Popular Science Summary

Galectins are a group of proteins that bind strongly to galactosides, which is a galactose, one type of sugar, that is connected or bound to another organic compound, which in many cases can be another sugar. Many different galectins have been discovered inside and throughout our bodies which has led to a lot of scientific and medicinal interest in galectins, and their function. What has been found is that they play a part in a wide range of biological processes where they are implicated in many diseases, such as diabetes, cancer, HIV, arthritis, and many more. Galectin-8 (abbreviated as Gal-8), as the name suggests, is a member of this protein group that is involved in multiple of diseases with ongoing research on its role in fibrosis, corneal inflammation, organ graft rejection, various cancers such as breast cancer, and inflammatory and immune diseases. Being implicated in such a plethora of disease makes it a highly interesting target for drug discovery and development.

By blocking the protein, we can stop (inhibit) the protein from carrying out its function leading to a cure or a reduction of the disease. This can be done by developing an inhibitor, which for the case of galectins, would be a drug that mimics the galactosides, “fooling” the galectin to bind to it instead of the natural galactoside, inhibiting the function of the protein. A key issue in drug development is called selectivity and it is the “promiscuity” of the drug to want to bind to other proteins other than the intended one which is something that often times should be avoided to prevent or minimize side effects of the drug. Selectivity is currently a big issue for drugs targeting Gal-8 inhibition, where the selectivity is quite poor meaning that the synthesized inhibitor is also binding to other galectins with similar affinities. This gives rise to another problem in drug development – affinity. Affinity describes how well the drug binds to the target and is defined by the dissociation constant, K_D, expressed in molars, M.

The best current Gal-8 inhibitors show good affinity, but not yet good enough, with a poor selectivity in regard to other galectins, which brings us to the aim of this thesis. Recent research on Gal-8 revealed that it has amino acids in its binding pocket different from those in other galectins. Designing, synthesizing, and testing inhibitors that bind to these amino acids would assist in solving both the selectivity and affinity issues. This was done by a combination of first studying the interactions between the protein and the inhibitor in computer models, followed by the synthesis, and testing of the compounds. A total of ten inhibitors were made with the best showing an affinity slightly worse than current Gal-8 inhibitors, but insight was gained regarding the development of future Gal-8 inhibitors. Thus, there is still some way to go before a Gal-8 inhibitor will reach the market. However, this project shone a light, albeit a small and dim one, illuminating a part of the path to the secret of potent galectin-8 inhibitors.