

# BIOMIMETIC POLYMERS

Researchers are designing peptoid-based lung surfactants and antibiotics that capture the sophisticated molecular features of bioactive polypeptides.

**Principal Investigator:** Annelise Barron

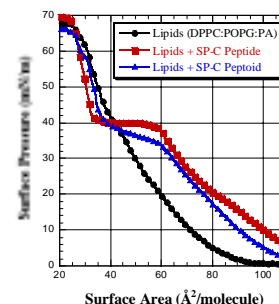
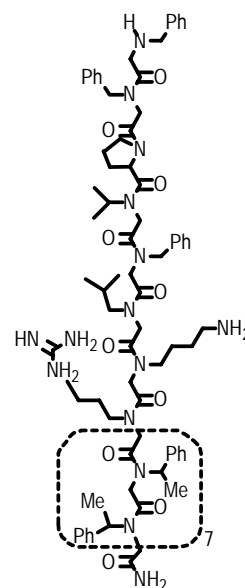
**Collaborators:** Ka Yee C. Lee (University of Chicago), Ronald N. Zuckermann (Chiron)

**Objective:** There is great interest in the creation of non-natural, sequence-specific polymers that adopt folded structures in solution and mimic the bioactivities of natural polypeptides. One novel class of such polymers is poly-*N*-substituted glycines or peptoids that differ from peptides in that their side chains are appended to the amide nitrogen rather than to the  $\alpha$ -carbon. Peptoids exhibit resistance to protease, raise a very low immune response *in vivo*, and have relatively low cost. The Barron group are designing, synthesizing, and characterizing polypeptoid-based analogs of human lung surfactant proteins (SP) and magainin class of peptides. The SP analogs will be used to treat respiratory distress syndrome (RDS) in premature infants, while magainin mimics will act as potent, broad-spectrum bactericides. At present, neonates suffering from RDS are treated with bovine-derived surfactant, an approach that raises some safety concern; medicinal applications of natural magainin are restricted by its poor bioavailability, potential immunogenicity, and low overall stability.

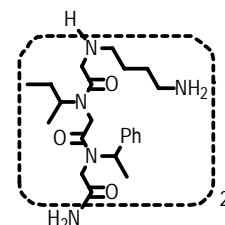
**Approach:** The synthesis of polypeptoids is achieved via a solid-phase submonomer method, using a commercial peptide synthesizer. Peptoids are purified by reverse-phase HPLC and characterized by mass spectrometry and circular dichroism. Their biophysical functions are measured using a pulsating bubble surfactometry and a state-of-the-art, home-built Langmuir-Wilhelmy surface balance in conjunction with fluorescence microscopy. Peptoids are tested for antibacterial activity by measuring their ability to inhibit bacterial culture growth (*E. coli* JM109 and *B. subtilis* BR151) with a UV-Vis microplate reader. Hemolytic activity of peptoids, which is an indicator of selectivity of an antibiotic for bacterial rather than eukaryotic cells, is measured using human blood cells and the UV-Vis microplate reader – note that a good antibiotic will be entirely non-hemolytic.

**Results:** The Barron group have succeeded in the preparation of a helical, structured peptoid that mimics both the structure and function of SP-C, a critical component of human lung surfactant. The peptoid analog of SP-C is comprised of twenty-two monomers of seven different types and is the longest and most complex non-natural peptidomimetic oligomer yet tested as a protein replacement. When integrated into a lipid film, it captures the unique surface-active behaviors of the natural proteins including the ability to adsorb rapidly to an air-water interface, to reduce and control surface tension as a function of surface area, and to respread quickly upon surface expansion. Optimization for an even closer mimicry of calf lung surfactant, which includes preparation of peptoid-based SP-B mimics – another protein shown to be important for lung surfactant functioning – is ongoing. In another development, the first generation of peptoid mimics of magainin of varying lengths and hydrophobicities has been prepared and evaluated for antibacterial activity. Optimal length appears to be a function of sequence and bacterial identity. Hemolytic activity seems to be a function of hydrophobicity, with more hydrophobic peptoids being more hemolytic. The best balance of high (micromolar) antibacterial activity and low hemolysis has been achieved in a 6mer of moderate hydrophobicity. All tested peptoids are more effective against Gram-positive bacteria.

**Selected Publications:** Sanborn TJ, Wu CW, Zuckermann RN, Barron AE, *Biopolymers* **2002**, 63: 12; Wu CW, Sanborn TJ, Huang, K, Zuckermann RN; Barron AE, *JACS* **2001**, 123: 6778; Wu CW, Lee KYC, Barron AE, *PNAS*, submitted; Wu CW, Zuckermann RN, Barron AE, *JACS* **2001**, 123: 2958.



Peptoid-based mimic of SP-C, a critical component of human lung surfactant (top), and its surface pressure isotherm (bottom).



Peptoid-based mimic of magainin, a potent bactericide.