Chemical synthesis of ganglioside TACAs and their conjugation to alpha-galactosyl ceramide for cancer vaccine constructs

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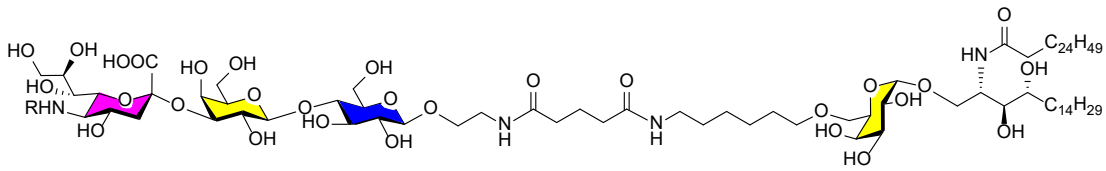
Immunotherapy is revolutionizing cancer therapy by harnessing the power of the innate and adaptive immune system against cancer cells and providing a more tumor-selective approach in assistance to traditional treatments.[1] The identification of tumor-associated carbohydrate antigens (TACAs), aberrant glycans decorating the surface of tumor cells, has paved the way for the development of TACA-based cancer vaccines.[2] TACA–based cancer vaccines have not yet reached the clinic and addressing some of the limitations that characterize classical approaches in carbohydrate cancer vaccine development can provide access to more effective candidates. In this context, iNKT cells have emerged as central players in cancer vaccine therapies. Indeed, recent reports have shown that iNKT cell-activating glycolipids, such as α-galactosylceramide (αGalCer), can enhance the immune response against co-delivered cancer antigens by stimulating iNKT cells to serve as universal T helpers.[3–5] As this strategy appears to be well-suited to break the natural immunotolerance against TACAs,[5] here we present our synthetic efforts towards the preparation of ganglioside TACAs-αGalCer conjugates, their formulation in liposomes, and their immunological evaluation *in vitro* and *in vivo*.[6] The synthesis relies on the preparation of a suitably functionalized αGalCer moiety, the expeditious preparation of ganglioside TACAs via improved reactions in sialic acid chemistry, and the conjugation of the two components to obtain novel cancer vaccine candidates.



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