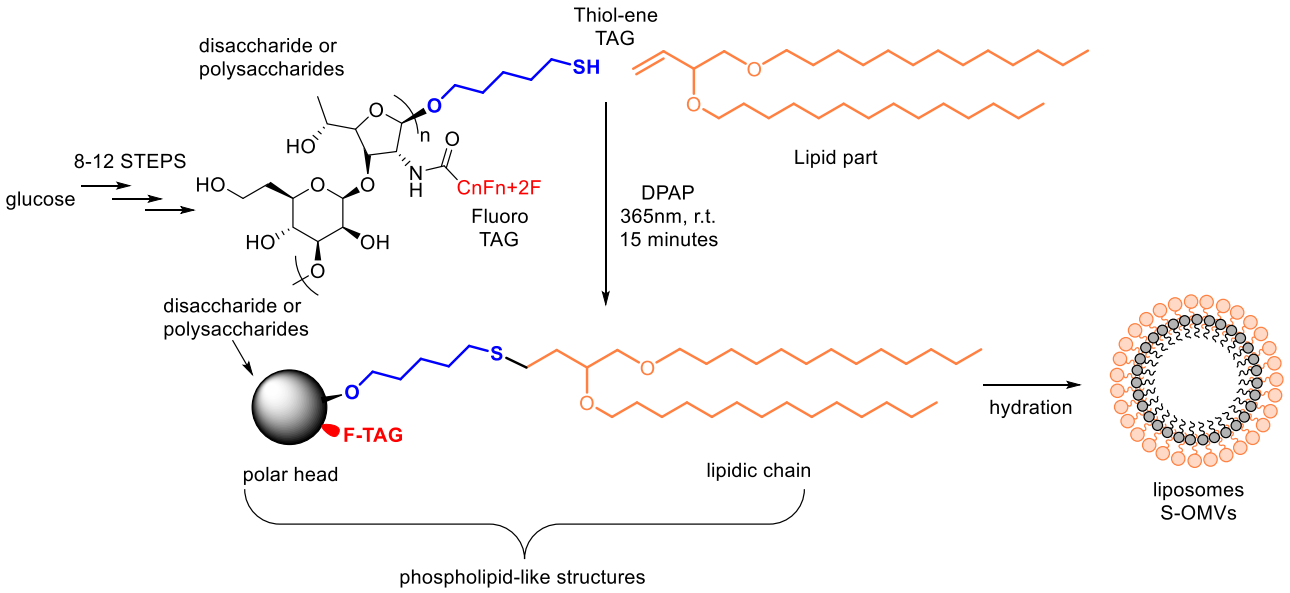
Project 2

NanoVaccines: Synthesis of defined carbohydrate antigens and immunostimulants and vaccine design using synthetic outer membrane vesicles

This research proposal aims to explore the use of nature-inspired synthetic outer membrane vesicles (s-OMVs) as vaccines or vaccine carriers for defined bacterial carbohydrate antigens and immunostimulants synthesized during the study. A critical challenge in vaccine development is the precise control over its composition. Fully synthetic vaccines based on defined carbohydrate antigens are gaining significant attention, with several currently in clinical trials or on the market. However, the formulation and architecture of their protein conjugates often remain inadequately defined, leading to potential variability in efficacy and delays in commercialization. This study proposes that synthetic outer-membrane vesicles (s-OMV), incorporating defined synthetic carbohydrate antigens and adjuvants, offer a more efficient approach to vaccine preparation and formulation, representing a substantial improvement over currently available vaccine.

In this project, we will use fluorous-tag methodology and flow chemistry to efficiently synthesize several fully synthetic bacterial carbohydrate antigens, T-cell activators, and PAMP-related adjuvants [1]. The main focus will be on creating bacterial antigens that contain heptose sugars. We aim to expand the use of fluorous tags not only for isolating synthetic intermediates but also for boosting the immune response and tracking how these components are incorporated into s-OMVs) Additionally, we will investigate how adding a heptose sugar to an oligosaccharide affects its properties. In order to incorporate these oligosaccharides, peptide T-cell activators, and adjuvants into s-OMVs, we will convert them into neoglycolipids using a photochemical biorthogonal ligation: the thiol-ene coupling (TEC) to attach them to a lipid analog.



A recent study, carried out in our laboratory, demonstrated the chemical synthesis of s-OMV prototypes, which combine phospholipids and neo-glycolipids that bear the appropriate carbohydrate structures to effectively promote immune system activation [2].

The induction of an immune response is a complex process that involves both passive and active mechanisms [2]. The key stages in immune activation include: (1) the recognition of the antigenic structure by the B-lymphocyte antigen receptor (BCRs); (2) the activation of T cells through the presentation of bacterial substructures on MHC class II molecules to the T-cell receptor (TCR); and (3) the stimulation of innate immune pathways by adjuvants containing pathogen-associated molecular patterns (PAMPs), such as TLR4 ligands. The development of these s-OMV prototypes significantly simplifies the traditionally labor-intensive conjugation and formulation processes, offering a more efficient approach for vaccine design [3].

Selected references

1. Idris Habibu Mahmud and Peter G. Goekjian. Applications of fluorous tag methodology in carbohydrate synthesis. *Carbohydr. Chem.* **2021**, *45*, 1–56.
2. a) Fayolle, D.; Berthet, N.; Doumeche, B.; Renaudet, O.; Strazewski, P.; Fiore, M. Towards the preparation of synthetic outer membrane vesicle models with micromolar affinity to wheat germ agglutinin using a dialkyl thioglycoside. *Beilstein J. Org. Chem.* **2019**, *15*, 937–946, doi:10.3762/bjoc.15.90; b) Chieffo, C.; Comte A.; Strazewski P.; Fiore M. Synthetic Outer Membrane Vesicles Bearing Tn Antigen. Eur. J. Org. Chem. **2023**, e202300820; doi.org/10.1002/ejoc.202300820
3. Pollard, A.J.; Bijker, E.M. A guide to vaccinology: from basic principles to new developments. *Nat. Rev. Immunol.* **2021**, *21*, 83–100, doi:10.1038/s41577-020-00479-7.

We are looking for a chemist with a strong background in synthetic organic chemistry and expertise in NMR analysis and characterization. Experience in carbohydrate and/or lipid chemistry is advantageous. Interest in immunology, vaccine design, and materials science is appreciated, these are not essential core competencies for the project.

Supervisor(s) name(s), Affiliation(s), eMail address(es) for contact:
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Proposed collaboration within ArchiFun network (not mandatory at this stage):

Vilnius University, Nanotemper Technologies and/or FidaBio Technologies (to be established)

Proposed list of secondments (not mandatory, but recommended if known already):

TBA

Main ArchiFun theme involved:

X Host-pathogen interactions;

Mechanisms of bacterial resistance and cancer onsets;

Neurodegenerative and autoimmune diseases;

X Translational research in prevalent diseases;

Physiology and ecology;

Neurosciences and cognition.