Structure-Guided Targeting of the Hyaluronan Binding Domain of CD44
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CD44 is a cell surface hyaluronan (HA) binding protein implicated in a variety of different cancers by modulating tumor cell adhesion, growth and therapeutic resistance. HA is synthesized as a high molecular weight (HMW-HA; $10^7$ Da) polymeric carbohydrate consisting of repeating disaccharides of glucuronic acid and $N$-acetyl glucosamine. HMW-HA is a major constituent of the extracellular matrix and is often present in elevated levels in cancer tissue. HMW-HA stimulates progression by binding to CD44 and activating oncogenic signals. These oncogenic signals can be inhibited using very small ($<10^4$ Da) HA fragments to disrupt HMW-HA/CD44 interactions. Therefore, the goal of this project is to limit cancer progression and improve response to therapies through the development and use of small molecules that selectively block binding of HMW-HA by CD44.

Previous work in the Finzel laboratory has confirmed that analogs containing an 8-amino tetrahydroisoquinoline (THIQ) pharmacophore can bind CD44 near the HA binding groove with moderate affinity [L.-K. Liu, B.C. Finzel. (2014) J. Med. Chem. 57:2714-25]. Visualization of THIQ analogs bound in the HA binding domain of CD44 by crystallography have substantiated the design of a series of THIQ-linked oligosaccharides that should extend into the binding site of HA. Computational modeling predicts increasing affinity with the addition of each oligosaccharide unit to the THIQ-derived molecule, while retention of the THIQ should impart selectivity for CD44 over other HA-binding proteins. The aim of our research is to prepare and evaluate some of these THIQ-saccharide conjugates in order to study their effect on cancer biology and assess their potential as possible therapeutic agents. Progress toward the preparation and characterization of the first of these conjugates will be presented.