

## PLL-g-PEG/PEG-mannose functionalized nanogels for cell-receptor-targeted drug delivery application

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**INTRODUCTION:** Polymeric nanoparticles are receiving considerable attention for several biomedical applications, including delivery of therapeutic drugs and gene delivery.<sup>1-4</sup> They hold a large potential in medicine, especially if biofunctionalities can be linked to their surface.<sup>5,6</sup> The purpose of this work is to develop sugar-functionalized nanoparticles for targeted drug/gene delivery mediated via C-type lectin receptors, e.g. DC-SIGN or mannose binding lectins, known to recognize oligosaccharides.

**METHODS:** Nanoparticles were prepared from a polycationic graft copolymer poly(L-lysine)-graft-poly(ethylene glycol) (PLL-g-PEG) through electrostatic interactions with negatively charged gelling crosslinkers, eg. hyaluronic acid. The ratio of the cationic polymer to the crosslinker was varied in order to obtain series of nanogels with different sizes. Graft copolymers with different lysine to PEG grafting ratios (g) were also used to vary PEG density, molecular weight and the positive charge density of the copolymer. Functional nanogels were then prepared using PLL-g-PEG conjugated with mannosides. The particles were characterized with regard to their size distribution and surface properties by means of dynamic laser light scattering and laser-Doppler anemometry, respectively. The size and particle morphology were also measured by atomic force microscopy (AFM).

**RESULTS:** The developed nanoparticles were in the size range of 100-500 nm. The zeta potentials were positive (between 10 and 30 mV) decreasing as the concentration of the hyaluronic acid was increased in the nanocomposites. The PEG grafting ratios of the copolymer influenced the zeta potential values, with the particles prepared from polymers with higher degree of PEGylation being less positive than the more open-structure ones. These results were also supported by AFM measurements that revealed the morphology of the particles to have a dense crosslinked central core (Figure 1). The stability of the nanoparticles was studied in water and in CaCl<sub>2</sub> for 2 weeks and 2 months after preparation. Cytotoxicity tested with macrophages *in vitro* decreased with increasing

PEG density demonstrating that the PLL charges become shielded by a PEG corona.

In the same way mannose functionalized nanogels were produced. The availability of the carbohydrate ligand for controlled cell uptake will be carried out via specific interaction with a model plant lectin and using different cell lines. Potential applications of DNA loaded particles for gene transfection are currently investigated.

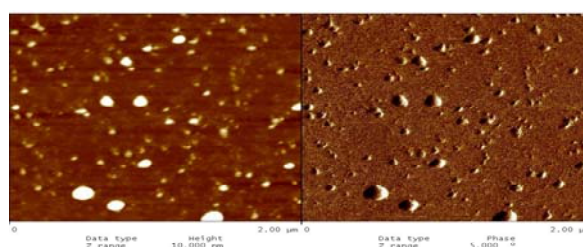


Fig.1 AFM micrograph ( $2 \times 2 \mu\text{m}^2$ ) of PLL-g[18.1]-PEG based nanogels crosslinked with hyaluronic acid (3/1 ratio).

**DISCUSSION & CONCLUSIONS:** The preparation of PLL-g-PEG/PEG based nanocomposites is feasible in a controllable and reproducible fashion. The methodology for the preparation of nanogels is straightforward, and would open up simple ways to design drug and gene delivery carriers or for the delivery of antigens to mediate specific immune response. The potential application of the platform using mannoside-functional polymers to target cell receptors on various human monocyte cell lines for gene delivery is currently under evaluation.

**REFERENCES:** <sup>1</sup>L. L. X. Yuan, A. Rathinavelu, J. Hao, M. Narasimhan, M. He, V. Heitlage, L. Tam, S. Viqar, M. Salehi, *J. Nanosci. Nanotech.* 6, 2821-2828 (2006). <sup>2</sup>A. A. S. Patnaik, S. Nimesh, A. Goel, M. Ganguli, N. Saini, Y. Singh, K.C. Gupta, *J. Controlled Release* 114, 398-409 (2006). <sup>3</sup>C. R.-L. P. Calvo, J.L.Vila-Jato, M.J.Alonso, *J. Appl. Polym. Sci.* 63, 125-132 (1997). <sup>4</sup>F. C. F. Qian, J. Ding, C. Yin, *Biomacromolecules* 7, 2722-2727 (2006). <sup>5</sup>A. R. S.T. Reddy, H.G. Schmoekel, J.A. Hubbell, A. Melody, *J. Controlled Release* 112, (1), 26-34 (2006). <sup>6</sup>S. P. J.M. de la Fuente, *Biochim. Biophys. Acta* 1760, 636-651 (2006).