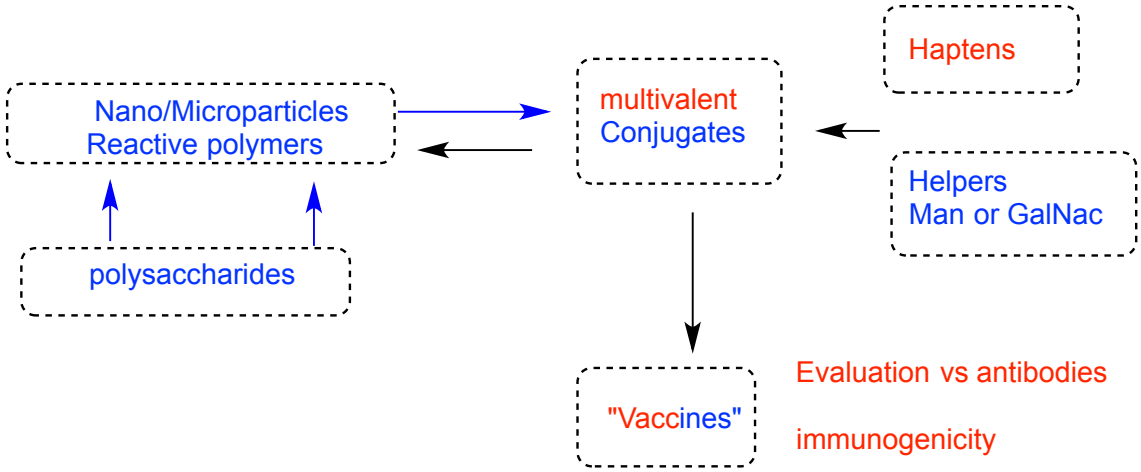
Résumé du projet de thèse = Development of Polymeric Vaccines for diarrheal pathogens

The aim of this PhD thesis project is to develop a new platform for the development of polymeric vaccines, by combining the expertise of Laurence Mulard (LM, Institut Pasteur) in synthetic carbohydrate-based and peptide-based conjugate vaccines (1) and of Jean-Maurice Mallet (JMM, LBM) in polysaccharides and polymer modifications for multivalent presentation (2).
The polymer vaccine approach (3) consists in delivering all-in-one conjugates, which feature all the components necessary to build a potent immune response. It is tackled as a possible alternative to licensed conjugate vaccines and other approaches under development such as liposome-based vaccines, whereby the different partners (key B and T epitopes, adjuvant, delivery tag…) are often simply combined. Interests in the concept include 1- the required multivalent presentation that potentiates immunogenicity, 2- the use of T-helper epitopes to avoid the risk of immunogenic interference, 3- the fixed and controlled composition, 4- the multiple bioorthogonal attachment sites, 5- the possible prolonged effect due to slower elimination. Herein, multivalency is brought in by a polymer backbone, selected in order to be degradable and non-immunogenic.

A five-step process (see figure 1) aimed at original vaccine candidates against major bacterial diarrheal diseases is envisioned:

- A library of ready-for-conjugation polymers varying in size, structure and composition will be prepared (JMM). The key problems to address include batch-to-batch reproducibility (syntheses and modifications) and the immunogenicity of the bare polymers. Biodegradable backbones to be investigated are based on polysaccharides selected primarily from dextran, starch, cellulose, and chitosan.- Indeed, we reasoned that in comparison to other classes of well-established polyester biodegradable polymers, such as polylactic acid, the advantage of polysaccharides can be summarized as follows:
  - 1/ the numerous diverse reactive groups already present (amine, acid and alcohol functions) that can be exploited to grafted active components, through adapted linkers
  - 2/ the large range of molecular weights available from commercial sources (from 10 to 500 kD).
  - 3/ the possibly to explore several polymeric constructs, from nanometric to micrometric particles, one of the critical parameters governing the quality of the induced the immune response
- Emphasis will be on ensuring the feasibility of bioorthogonal conjugation to enable different appendages.
- Relevant linker-equipped synthetic glycan haptens, representative of known protective antigens of two major diarrheal pathogens *Shigella*, especially *Shigella flexneri* (1) and *Campylobacter*, respectively; universal T helpers peptides; glycotags to address the conjugates to DC and antigen presenting cells (APC), will be prepared in various combinations (LM). Hapten, T helper peptide, and tag quantification will rely on mass spectrometry, colorimetric assays and amino acid analysis. The SF2a-TT15 vaccine candidate developed against *S. flexneri* 2a (LM (1)), will be used as reference for construct pre-optimization, followed by investigating more novel haptens. In particular, hapten combination toward a broad coverage vaccine candidate against bacterial diarrhea is the ultimate goal.



- Fig 1 General strategy for polymeric vaccines preparation (in Blue (JMM's lab) Red (LM's lab))

- The selected active components will be site-selectively covalently linked to the polymer (LM and JMM), possibly further modified with lipids, to give panels of multi-component candidate vaccines, which will then be evaluated in mice (LM).