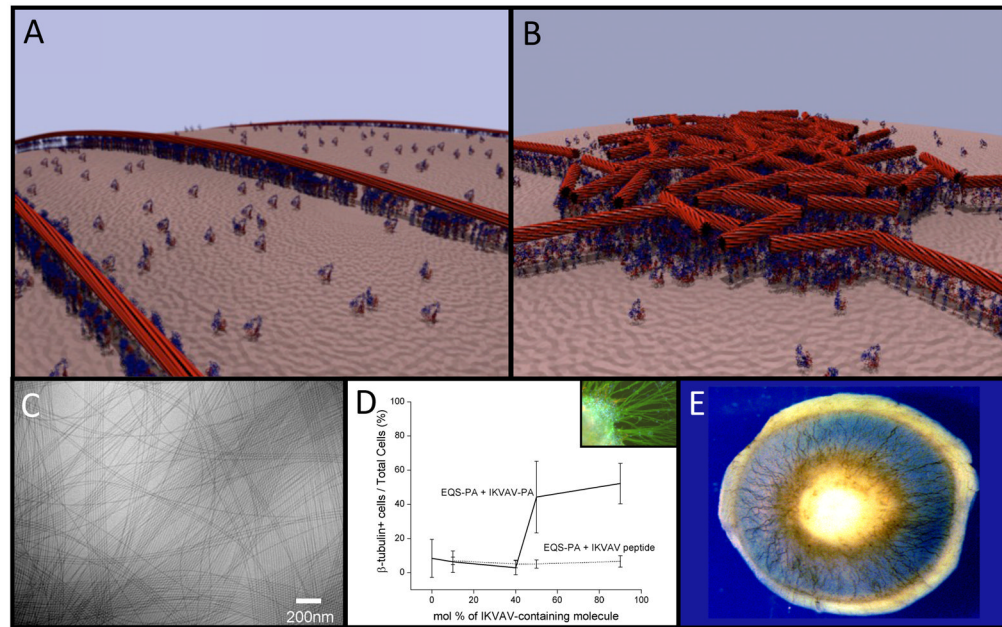
Figure 3.
A. Schematic representation of a bioactive supramolecular filament displaying high densities of biological signals that bind to receptors on the cell surface. The high signal density and stiffness of the ordered supramolecular polymer should be effective at recruiting and co-localizing large numbers of receptors for effective signaling. B. Strong interactions between molecular signals and cell receptors could reconstruct a non-covalent supramolecular assembly with relatively weak bonds to match a raft of receptors. C. Cryo electron micrograph image of peptide amphiphile nanofibers. D. Plot of the number of new neurons developed from a population of neural stem cells upon contact with supramolecular nanofibers containing various mole per cents of monomer displaying the bioactive pentapeptide signal IKVAV (the number of cells is obtained counting β-tubulin III positive cells, a marker for neuronal lineage); the inset reveals a cluster of neural stem cells undergoing differentiation into neurons (the green color indicates the presence in the cells of β-tubulin III). The dotted curve in D. shows that adding various mole per cents of the soluble IKVAV signal to a network of non-bioactive supramolecular polymers has no effect on differentiation of the neural stem cells E. A rat cornea showing the growth of many new blood vessels 7–10 days after placing in the tissue peptide amphiphile nanofibers that display heparin and bind angiogenic growth factors.

Figure 4.
A. Schematic representation of the vision for photovoltaic devices containing large bundles of aligned semiconducting ordered supramolecular polymers with built-in *p/n*-heterojunctions. B. Molecular graphics representation of the monomer and the resulting supramolecular nanotube containing a co-axial p/n-heterojunction. The donor moiety in the monomer is hexabenzocoronene (HBC, in blue) and the acceptor is trinitrofluorenone (TNF, in green); other parts of the monomer structure include triethylene glycol (TEG) and dodecyl (C_{12}) chains for solubility. C. Current-voltage profiles of supramolecular coaxial nanotubes films at ambient temperature with photoirradiation (orange) and without (green) [λ = 300 to 650 nm]; the inset shows the modulation of electric current using photoirradiation of a cast film of photoconductive nanotubes at room temperature. A large current increase is observed with illumination (orange) versus without (green).