MIMICKING THE BARRIER: SULFATED GLYCOSAMINOGLYCAN MIMETICS TO PROBE VIRAL INTERACTIONS

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Eukaryotic cells are covered by a dense layer of glycans, commonly referred to as the glycocalyx. While the glycocalyx is involved in manifold vital biological processes, such as cellular communication, protection and signalling, many pathogenic microorganisms, such as viruses, have evolved to exploit distinct components of the glycocalyx in order to infect host cells. Native glycans recognized by viruses are diverse and complex, most often containing terminating sialic acids (Neu5Ac) and glycosaminoglycans (GAGs) such as heparan sulfates (HS), making them hard to access and analyse properly.
Previous work from our lab has shown that globally sulfated glycomacromolecules as mimetics of native heparan sulfates (sGAG mimetics) can act as broadband inhibitors for viral adhesion and infection, rendering this class of synthetic sGAG mimetics a suitable tool to study virus-glycan interactions in a more controlled setting [1]. In our ongoing studies, we employ Solid-Phase Polymer Synthesis (SPPoS) and TIRP (thiol-induced, light-activated controlled radical polymerization) to prepare highly tailorable sGAG mimetics featuring key structural parameters such as site-specific glycosylation, valency, sulfation patterns as well as site-selective functional handles, e.g. lipid moieties for membrane tethering and fluorophores for probing [2,3].
Intercalation of the thusly prepared sGAG mimetics into phospholipid bilayers (e.g. GUVs) then allows us to construct highly defined models of native glycocalyces presenting sGAGs, yielding a versatile platform to study the fundamental mechanisms of viral interactions with sGAG-decorated membrane surfaces regarding e.g. ligand density, valency and spatial distribution.

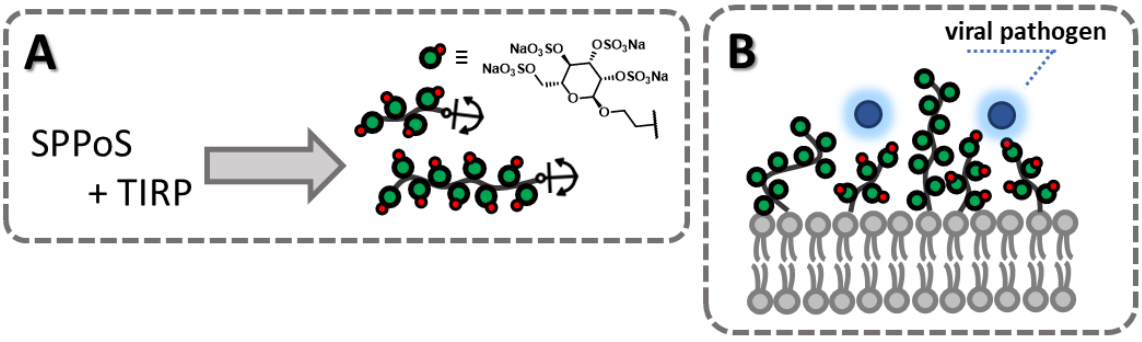

Figure 1.
A: A combination of SPPoS and TIRP yields highly tailorable sGAG mimetics, enabling precise editing of key structural parameters e.g. valency, glycosylation and lipid anchor.
B: Incorporation of sGAG mimetics into phospholipid bilayers enables the construction of glycocalyx models to study viral interactions with sGAGs.

References:
1. Soria-Martinez et al., *JACS* **2020**, 142, 11, 5252–5265.
2. Blawitzki et al., *Biomacromolecules* **2024**, 25, 9, 5979–5994.
3. Blawitzki et al. *Angew. Chem. Int. Ed.* **2025**, 64, e202414847.