

NDnano Summer Undergraduate Research 2017 Project Summary

1. Student name & university: Calvin Nazareth - University of Notre Dame

2. ND faculty name & department: Matthew J Webber - Chemical and Biomolecular Engineering

3. Project title: Project: Engineering responsive peptide-based drug nanocarriers

4. Briefly describe new skills you acquired during your summer research:

During my summer research, I learned how to synthesize both peptides and peptoids manually. I learned how to use a lyophilizer, and an HPLC machine. I became more proficient at reading HNMR, mass spectrometer and HPLC data.

5. Briefly share a practical application/end use of your research:

My summer research is a continuation of a project that I worked on during the school year. The purpose of both projects is further understanding of peptidic chemistry and supramolecular interactions that cause gelation of peptides in water.

6. 50- to 75-word abstract of your project:

Previously, we have established a library of amphiphilic that form nanostructures and gels. Near UV circular dichroism and infrared spectroscopy on the peptide gels show minimal signs of beta sheets. We developed analogous 'tripeptoids' to analyze the importance of hydrogen bonding in the peptide hydrogels. Peptoids have a side chain on the nitrogen rather than the carbon. Our peptoids did not form hydrogels however, they formed nanostructures similar to the peptides.

7. References for papers, posters, or presentations of your research:

Sahoo J. K.; Nazareth C. D.; VandenBerg M. A.; Webber M. J. Self-assembly of amphiphilic tripeptides with sequence-dependent nanostructure. *Biomaterials Science*. **2017**. DOI: 10.1039/c7bm00304h

Webber M. J.; Appel E. A.; Meijer E.W.; Langer R. Supramolecular Biomaterials. *Nature Materials*. **2015**. 15. 13-26.

Zuckermann R. N.; Kerr J. M.; Kent S. B. H.; Moos W. H. Efficient Method for the Preparation of Peptoids [Oligo(N-substituted glycines)] by Submonomer Solid-Phase Synthesis. *J. Am. Chem. Soc.* **1992**. 114. 10647-10647.

Zhang S.; Altman M. Peptide self-assembly in functional polymer science and engineering. *Reactive & Functional Polymers*. **1999**. 41. 91-102.

One-page project summary that describes problem, project goal and your activities / results:

Supramolecular biomaterials enable formation of a variety of nanostructures and properties. Peptides specifically offer an assortment of self-assemblies with numerous biomedical applications. The self-assemblies generally form due to beta-sheet formation and hydrogen bonding. Previously, we have established a library of amphiphilic tripeptides (peptides comprised of three amino acids) that form a diversity of nanostructures and gels. We designed them based on a traditional peptide amphiphile consisting of a hydrophobic N-terminus and a hydrophilic C-terminus. Our terminal amino acids stayed constant while we varied our middle amino acid. To test our peptides, we dissolved them in water at different concentrations. Three of our five peptides formed gels, and for those we found the minimal gelation concentration. We also ran transmitting electron microscopy (TEM) on all the peptides. The TEM data showed that as the hydrophobicity of the central amino acid increased, the gels grew in strength and the nanostructures increased in aspect ratio. We also ran near ultraviolet rheology, circular dichroism (CD) and infrared spectroscopy (IR). The rheology data showed that our gels are in fact gels because the elastic modulus (G') is approximately ten times greater than the loss modulus (G''). Contrary to most self-assembling hydrogels, near UV circular dichroism and infrared spectroscopy on the peptide gels show minimal signs of common secondary structures (i.e. beta sheets) which are normally integral to gelation of peptides.

In order to probe the importance of these interactions to self-assembly, we developed analogous 'tripeptoids' to analyze how peptoid interactions compare to peptide interactions and the importance of hydrogen bonding in the peptide hydrogels. Peptoids are peptidomimetic polymers comprised of N-substituted Glycines that are not found in nature. Though they have a similar structure to peptides, peptoids have a side chain on the nitrogen rather than the alpha carbon. This minimizes hydrogen bonding as well as degradation by proteolytic activity in vivo. Two of our peptides were chosen to create peptide analogues: one that formed a gel, and one that did not form a gel. We synthesized our peptoids using a solid-phase submonomer synthesis. We swelled and deprotected our rink amide resin, then used a bromoacetylation reaction to add the carbonyl group. To add the side chains, we used an S_N2 reaction with our primary amine side chain displacing the bromine. Similar to how we tested our peptides in water, we did the same with our peptoids. These peptoids were unable to form hydrogels however, one of the peptoids formed similar structures to its analogous peptides as observed using TEM. The other peptoid was much different than its peptide analogue, both macroscopically and microscopically. However, due to the similarities, we can conclude that the minimal amphiphilic tripeptides may have been able to form self-supporting hydrogels without significant presence of hydrogen bonding. In the future, we will further purify our current peptoids and begin synthesis of peptoid analogues for the other three peptides and test them.

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