Karen Buchmueller’s Research Group

Our research focuses on the mechanisms by which small molecules compete with proteins for DNA binding. There is little understanding of the dynamics of this competition and better understanding will aid in the development of compounds with improved ability to selectively inhibit proteins from binding to DNA. Specifically, the Buchmueller lab has focused on disrupting High Mobility Group A proteins from binding to DNA.

The high mobility group A (HMGA) family of proteins regulates a wide variety of genomic functions, including RNA transcription. This group of proteins uses a variety of different mechanisms that depend on the other proteins involved. For example, HMGA proteins bind to DNA and subsequently facilitate the binding of transcription factors. HMGA proteins bind to DNA via A/T hook motifs that recognize the minor groove of A/T rich DNA sequences.

HMGA proteins are primarily expressed during development; however, high levels of HMGA1 proteins have been detected in many adult human malignant tumors, such as pancreatic and breast carcinomas. Increased levels of HMGA1 proteins are indicators of poor prognosis for cancer patients and correspond to metastasized cancer. As a result of its involvement in late stage cancers, HMGA1s are important targets for the development of effective therapeutic anti-cancer compounds.

To develop novel, effective inhibitors of HMGA1, it is necessary to develop a thermodynamic and kinetic understanding of the competition between existing small molecules and HMGA1 proteins for binding DNA. Towards this end, we have utilized isothermal titration microcalorimetry (ITC), filter binding and fluorescence experiments. Initial studies focused on the small molecule distamycin, which also binds to the minor groove of A/T rich sections of DNA. It is not possible for distamycin and the A/T hook to simultaneously bind the minor groove of DNA. We have observed that distamycin binds to the DNA with negative cooperatively, regardless of whether the A/T hook is pre-associated with the same region of DNA. In addition to studying the thermodynamics of competition, the group is currently developing techniques to study the kinetics of competition.