Title: Exploring the impact of protein–nanoparticle interactions in human blood

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Abstract: Understanding the interactions of nanoengineered particles with specific proteins and cells is necessary to unlock their medicinal utility. Upon exposure to biological fluids, nanoparticles adsorb proteins, lipids and nucleic acids, resulting in the formation of a "biomolecular corona". This corona modulates downstream biological responses, including recognition by immune cells. Resolving the complexity of human plasma has been a major barrier to understanding the role of corona on biological response. We have previously investigated the formation of personalized biomolecular coronas on particles using plasma from a cohort of healthy donors and their impact on particle–immune cell interactions using an ex vivo human blood assay (ACS Nano 2020, 14, 15723). We demonstrated that the enrichment of immunoglobulins and complement proteins in biomolecular coronas is correlated with donor-specific nanoparticle association with human blood immune cells. We further demonstrated that the protein corona composition can be modulated by particle building blocks (*ACS Nano* **2021,** *15*, 10025) and protein pre-coatings (*J. Mater. Chem. B* **2022**, *10*, 7607). Built on the previous works, we have recently studied the boost of poly(ethylene glycol) (PEG)-specific antibodies by SARS-CoV-2 mRNA lipid nanoparticle (LNP) vaccines. After studying plasma samples from 130 adults, we discovered that anti-PEG antibodies were significantly boosted by mRNA-1273 vaccine and to a lower extent by BNT162b2 vaccines (ACS Nano 2022, 16, 11769). We found that anti-PEG antibodies have a significant impact on PEGylated nanoparticle−immune cell interactions in human blood. Our study addresses timely and important questions regarding the anti-PEG antibody responses in healthy adults following SARS-CoV-2 mRNA-LNP vaccination and whether the induced anti-PEG antibody may impact the fate of other PEG-containing nanomedicines (Nat. Rev. Immunol. 2023, 23, 135).

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