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Tumor Associated Carbohydrate antigens: Synthetic chemistry and molecular modelling studies

Carbohydrates constitute the most abundant class of natural products. In addition to being a source of energy, numerous oligo- and poly- saccharides have functional roles in various biological events such as cell-cell interactions, immune reactions, and molecular signaling. Specific Carbohydrate Antigens are expressed in at the surface of tumor cells, non-host cells (i.e. red blood cells in transfusions) or bacteria and can be involved in antigen specific immune responses. Such immune reactions are mostly resulting in the production of antibodies that bind specifically to a three-dimensional Carbohydrate Epitope displayed within the antigen by a di- or tri- saccharide fragment of the antigen. In that context, I am interested in the identification of such Epitopes displayed at the surface of tumor cells (TACEs) or bacteria and their use as immunotherapeutics in the fight against cancer or bacterial infection.

Here, I will describe a combination of synthetic carbohydrate chemistry and molecular modeling experiments are used to design anti-tumor vaccines based on the tumor associated carbohydrate antigens (TACAs) dimeric Le^x ($dimLe^x$) and Le^aLe^x. While it has been shown that these TACAs displayed internal epitopes that are only found at the surface of tumor cells, the non-reducing end trisaccharides (Le^x and Le^a) are also expressed on non-cancerous tissues. Thus, using the hexasaccharides as vaccine candidates carries the inherent risk of triggering an auto-immune response targeted against the terminal Le^x and Le^a antigens. To avoid such cross-reactivity, our program aims at characterizing internal epitopes displayed by the hexasaccharides as well as searching for analogues of the hexasaccharides that would not contain the Le^x or Le^a trisaccharides at the reducing end but still retain the internal epitopes found in the hexasaccharides. We will describe the synthesis of hexasaccharide vaccine candidates and that of fragments and analogues of these TACAs. We will also report our findings on the conformational behavior of the $dimLe^x$ and Le^aLe^x TACAs in solution.