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FROM DYNAMIC STRUCTURES TO FUNCTIONAL MATERIALS

Engineering Supramolecular Biomaterials through Self-Assembly of Minimalist Peptides for Tissue Regeneration and Drug Delivery

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Supramolecular assembly is a ubiquitous phenomenon in nature for the synthesis of various functional materials required for the sustainability of life. From DNA condensation in the nucleus to the actin filaments that support cytoskeletal dynamics, most processes are predominantly governed by non-covalent interactions of their biomolecular assemblies. Peptides form self-assemblies, which are stable, biocompatible, and highly tunable and can be used to develop biomaterials, sensors, piezoelectric materials, and energy storage devices. The self-assembling peptides were first reported by Zhang *et al*., who used a 16-amino acid beta-sheet-forming peptide to form nanofibers.[1] Later, Gazit *et al*. adopted a minimalist approach, using the Phe-Phe sequence to form supramolecular assemblies.[2] In recent years, many dynamic and adaptive systems have been designed through peptide self-assembly, addressing fundamental to advanced questions in science.[3] In the current work, we have designed a minimalist peptide, Fmoc-Phe-Lys-Ser-OH, which self-assembles in aqueous medium at 1.5% w/v to form a supramolecular gel. This gel exhibited a nanofibrous morphology, as evidenced by AFM imaging, and its rheological characterization revealed its viscoelastic nature. We further used it as a supramolecular template and conjugated a functional DGEA peptide sequence to its carboxyl terminus. The Fmoc-FKSDGEA sequence so formed self-assembled into a rigid gel with an ECM-like nanostructure. The gel was found to be cytocompatible towards murine fibroblasts (L929 cells) and macrophages (RAW 264.7 cells). The nanofibrous network-coated plates effectively modulated LPS-induced proinflammatory macrophages, promoting their transition to an anti-inflammatory phenotype, hence, showing potential in immunomodulatory tissue engineering. We have further used the Fmoc-FKS tripeptide template to develop a supramolecular drug depot. The serine side-chain hydroxyl group was functionalized with the NSAID, naproxen, via an ester linkage, and we are currently assessing its esterase-responsive drug-release behavior for application in inflammatory disease conditions.

1. S. Zhang *et al*., *Proc. Natl. Acad. Sci. USA*, **90**, 3334 (1993**).**
2. E. Gazit *et al., Science,* **300**, 625 (2003**).**
3. K. Kaygisiz *et al*., *Nat. Rev. Mater*., **10**, 449 (2025).