Combining supramolecular chemistry, physico-chemical characterization and theoretical modeling to understand multivalent interactions at the cell-hyaluronan matrix interface

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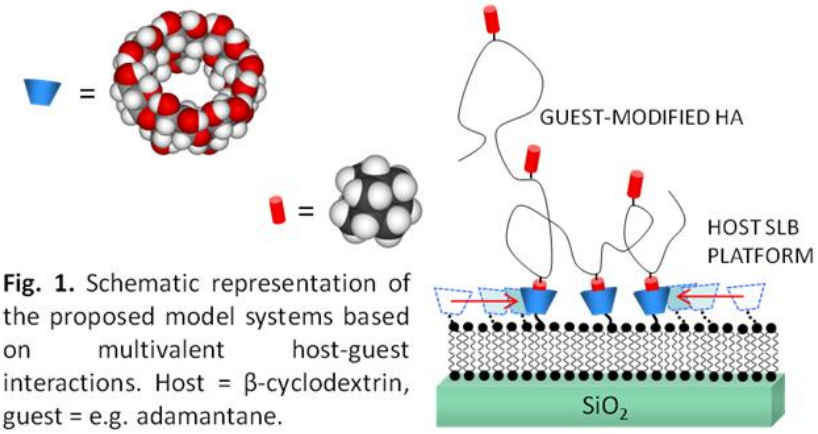

Fig. 1. Schematic representation of the proposed model systems based on multivalent host-guest interactions. Host = β-cyclodextrin, guest = e.g. adamantane.

Multivalent interactions are characterized by the simultaneous binding of multiple ligands on one entity to multiple receptors on another. Multivalency provides the basis for mechanisms of both agonizing and antagonizing biological interactions that are fundamentally different from those available in monovalent systems. Even though multivalent interactions occur broadly in biological systems, they are still poorly understood and assaying them remains a fundamental challenge.

We propose a new approach to reveal the mechanisms underlying multivalent interactions at cell surfaces. We apply this approach to the investigation of the hydrogel-like matrices that are rich in the polysaccharide hyaluronan (HA) and surround many cell types. The supramolecular organization of the HA-rich matrix and its attachment to the cell surface has been associated to a variety of cellular functions and numerous biological processes, including fertility, inflammation and cancer. Our goal is to understand how multivalent interactions regulate the attachment of HA to the cell surface and the physico-chemical properties of HA-rich matrices, and how these mechanisms are connected to biological functions.

To this end, we develop highly controlled and tunable in vitro model systems that are based on multivalent host-guest interactions. In these model systems, purpose-designed HA and solid supports are equipped with host/guest functionalities using modern synthetic and surface chemistry (Fig. 1). The binding of HA to the supports and physico-chemical properties of HA-rich matrices will be interrogated using a toolbox of surface-sensitive biophysical techniques. Theoretical simulations will help to obtain mechanistic insights into the regulation of multivalent interaction at the cell-HA matrix interface.