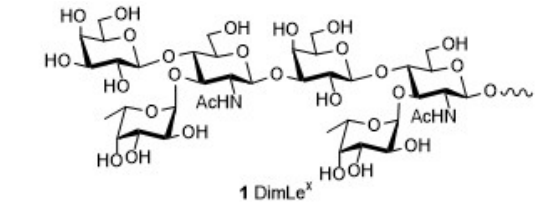
Synthesis of dimeric Lewis X fragments and mapping of mAbs SH2 and 1G5F6

France-Isabelle AUZANNEAU [1], Ali NEJATIE [1], Sinthuja JEGATHEESWARAN [1]

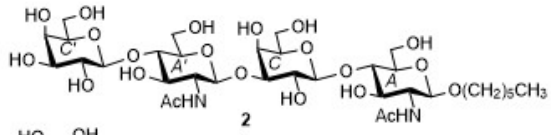
[1] Department of Chemistry, University of Guelph, Canada

fauzanne@uoguelph.ca

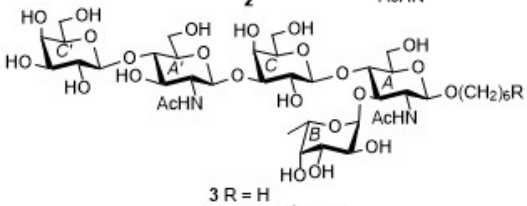
Aberrant glycosylation of tumor cell surface oligosaccharides is a universal hallmark of cancer pathogenesis. Indeed, several clinical and preclinical studies have shown that antibodies raised in response to tumor-associated carbohydrate antigens (TACAs) can eliminate tumor cells. One such TACA of interest dimeric Lewis X has been reported to accumulate in colonic and liver adenocarcinomas.[1] Although dimLe^x is tumor specific, it has been well-established that the Le^x antigenic determinant expressed at the non-reducing end of dimLe^x, was also displayed at the surface of many non-cancerous cells.[1] Interestingly, a few mAbs (SH2, 1G5F6) raised against polyfucosylated type 2 chain oligosaccharides were found to have higher affinity for polymeric Le^x structures than monomeric Le^x.[1-2] Such findings suggest that the dimLe^{x}TACA displays internal epitopes that do not involve the Le^x trisaccharide and, if identified, could be used for the development of dimLe^x-based cancer immunotherapeutics. In this context, we will describe the preparation of tetra- and pentasaccharide fragments **2-4**, which lack the non-reducing end Le^x trisaccharide. The pentasaccharide **4** was conjugated to BSA and used in ELISA titrations to assess the binding specificity of mAbs 1G5F6 and SH2.[3] We will also present some of our results mapping the epitopes of mAbs 1G5F6 and SH2 using various other fragments and analogues of Le^x and dimLe^x.[4]



1 DimLe^x



2



3 R = H
4 R = NH_3^+, AcO^-

Bibliographic references:

[1] a) S. I. Hakomori, Chem. Phys. Lipids 1986, 42, 209-233; b) A. K. Singhal, T. F. Ørntoft, E. Nudelman et al., Cancer Res. 1990, 50, 1375–1380.

[2] E. Altman, B. A. Harrison, T. Hirama, et al., Biochem. Cell Biol. 2005, 83, 589–596.

[3] A. Nejatie, S. Jegatheeswaran, F. I. Auzanneau, Eur. J. Org. Chem. 2019, 2019, 6631-6645.

[4] a) S. Jegatheeswaran, F. I. Auzanneau, J Immunol 2019, 203, 3037-3044; b) S. Jegatheeswaran, A. Asnani, A. Forman, et al., Vaccines (Basel) 2020, 8.