Single nanoparticle analytics: from viruses via exosomes to drug delivery carriers

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Biological nanoparticles such as viruses, extracellular vesicles and exosomes are generating a rapidly growing interest due to the key roles they play in various biological processes and because of their potential use as biomarkers in clinical diagnostics and as efficient carriers in drug-delivery and gene-therapy applications. A large set of tools with single-nanoparticle sensitivity is now available, to which we recently contributed a concept that enables simultaneous fluorescent and scattering-based label-free imaging of surface-bound biological nanoparticles [1]. Examples will be shown that illustrates the use of scattering microscopy to i) investigate supported lipid bilayer formation, ii) label-free measurements of protein binding to individual liposomes and iii) characterize DLVO-controlled non-specific interactions at cell-membrane mimics.[2] Further, with this setup, the fluorescence and scattering intensity of surface-bound nanoparticles can be very precisely determined, but their individual size remains unknown. The size of individual biological nanoparticles can instead be determined by tracking their 3D motion in a bulk solution, using e.g. nanoparticle tracking analysis (NTA). However, due to the random motion of nanoparticles through the illumination volume, NTA does not offer reliable information about their individual scattering and fluorescence intensity. Hence, either the size or emission intensity of nanoparticles can be determined, not both. Since the combination of size and content is decisive for many functions tailored into nanoparticles, this is a severe analytical limitation. By replacing water as the mobile phase, as used in NTA, for a two dimensional fluid supported lipid bilayer, to which biological nanoparticles are directly anchored and imaged, we have developed a new means to simultaneously determine both nanoparticle size and fluorescence / scattering intensity,[3] which may potentially offer flow-cytometry-like sorting based on distinct features of individual nanoparticles. This 2D flow nanometry concept will be discussed in the context of improved characterization of individual nanoparticles of diagnostic and therapeutic significance.

1. ”Evanescent Light-Scattering Microscopy for Label-Free Interfacial Imaging: From Single Sub-100 nm Vesicles to Live Cells.” Agnarsson, B.; Lundgren, A.; Gunnarsson, A.; Rabe, M.; Kunze, A.; Mapar, M.; Simonsson, L.; Bally, M.; Zhdanov, V. P.; Hook, F., *ACS Nano* 2015, 9, 11849 (2015).

2. ”Nonspecific Colloidal-Type Interaction Explains Size-Dependent Specific Binding of Membrane-Targeted Nanoparticles.” Lundgren, A.; Agnarsson, B.; Zirbs, R.; Zhdanov, V. P.; Reimhult, E.; Hook, F., *ACS Nano* 2016, 10, 9974 (2016).

3. “Two-dimensional flow nanometry of biological nanoparticles for accurate determination of their size and emission intensity.” Block, S.; Fast, B. J.; Lundgren, A.; Zhdanov, V. P.; Hook, F., Nature Communication 7, 12956 (2016)