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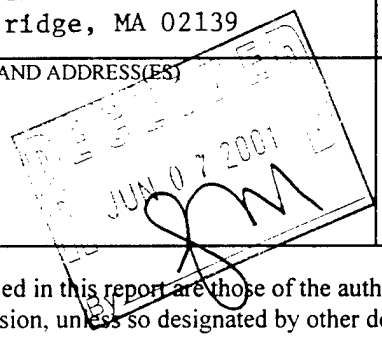

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13. ABSTRACT (Maximum 200 words)

Understanding new materials at the molecular level has become increasingly critical for a new generation of nanomaterials for nanotechnology, namely, the design, synthesis and fabrication of nano-devices at the molecular scale. New technology through molecular self-assembly as a fabrication tool will become tremendously important in coming decades. Basic engineering principles for microfabrication can be learned by understanding molecular self-assembly phenomena. Self-assembly phenomenon is ubiquitous in nature. The key elements in molecular self-assembly are chemical complementarity and structural compatibility through non-covalent interactions. We have defined the path to understand these principles. **Numerous self-assembling systems have been developed ranging from models to study protein folding and protein conformational diseases, to molecular electronics, surface engineering, and nanotechnology. Several** distinctive types of self-assembling peptide systems have been developed. Type I, "molecular Lego" forms a hydrogel scaffold for tissue engineering; Type II, the "molecular switch" as a molecular actuator; Type III, the "molecular hook" and "molecular Velcro" for surface engineering; Type IV, "molecular capsule" for protein and gene deliveries; and Type V, "molecular cavity" for biomineralization. These self-assembling peptide systems are simple, versatile and easy to produce, representing a significant advance in molecular engineering for diverse technological innovations.

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SELF-ASSEMBLING IONIC OLIGOPEPTIDES

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Molecular self-assembly is a powerful tool to create novel biological materials. In our laboratory, we use fragment of proteins and de novo designed peptides to produce a diverse of functional biological materials. Four distinctive systems have been studied so far. Each opens a new avenue of research areas with a tremendous opportunity to produce novel materials for a number of applications in materials science and biomedical engineering.

One of the self-assembly peptide systems mainly form hydrogels and matrices through complementary intermolecular interactions. The molecular structure of these self-assembling peptides consists of two distinctive faces of alternating ionic hydrophilic and hydrophobic amino acid residues. The side chains of these oligopeptides consist of repetitive positively charged residues, arginine and lysine, and negatively charged residues, glutamate and aspartate, on the hydrophilic face. The alanines and other hydrophobic residues are on the other face. A defining characteristic of this oligopeptide class is that their charged side chains can form complementary ionic bonds. In most cases, these oligopeptides form exceedingly stable beta-sheets in water. The ionic complementary oligopeptides have been classified into several modulus, i.e. modulus I, II, III, IV, etc., and mixed moduli. This classification is based on the ionic surface of the molecules which have alternating + and - charged amino acid residues, either alternating by 1, 2, 3, 4 and so on. For example, molecules of modulus I have the ionic arrangement - + - + - + - +, of modulus II - - + + - - + +, and modulus IV - - - - + + + + or the reversed charge orientation. Such a systematic analysis also show that modulus I peptides $(- +)_n$ are somewhat less stable than those of modulus II peptides $(- - + +)_n$.

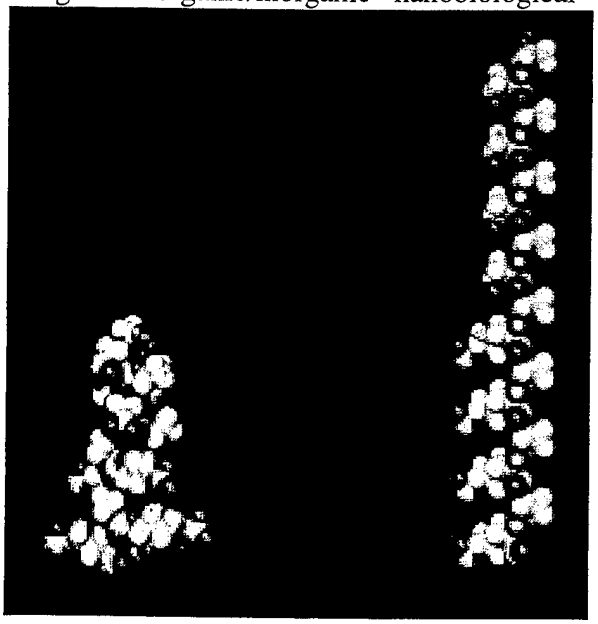
These ionic beta-sheet peptides can undergo self-assembly to form macroscopic biological materials and can be readily stained with Congo Red. This class of biological materials represent a new generation of biological materials and is now being further developed as scaffolding for tissue engineering. The peptides of the second self-assembly system form both intermolecular and

intramolecular self-assemblies. When the peptides are in the beta-sheet structure, their backbone is fully extended. They undergo intermolecular self-assembly through both the side chain interactions and backbone hydrogen bonding interaction. Whereas, when the beta-sheet lattice is disrupted by heat or change of pH, these peptides transform into an intramolecular self-assembly to form stable monomeric helices, namely a spring-like structure. The peptides of the third self-assembly system spontaneously assemble onto surface to form monolayers, thereby modify the surface properties for a number of biological applications, much like creating different texture and patterns of carpeted floors. Furthermore, we also designed a variety of simple and complex geometric patterns to create unique connections to ask some fundamental biological questions. The peptides of forth self-assembly system spontaneously bind with DNA and RNA. The peptides can condense and encapsulate DNA for high efficient gene delivery. Additional peptide self-assembly systems are being developed currently in the laboratory.

