Towards self-adjuvanting cancer vaccines with synthetic TACA–αGalCer conjugates

Cecilia ROMANÒ [1], Hao JIANG [1], Peng WEI [1], Sahar TAHVILI [1], Mads H. CLAUSEN [1]

[1] Department of Chemistry, Technical University of Denmark, Denmark

ceroma@kemi.dtu.dk

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. 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.

While significant progress has been made, 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 are emerging as central players in cancer vaccine therapies. Indeed, recent reports have shown that iNKT cell-activating glycolipids, such as α-galactosylceramide (αGalCer),[1] can enhance the immune response against co-delivered cancer antigens by stimulating iNKT cells to serve as universal T helpers.[2,3] As this strategy appears to be well-suited to break the natural immunotolerance against TACAs,[3]here we present our synthetic efforts towards the preparation of novel ganglioside TACAs–αGalCer conjugates, their formulation in liposomes, and their immunological evaluation.[4] Furthermore, we illustrate their application as tool compounds for dissecting the molecular mechanisms driving the action of TACA–αGalCer conjugates.

Bibliographic references:

[1]C. Romanò, M. H. Clausen, Eur. J. Org. Chem. 2022, e202200246.

[2]Y. Zhang, R. Springfield, S. Chen, X. Li, X. Feng, R. Moshirian, R. Yang, W. Yuan, Front. Immunol. 2019, 10, 11–15.

[3]F. Broecker, S. Götze, J. Hudon, D. C. K. Rathwell, C. L. Pereira, P. Stallforth, C. Anish, P. H. Seeberger, J. Med. Chem. 2018, 61, 4918–4927.

[4]C. Romanò, H. Jiang, S. Tahvili, P. Wei, U. B. Keiding, G. Clergeaud, J. R. Henriksen, T. L. Andresen, A. E. Hansen, D. Christensen, M. H. Clausen, ChemRxiv 2021