Bioinspired Engineering of Surface Coatings for Protein Corona Control

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Nanoparticles have emerged as highly versatile platforms in modern biomedicine, offering unprecedented opportunities for drug delivery, imaging, diagnostics, and therapeutic interventions. Their tunable size, shape, and surface chemistry allows researchers to engineer materials capable of navigating complex biological environments with precision. However, despite their enormous potential, a major challenge arises the moment these nanomaterials encounter biological fluids. Upon contact with serum, plasma, or any protein-rich medium, their surface becomes rapidly covered by a dynamic layer of adsorbed proteins and biomolecules known as the *protein corona* . This corona effectively redefines the nanoparticle's biological identity, influencing its colloidal stability, cellular uptake, biodistribution, immune recognition, and overall bioactivity. In many cases, the formation of an uncontrolled corona leads to loss of targeting ability, accelerated clearance, or unexpected biological responses, which has driven intense efforts to develop reliable "stealth" or antifouling surface strategies.

A wide range of antifouling strategies has been explored to control protein corona formation, including peptide-based coatings, zwitterionic polymers, and hydrophilic polymer layers designed to minimize nonspecific adsorption. However, we propose a different approach: looking directly at nature, and specifically at the complex surfaces of endogenous proteins. These biomolecules present heterogeneous charge distributions and well-defined domains that allow them to travel through the bloodstream while avoiding nonspecific interactions with other proteins and biomolecules. Inspired by this natural design, we aim to mimic the charge balance of human serum albumin (HSA) surface (the most abundant protein in plasma) by combining PEG-SH molecules functionalized with amino, carboxyl, and methoxy terminal groups. [1]

Since protein corona formation is strongly influenced by multiple physicochemical and environmental factors, we aimed to evaluate the generality and robustness of our biomimetic coating by systematically varying several key parameters. For this purpose, we studied corona formation on gold nanoparticles while modifying i) the overall surface charge, ii) nanoparticle curvature [2] , iii) particle shape, iv) PEG chain length, v) the biological environment (including exposure to isolated proteins such as HSA and γ-globulin, human serum, and plasma), and vi) flat gold surfaces. Corona formation was characterized by using TEM, DLS, QCM, and UV-VIs

Our results shed light on the curvature, chain length, and shape of nanoparticles as relevant parameters influencing the protein corona inhibition. They reveal a markedly drastically enhanced stealth behavior in nanoparticles coated with the biomimetic PEG system, while demonstrating significantly reduced protein adsorption across a wide range of conditions. These findings deepen our understanding of structure–property relationships in biomimetic surface engineering and highlight the potential of charge-balanced, protein-inspired coatings as a broadly applicable strategy for next-generation biomedical nanomaterials.

Keywords:
Biomimicking, protein corona, nanoparticles, stealth, and antifouling surfaces.

References:

[1] *ACS Nano* **2023** , 17, 955-965
[2] *Bioconjugate Chem.* **2017** , 28, 88-97