Targeting macrophage polarization states for precision immunotherapy

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Macrophages are crucial immune system components, safeguarding our tissues from external threats such as injuries, toxins, and infections [1]. When faced with an insult, resident macrophages initiate the inflammatory process, transitioning from a resting state (M0) to an activated state and changing their effector function into a pro-inflammatory (or M1) and anti-inflammatory (or M2) phenotype [2]. This dynamic activation of macrophages plays a pivotal role in disease progression and can lead to unresolved inflammation if impaired. To address this, macrophage-targeting nanomedicines have emerged as a revolutionary approach for treating a wide range of human diseases, including infections, chronic inflammatory disorders, neurodegenerative diseases, and cancer. Traditionally, targeted strategies have relied on high-affinity ligands like antibodies. However, these interactions can lead to indiscriminate targeting of any cell expressing the corresponding receptor, resulting in a loss of selectivity. One strategy to overcome such a challenge involves employing low-affinity ligands within a multivalent scaffold, thereby achieving super-selectivity [3]. This approach relies on the collective effect of individual affinities, ensuring that associations only occur when receptors are expressed at specific densities, effectively targeting cells expressing the desired receptor while minimizing non-specific interactions. We propose using engineered polymer-based self-assembled nanoparticles (polymersomes) where multiple ligands are expressed alongside polymers that prevent non-specific interactions and act as steric modulators [4]. In vitro experiments show that nanoparticle binding to the cell surface is non-linear, dependent on the number of ligands present. This behavior allows for identifying an optimal ligand density, creating on-off association profiles that enable precise targeting of specific macrophage phenotypes. Through this approach, we can achieve phenotypic targeting of macrophages while enhancing selectivity and therapeutic efficacy.

References

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Figures

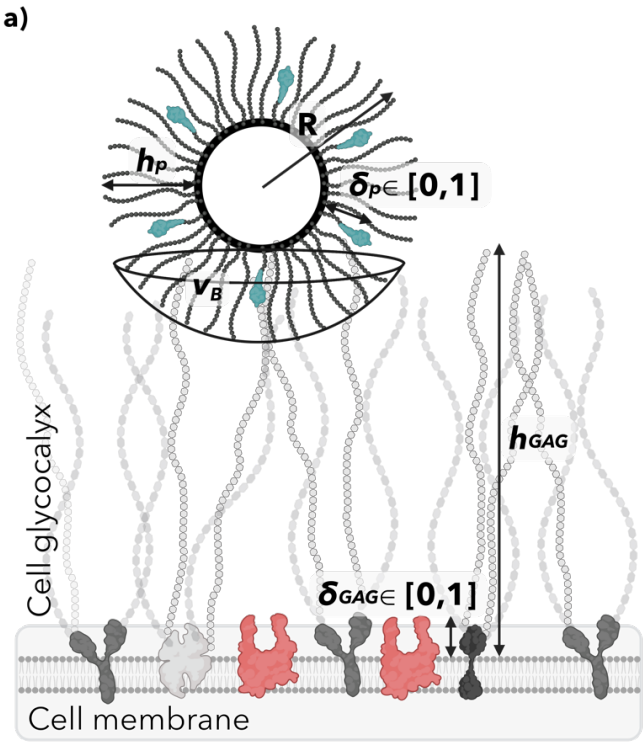

Figure. Nanoparticle (NP) - cell interaction. a) The multivalent system is described by the NP topology, size (radius, R), number of ligands, and length of the ligand tether with respect to the polymer brush length, h_P, given by the polymer inference parameter, δ_P. The target, the cell, is relatively larger that the NP, hence considered as a flat surface with a density of receptors (targeted receptors and glycans) that characterizes the cell phenotype. NP effective binding to the cell requires high avidity associations that can overcome the repulsive forces arising from the NP polymer brush and from the sugar-rich cell membrane brush, the so called glycocalyx that can reach an extension of a hundred nanometers long, h_{GAG}. Abbreviations. V_B: Binding volume. δ_{GAG}: