In situ detection of the protein corona in complex environments

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Colloidal nanoparticles (NPs) may undergo drastic changes *in vivo* by the formation of a protein corona [1]. The dynamic development of protein corona formation has been studied extensively by mass spectroscopy or other techniques. Such measurements have been performed in relevant solutions such as blood4, which, however, requires extraction of the NPs and removal of unbound excess proteins, leading to a loss of the equilibrium properties. Alternatively, protein corona formation can be observed based on measuring the associated increase in the NPs' hydrodynamic radius and reduction in diffusion coefficient. In case only protein–NP complexes, but no free proteins, are subject to diffusion coefficient measurements, protein corona formation can be quantified *in situ*, without removal of excess proteins. Several optical methods, such as fluorescence correlation spectroscopy (FCS) or depolarized dynamic light scattering (DDLS), have been established for *in situ* quantification based on diffusion coefficient measurements. However, in complex media such as blood or even tissue, optical detection suffers from light scattering. Unfortunately, the *in vivo* corona cannot be completely emulated by the corona formed in blood. Thus, *in situ* detection in complex media, *i.e.*, ultimately *in vivo*, is required. In this work, we present a non-optical methodology for determining protein corona formation in complex media. NPs are labeled with ^{19}F and their diffusion coefficient is measured using ^{19}F diffusion nuclear magnetic resonance (NMR) spectroscopy, recording a diffusion-ordered nuclear magnetic resonance spectroscopy (DOSY) experiment [2]. Herein we propose the use of ^{19}F diffusion NMR to observe changes in hydrodynamic radius of NPs upon adsorption of proteins in solution and also in complex media such as blood. For this purpose, three types of Au NPs labeled with fluorinated polyethylene glycol (PEG) ligands were synthesized. Two of them contained additional PEG chains bearing either $–CO_2H$ or $–NH_2$ head groups and the third type was further coated with poly(isobutylene–alt-maleic anhydride) (PMA), which in water also presents $–CO_2H$ groups at its surface. The diffusion of these nanoparticles was studied in the presence of several proteins, blood, plasma and cells.

References

[1] C. Carrillo-Carrion, M. Carril, W.J. Parak, Curr. Op. Biotech., (2017) 106.
[2] M. Carril, D. Padro, P. del Pino, C. Carrillo-Carrion, M. Gallego, W.J. Parak, Nat. Commun., (2017) 1542.

Figures

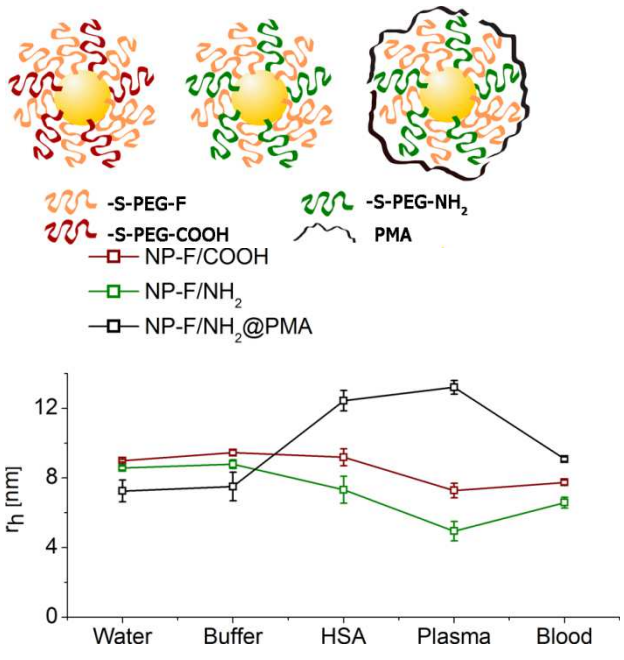

Figure 1: Illustration of the ^{19}F-labeled NPs and size measurements in different media.