Molecular Switches

The second self-assembling peptide system of an ionic self-complementary oligopeptides that transform from a beta-sheet to an alpha-helix under stimuli of temperature and pH changes has been studies more in detail with additional examples. These oligopeptides are derivatives of first class of self-assembling ionic oligopeptides, now classified as Type II. In addition of having two distinctive faces with regular repeats of alternating ionic hydrophilic and hydrophobic side chains, they also have an orientation of charges. A defining characteristic of this class of peptide molecular switch is that there is a cluster of positively charged arginine or lysine locating toward the C-terminus and the negatively charged glutamate and aspartate locating toward the N-terminus of the ionic oligopeptides. Such an arrangement of charge clusters balances the alpha-helical dipole moment (C-terminus-->N-terminus), promotes and stabilize helical formation. The compositions of both aspartate-alanine-arginine (DAR) and glutamate-alanine-lysine (EAK) are effective acting as a molecular switch in structural transformation. Changes of the orientation of the charged clusters and a single alteration or substitution of a charged residue completely hinder the direct

structural transition. Furthermore, the substitutions also abolish the capability of peptide self-assembly for matrix formation. The length change accompanying the structural changes is approximately twofold, in our cases, 2 to 4 nm or 2.5 to 5 nm, thus such change is analog to an on/off molecular switch. Such findings could be further developed for biological sensors and molecular detection devices. Developing of a self-assembly nanotechnology using this type of ionic peptides for coating to metallic and polymer surfaces may produce a new generation of integrated organic/inorganic nanobiological materials for a broad range of applications.



Peptide-Nanotubes

Several new types of biomaterials has already shown considerable potential in a number of applications such as scaffolding for tissue engineering, peptide medicine and biological surface engineering and thus may be well adapted for the goals of drug delivery. Based on our expertise, we recently design a new type of short oligopeptides whose properties closely mimic those found in surfactant molecules. The objective being to form new self-assembled nanostructures, very similar to those observed in surfactant solutions. It is well known that most surfactants are amphiphilic molecules that tend to aggregate in order to isolate the hydrocarbon chain from the contact with water. The common feature for this self-association is the formation of a polar interface, which

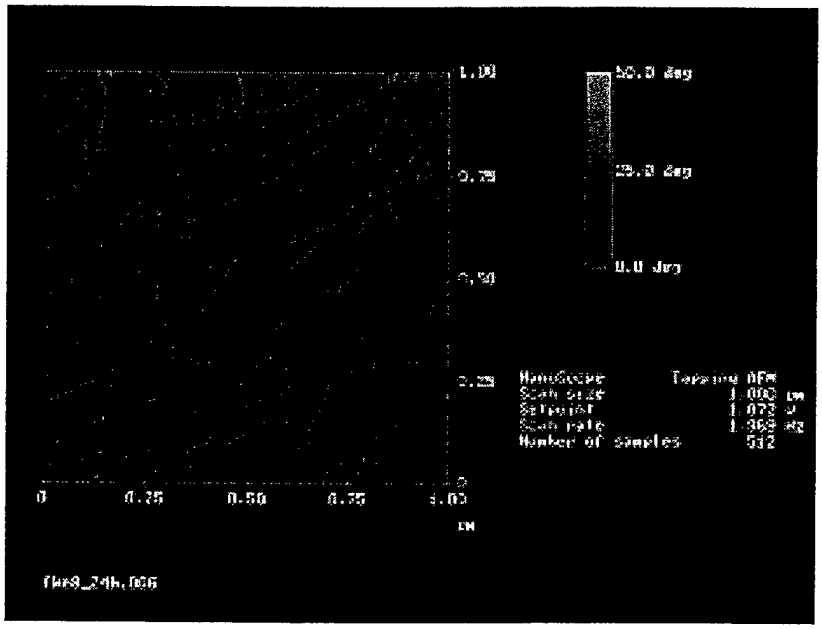
separates the hydrocarbon and water regions. Perhaps the most common structure formed in water is the spherical micelle consisting of typically 50-100 lipid molecules arranged so that their hydrocarbon tails form the interior of the micelle, and the polar head groups act as a shield against the surrounding water. The micelle, however, is only one of many aggregate types formed. Depending on the surfactant and its concentration, various structures are found, including liposomes, lamellar phase, hexagonal and cubic structures. Among the later, liposomes have attracted a particular interest due to its potential utility for conventional drug delivery.

The initial results based on the self-assembly of short amphiphilic oligopeptides have shown very defined structures of about 50 nm. It has also been observed that these self-assembled structures can be modified by external parameters such as pH. Moreover, an adequate design of the peptide allows fine-tuning the self-assemblies properties, giving a high flexibility for various potential applications. Regarding these different issues, the development of controllable and reproducible liposomal systems for systematic drug delivery system has been relatively ineffective. In this context, it is strongly believed that structures based on oligopeptides self-assemblies may have the ability to entrap and deliver molecules with a high degree of efficiency and thus could open innovative avenues for novel drug/gene delivery systems.

Molecular Self-assembly of Peptide into Nanofiber Structures

A class of ionic self-complementary oligopeptides had previously been shown to form β-sheet structures in aqueous solution that, in the presence of monovalent alkaline salts, spontaneously self-assemble to form macroscopic matrices. We now show that FKFEFKFE, a peptide of this class, self-assembles into well-ordered helical nanofiber structures in pure water. The self-assembly process has been monitored at different incubation times via adsorption on mica and graphite and

imaged with atomic force microscopy. These nanofibers in the early stages of incubation look like helical ribbons with a periodicity of ca. 20 nm and a diameter of ca. 8 nm. These features resemble those of β-Amyloid fibers. This finding has significant implication in producing new functionalities for a broad application of nanomaterials.



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