Interactions of nanoparticles and block copolymers with lipids in bilayer membranes

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Introduction

Nanoparticles (NPs) and polymers are being developed for next generation medical therapies. These materials can be used to target the delivery of drugs to specific cells or tissues, or as highly sensitive image contrast agents in medical diagnostics. The engineering parameter space of these novel materials is vast and so it is essential to develop a fundamental understanding of the interactions between nanomaterials and biological systems to guide material optimisation for a given application. Cellular complexity dictates that minimal model systems are required to gain detailed understanding of interaction mechanisms. We focus our work on investigating the interactions of NPs with lipid bilayers, the structural matrix of the cell's plasma membrane and gateway to the cell's internal biochemistry.

Reconstituted lipid vesicles, whilst mimicking biomembranes, also have many technological applications including drug delivery, biosensors, food and cosmetics. Hybrid materials often have many functional advantages over unitary systems: we are therefore interested in exploring the structure and properties of hybrid lipid-polymer and lipid-NP composites.

Nanoparticle – membrane interactions

We have recently explored the NP size-dependence in the interaction between silica NPs and phospholipid bilayers in the form of giant vesicles (GUVs). Silica NPs are currently being developed as drug delivery vehicles due to their inherant ability to cross membranes and enter cells. We found the interaction mechanism is strongly size-dependent (Fig. 1). Small (18 nm) NPs adsorb on the membrane, condensing the lipids and rigidifying the bilayer. The resultant stress induced within the membrane is released through formation of a microscale pore.

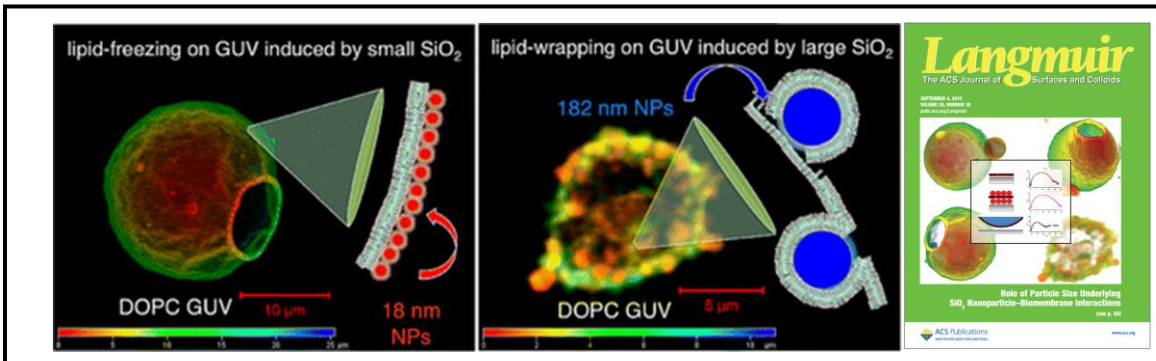

Figure 1: small (18 nm) NPs adsorb on the membrane and cause the lipids to condense. The resultant stress caused by "freezing" of the membrane is released by the formation of a microscale hole in the bilayer (*left*). Conversely, larger (182 nm) NPs are wrapped by the lipid bilayer causing membrane invaginations reminiscent of endocytosis (*centre*). This work featured on the cover of the September 4th 2012 edition of *Langmuir* (*right*).

Larger NPs (182 nm) are wrapped by the membrane and deplete lipid through a passive mechanism reminiscint of active endocytosis processes in cells. Fluorescence recovery after photobleaching (FRAP) studies demonstrate a reduced fluidity in the lipid bilayer of 1-2 orders of magnitude after interaction with 18 nm silica NPs but a slight increase in lipid mobility induced by the wrapping mechanism from larger NPs. A simplified theoretical model was used to explore the NP-membrane interaction in terms of the adsorption energy of the NP on the membrane and the bending mechanics of the lipid bilayer. This model predicts a cross-over in interaction mechanism for NPs in the size range ~30-40 nm, consistent with

our experimental findings. This suggests that the competition between these two energetic processes encompasses the key underlying physics in this NP-membrane interaction.

Hybrid lipid – diblock copolymer vesicles

We have demonstrated the ability to create hybrid bilayer membranes composed of phospholipids and amphiphilic diblock copolymers. These materials combine the inherent biocompatibility of liposomes with the robust mechanical strength of synthetic polymersomes. We anticipate that these versatile, composite materials will find many uses in biotechnology and nanomedicine. We have formed GUVs with well-mixed membranes composed of the block copolymer poly(butadiene-b-ethylene oxide) (PBd-PEO) and the common phospholipid POPC. The mechanical moduli and fluidity of these hybrid membranes vary with the relative composition of these two components, affording a broad range of tune-ability for vesicle properties.

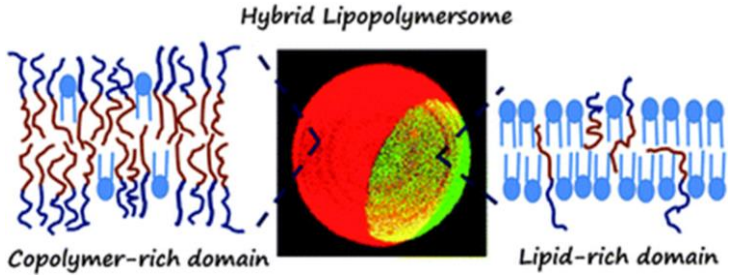

Figure 2: hybrid giant vesicles were formed from the diblock copolymer PBd-PEO and mixture of phospholipids and cholesterol. Well mixed membranes could be formed that, under appropriate conditions of temperature and composition, phase separate into coexisting lipid-rich and copolymer-rich domains.

Textured, hybrid vesicles can be created by phase separation of lipids into liquid-ordered or solid-like phases (Fig. 2). Domain morphology can be controlled via cooling rate and the nature of the particular phase formed by the lipids. Lipid-active membrane perturbants (e.g. cyclodextrin, phospholipases) can be used with these textured, hybrid vesicles to dissolve or otherwise remodel the lipid domains, or to initiate controlled release of the vesicle's encapsulated contents.

Publications

Nam, J., Vanderlick, T. & Beales, P. (2012) Formation and dissolution of phospholipid domains with varying textures in hybrid lipo-polymersomes. *Soft Matter* **8:** 7982-7988.

Zhang, S., Nelson, A. & Beales, P. (2012) Freezing or wrapping: the role of particle size in the mechanism of nanoparticle-biomembrane interaction. *Langmuir* **28:** 12831-12837.

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Collaborators

External: T. K. Vanderlick, Yale University. J. Nam, Amore Pacific Corporation.