## P.31 Key factors regulating the mass delivery of macromolecules to model cell membranes: gravity and electrostatics

R A Campbell[1], E B Watkins[1], V Jagalski[2], A Åkesson-Runnsjö[2] and M Cárdenas[2]

[1]Institut Laue-Langevin, France, [2]Department of Chemistry, University of Copenhagen, Denmark

An immense research effort has been invested to understand the mechanisms of interactions between macromolecules and cell membranes.[1] Positively charged macromolecules can be recruited into the cell by the endocytosis pathway and then trafficked by different organelles according to their charge.[2] A key challenge is to develop drug delivery systems involving the efficient transport of therapeutic agents to lipid membranes.[3] One approach is to position reservoirs of the drug in contact with the membrane for continuous delivery by slow diffusion.[4] In this case the drug may be encapsulated into aggregates of lyotropic phase,[5] providing a way to reduce dosages and the frequency of injections administered to patients.

Here we show that both gravity and electrostatics are key factors regulating interactions between model cell membranes and self-assembled lamellar aggregates of dendrimers and phospholipids. The system is a proxy for the trafficking of reservoirs of therapeutic drugs to cell membranes for slow diffusion. Neutron reflectometry measurements were carried out on supported lipid bilayers of varying charge and on hydrophilic silica surfaces. Using a novel approach, we made measurements both above and below the bulk liquid to highlight effects of bulk phase separation and gravity on the interfacial properties. Translocation of the macromolecule across the membrane and adsorption of the lamellar aggregates occur only when the membrane (1) is located above the bulk liquid and (2) has sufficient negative charge. The directionality effects were dramatic and we seek to emphasize their effects to researchers involved in biochemical investigations of complex formulations in the future. Further, our findings indicate the potential to switch on the interaction mechanism through tuning the charge of the aggregates to activate endocytosis pathways on specific cell types, which we discuss in the context of future targeted drug delivery applications.

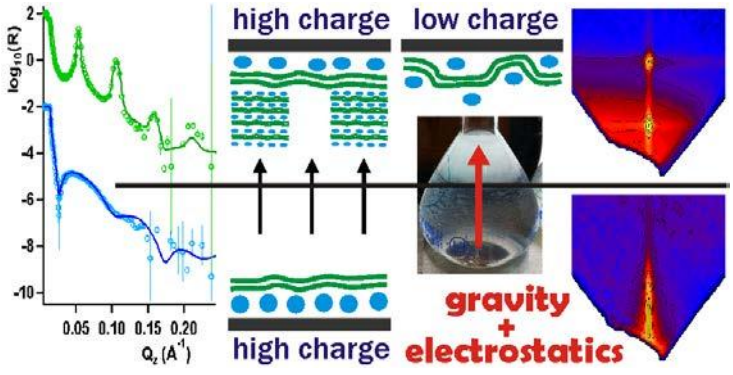


Figure. Left. The unique solid/liquid/solid interface designed specifically for this study. Right. Table-of-contents image from our publication in *ACS Macros Letters* from January 2014.[6]

[1] Leroueil, Hong, Mecke, Baker, Orr & Banaszak Holl *Accounts Chem. Res.* 2007, *40*, 335
[2] Yeung, Gilbert, Shi, Silvius, Kapus & Grinstein *Science* 2008, *319*, 210
[3] Faraji & Wipf *Bioorg. Med. Chem.* 2009, *17*, 2950
[4] Esposito, Cortesi, Drechsler, Paccamiccio, Mariani, Contado, Stellin, Menegatti, Bonina & Puglia *Pharm. Res.* 2005, *22*, 2163
[5] Bitan-Cherbakovski, Libster, Aserin & Garti *J. Phys. Chem. B* 2011, *115*, 11984
[6] Campbell, Watkins, Jagalski, Åkesson-Runnsjö & Cárdenas *ACS Macro Lett.* 2014, *3*, 121