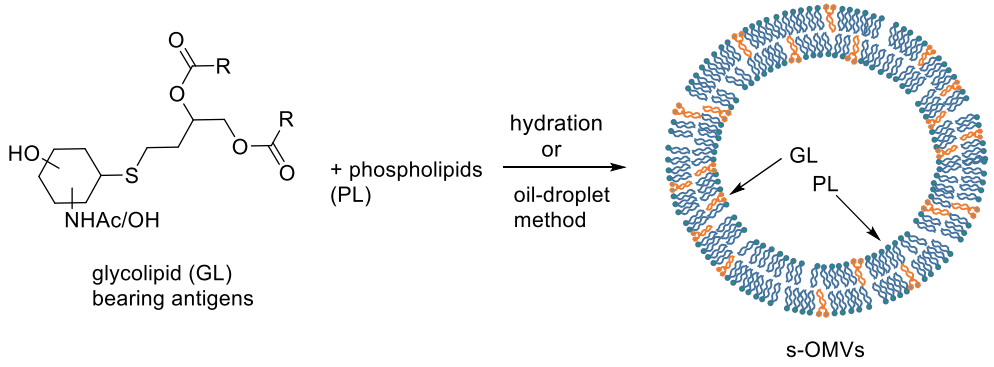
Vaccine design using synthetic outer membrane vesicles incorporating defined carbohydrate antigens and immunostimulants

Nature-inspired synthetic outer membrane vesicles (s-OMVs) will be used as vaccines or vaccine carriers. Bacterial infections and cancer represent two major causes of death worldwide. In most cases known therapies such as antibiotics, chemo- or radiotherapy are insufficient and vaccination becomes a vital alternative. The control of the composition of a vaccine is one of the main issues of their preparation. Synthetic vaccines are today of great interest and some are in early clinical stage. However, their formulation often still remains ill-defined, which slows their possible commercialization and introduces variability in individual responses. Fully synthetic vaccines based on synthetic OMVs incorporating defined, synthetic carbohydrate antigens and adjuvants, are more feasible in terms of preparation and formulation representing a significant improvement on commercially available vaccines.

A recent study reported the chemical synthesis of s-OMV prototypes combining phospholipids and synthetic glycolipids bearing the appropriate carbohydrate to promote biological activity as the stimulation of immune system[1]. Activation of an immune response involves extremely complex mechanisms and can be achieved mainly as passive or active mechanisms[2]. The key steps in immune stimulation are (1) recognition of the antigenic structure by the B-lymphocyte antigen receptor (BCRs); (2) activation of T cells by presentation of bacterial substructures on the MHC type II by the T-cell receptor (TCR); (3) activation of cellular (innate) immunity pathways by adjuvants bearing pathogen-associated molecular patterns (e.g. TLR4).



Several fully synthetic carbohydrate antigens, T-cell activators, and PAMP-associated adjuvants will be synthesized in Peter Goekjian's group using fluorous-tag methodology [3] and flow chemistry to streamline the synthesis process. We are particularly interested in extending the role of fluorous tags beyond isolating synthetic intermediates to increasing immunogenicity and monitoring s-OMV incorporation.

1. 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

2. 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.

3. Idris Habibu Mahmud and Peter G. Goekjian. Applications of fluorous tag methodology in carbohydrate synthesis. *Carbohydr. Chem.* **2021**, *45*, 1–56.

Supervisor(s) name(s), Affiliation(s), eMail address(es) for contact:

Dr Michele FIORE, UMR 5246 ICBMS, CO2Glyco, michele.fiore@univ-lyon1.fr
Prof Peter GOEKJIAN, UMR 5246 ICBMS, CO2Glyco, peter.goekjian@univ-lyon1.fr

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.