Supramolecular Materials for the Advancement of Medicine

Abigail Halmes Literature Seminar September 29, 2016

As biomaterials become increasingly important to the treatment of disease, there is a need for materials used in medicine to be more dynamic and able to respond to physiological signals.[1] Improvements must be made upon traditional covalent polymers. These needs are currently being addressed by using supramolecular chemistry. Generally, non covalent interactions are used to bind complex molecular units together to form materials. Two intermolecular interactions useful for designing supramolecular biomaterials are host-guest interactions and hydrogen bonding. Host-guest interactions have been recently used to construct materials that show promise for use in applications ranging from medical imaging to tissue regeneration.[2,3] Materials based on hydrogen bonding interactions show great promise in the field of tissue engineering as well as having applications analogous to those of host-guest based materials.[4–6]

Host-guest interactions occur when a molecule containing a cavity, the cavitand, meets with a corresponding guest molecule.[7] For medical applications, cavitands are usually macrocycles that are large enough to allow certain guest molecules to enter. Cyclodextrin is commonly used in host-guest systems due to its natural abundance and biocompatibility.[2,3,7,8] Guest molecules with nonpolar functionalities fit into the cavity of cyclodextrin and form a host-guest pair in aqueous conditions via hydrophobic interaction.[7] Work in the Liu group has shown the host-guest interaction protects metal ions from unwanted oxidation, improving medical imaging contrast agents such as those used for MRI.[2] In this work, the cavitand molecule used was bridged bis(permethyl β-cyclodextrin) and the guest was 5,10,15,20-tetrakis(phenyl)porphyrin (TPP). Manganese was incorporated into the porphyrin to form the guest species as can be seen in Figure 1. The stabilities of both Mn^{III}-TPP and Mn^{II}-TPP were investigated both alone and while interacting with a host molecule in .1 M phosphate buffer. It was found through UV-Vis studies that the cyclodextrin host is instrumental in the protection of Mn^{II} from unwanted oxidation.[2] The supramolecular material was found to be nontoxic to cells.[2] Additionally, the supramolecular polymer was found to have improved T_1 relaxivity compared to commercially available Gadolinium dye.[2] The positive findings in this work show that supramolecular polymers are a promising new material for medical contrast agents.[2]

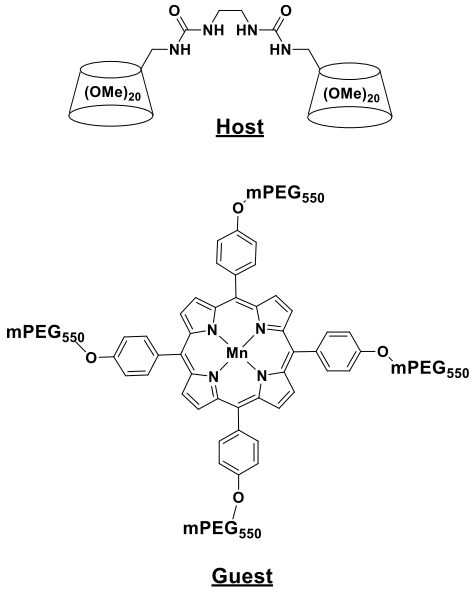

Figure 1. The host and guest molecules used to construct a supramolecular polymer contrast agent.[2]

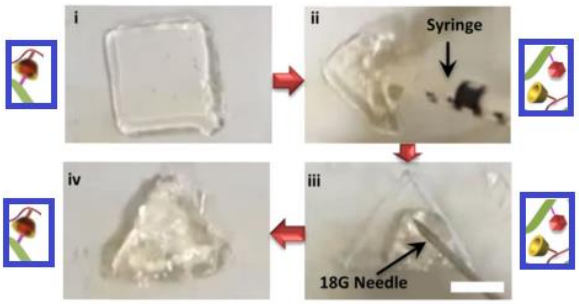

Figure 2. The remolding of HGM. As the gel is drawn into a syringe the physical crosslinks break, and then reform once the material is injected into a mold. Scale bar is 1 cm.[3]

Host-guest chemistry has also improved the properties of biocompatible hydrogels used in applications such as tissue regeneration.[3] Hydrogels are needed that can also fulfil requirements for being used in medical applications such as easy preparation, biocompatibility, and desirable mechanical properties.[8–10] The Bian group recently reported an injectable hydrogel based on host-guest interactions.[3] A hydrogel "macromer" was formed by host-guest complexation between aromatic gelatin residues and acrylated *β*-cyclodextrins.[3] Then UV initiated polymerization of the acrylates yielded a hydrogel physically crosslinked by host-guest interactions (HGM).[3] In swine bone adhesion studies, the HGM hydrogel performed better than the covalent polymer control hydrogel.[3] Further, the host-guest crosslinks were reversible when subjected to high shear strain, which resulted in an injectable material as is shown in Figure 2.[3] Gels were formed into a shape, drawn into a syringe, and molded into a different shape without sacrificing mechanical robustness.[3] Excess *β*-cyclodextrins present in the material also delivered hydrophobic drugs from their hydrophobic cavity. Studies of the HGM hydrogels implanted in rats showed that the gels support tissue regeneration without the use of exogenous cells. This finding has the effect of simplifying regenerative therapy and avoiding the regulatory approval needed to use exogenous cells.[3]

Supramolecular materials based on hydrogen bonding interactions also show promise for applications involving tissue regeneration.[4] Tissue engineering often demands anisotropic scaffold materials which are commonly achieved through the use of bilayered scaffolds.[4] Developing materials that can mimic the extra cellular matrix (ECM) is also important as the ECM is a critical component of tissue regeneration. Hydrogen bonding ureido-pyrimidinone (UPy) functionalities are often used as hydrogen bonding end groups to assemble supramolecular polymers.[4–6,11] UPy groups have two modes of self-assembly: dimerization through hydrogen bonding as well as π-π stacking. The Dankers group reported the use of two different UPy functionalized polymers to fabricate a scaffold when paired with UPy-modified peptides. These three building blocks, one of which is shown in Figure 3, were then electrospun into bilayered scaffolds. The resulting scaffolds allowed human kidney epithelial cells to adhere and spread through the network. Surfaces with longer fibers were found to better support the adherence and spread of cells than those with shorter fibers.[5] The properties of scaffolds made from supramolecular building blocks are able to be tuned by mixing and matching the different

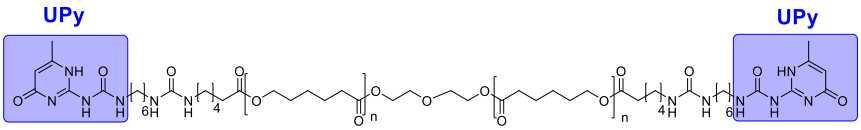

Figure 3. A supramolecular building block featuring hydrogen bonding UPy endgroups.[4]

blocks. This approach will allow scaffolds to be customized and future work will focus on the optimization of a bioactive building block to further improve cell attachment and spreading.

In order for medical treatments to advance, new materials need to be made that function in ways more analogous to biological systems. The self-assembly and reversible bond formation of supramolecular materials make them prime candidates to meet these needs. For certain medical applications, the properties of supramolecular polymers have been shown to be preferable to conventional materials. The materials from this body of work will undoubtedly find their way into modern medicine.

References

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