Structural Exploration of The HA-Binding Groove in CD44 Using Disaccharide Mimetics
William McCue, Soma Maitra, Gunda I. Georg, James B. McCarthy and Barry C. Finzel

CD44 is a cell surface hyaluronan (HA) binding protein implicated in a variety of different cancers because it can modulate tumor cell adhesion, growth, and therapeutic resistance. High molecular weight-HA (HMW-HA; 10^7 Da) stimulates cancer progression by binding to CD44 and activating oncogenic signals which can be inhibited using very small (<10^4 Da) HA fragments to disrupt HMW-HA/CD44 interactions. The goal of this project is to develop small molecules that selectively block binding of HMW-HA by CD44 to evaluate their potential to limit cancer progression and improve response to existing anticancer therapies.

Our previous work has confirmed that analogs containing an 8-amino tetrahydroisoquinoline (THIQ) pharmacophore bind CD44 with moderate affinity. Crystallography has shown that THIQ analogs bind near the CD44 HA binding groove, leading to the design of a series of THIQ-linked oligosaccharides predicted to extend into the binding site of HA at subsites Glc-5 and NaG-6. The THIQ should impart selectivity for CD44 over other HA-binding proteins, while computational modeling predicts increasing affinity with the addition of each additional saccharide unit to the pharmacophore. However, when a THIQ-glucuronate conjugate was synthesized and tested with our immobilized HMW-HA SPR assay, it produced no effect on CD44 binding at 10 mM. Currently, we are employing computational methods to design alternatives to the glucuronate portion so extended analogs may span the Glc-5 subsite without strain and reach into NaG-6 where additional strong interactions with CD44 are possible. A summary of recent modeling studies will be presented.