342c Non-Natural, Helical Peptoid Mimics of Lung Surfactant Protein B: Interactions with a Lipid Film

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Due to the low efficacy of current peptide therapies, there is great interest in developing non-natural oligomers that can mimic peptide activities, but that are protease-resistant, non-immunogenic, and cost-effective. One such class of molecules is peptoids, or poly-*N*-substituted glycines. Peptoids have close structural similarity to peptides, and can be designed to adopt stable, helical folds, but are essentially invulnerable to protease degradation. In our lab we are working to mimic the helical, amphipathic *N*-terminal domain of lung surfactant protein B (SP-B), which is necessary for the treatment of respiratory distress syndrome (RDS) in premature infants.

We have created helical, non-natural mimics of SP-B that have good biophysical activity *in vitro*. SP-B is a relatively small, but complex, protein containing 79 amino acids, three intramolecular disulfide bonds, and one intermolecular disulfide bond, forming a homodimer. A short, helical segment from the amino terminus ($SP\text{-}B_{1\text{-}25}$) has been shown to mimic the biophysical function of the full-length protein. The sequence patterning of our non-natural mimics is based on this segment of SP-B, retaining cationic and non-polar faces, helical secondary structure, and overall hydrophobicity. We have designed and synthesized peptoid-based SP-B mimics comprising 17-25 residues. We have further investigated the necessary design characteristics by studying peptoid dimers, mimicking the SP-B dimer that occurs naturally, as well as peptoids including a hydrophobic stretch or "insertion domain" at the *N*-terminus, found naturally in $SP\text{-}B_{1\text{-}25}$. The helicity of the peptoid and peptide mimics was determined both in organic solution and in LS-mimetic liposomes using circular dichroism. Pulsating bubble surfactometry, Langmuir-Wilhelmy surface balance experiments, and fluorescence microscopic examination of film morphology indicate that the various lipid/SP-B peptoid films exhibit surface activities comparable to that of the lipid/$SP\text{-}B_{1\text{-}25}$ films. With further study and optimization of the material, these novel synthetic lung surfactant replacement formulations may have therapeutic applicability for the treatment of RDS. *In vivo* testing of these novel compounds in animal models of RDS is ongoing.