

Research Interests:

Sickle cell disease is a blood disorder that is caused by a single point mutation in the gene coding for the β chain of hemoglobin. This mutation results in the incorporation of the hydrophobic amino acid valine in place of the polar residue glutamic acid at the sixth position in the chain. The isopropyl side chain of valine is capable of interacting with a neighboring molecule of mutant hemoglobin (Figure 1) and through these interactions results in the formation of polymeric strands that deform the red blood cell and block bloodflow through capillaries.

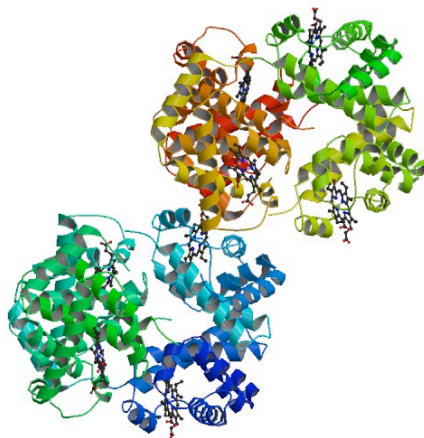


Figure 1: Interactions between sickle cell hemoglobin.¹

The current treatments for sickle cell disease typically involve the administration of pharmaceuticals that increase fetal hemoglobin concentrations in the cell. Since fetal hemoglobin contains a γ chain in place of its β counterpart, it does not contain the valine mutation and will not incorporate into polymers. Unfortunately the lack of specificity of this treatment leads to numerous undesirable side effects. As an alternative method of treating sickle cell disease I would like to discover molecules capable of binding to sickle cell hemoglobin and disrupting protein polymerization.

Recent developments in solid-phase organic synthesis have allowed for the construction of diverse chemical libraries with relative synthetic ease. A chemical library is a group of compounds that are candidates for a specific application. Through a screening approach, these libraries can be used to discover compounds capable of perturbing complex biological systems, such as the polymerization of sickle cell hemoglobin. While my initial libraries will include peptides and peptidomimetics, this approach can easily be expanded to the screening of more “drug-like” small molecules and lead to the possibility of creating a novel therapeutic for this devastating disease.

The multidisciplinary approach of this research gives students the unique opportunity to use chemistry to solve a biological problem. The mastery of techniques such as solid-phase synthesis, protein expression and purification, enzyme-linked immunosorbent assays (ELISA), and fluorescence polarization will prove invaluable as student researchers begin their scientific careers.

¹ PDB ID: 2hbs

Harrington, D. J.; Adachi, K.; Royer, W. E.

The High Resolution Crystal Structure of Deoxyhemoglobin S.

J. Mol. Biol. **272** pp. 398 (1997)