Temperature for tuning the surface of hybrid nanogels

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In the design of a thermoresponsive polymer hydrogel, the poly(N-isopropylacrylamide), p(NiPAAm), moiety is often included. Its lower critical solubility temperature (LCST) displayed in water is close to the physiological temperature and is used to obtain a "smart" structural responsivity, consisting in the hydrogel shrinking [1]. However, in a hybrid network, the presence of other components is equally important in determining the overall hydrogel behaviour. In this respect, hyaluronic acid (HA), the co-participant with p(NiPAAm) in this hybrid nanogel, is known to be stable, biodegradable, and able to interact preferentially with tumour cells overexpressing integrins, thus adding a huge therapeutic value to the construct. In this framework, we recently realized nanosized, chemically cross-linked, HA-p(NiPAAm) hydrogel particles, in which HA is derivatized with azyde-bearing side chains and "clicked" with a telechelic p(NiPAAm) synthetized by reversible addition-fragmentation chain transfer, RAFT, and bearing terminal alkyne groups [2].
In this contribution, we highlight the peculiar temperature behaviour of the HA-p(NiPAAm) hybrid nano-hydrogels in connection to their biomedical relevance. Photon correlation and z-potential spectroscopies show that at 25°C the nanogel particles have a size of ~150 nm. Around a temperature of 33 °C, in the place of the expected shrinking, a change of the surface properties of the hybrid HA-pNiPAAm nanogel particles occurs. In particular, we observe a dramatic change of the zeta-potential of the water-hydrogel particles, suggesting a prevalence of HA at the surface and a transfer of p(NiPAAm) in the core of the nanogel particles. This process was monitored by small angle neutron scattering (SANS) and atomic force microscopy (AFM) to corroborate such hypothesis and to give a further detailed description of the process at the nanoparticle interface. We found that that below LCST the particles surface is biphasic and patchy (**Fig. 1**), probably reflecting a limited compatibility between the two polymer components. Approaching the temperature of 33°C, the particles form clusters, which break apart once they reach physiological temperature, where they exhibit a smoothest surface of almost only HA. Moreover, we demonstrated that such a reorganizational process of the nanogel surface has remarkable fallout in terms of selective targeting of anticancer drugs in tumour cells. In particular, the delivery of doxorubicin drug via the HA/p(NiPAAm) nanogel particles reduced by 50% the viability of HT 29 tumour cells with respect to healthy fibroblasts NIH3T3.

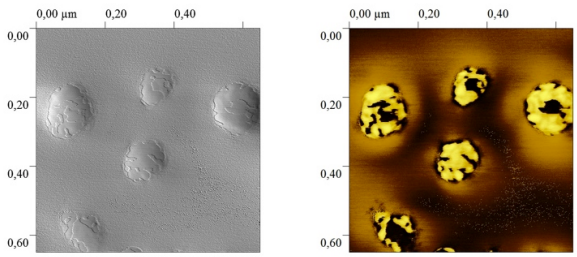

Fig. 1. Tapping mode AFM topography (left side) and phase images of HA-pNiPAAm nanogels laid on a flat silicon surface in water condition.

References

[1] Hamner, K. L.; Alexander, C. M.; Coopersmith, K.; Reishofer, D.; Provenza, C.; Maye, M. M. *ACS Nano* 2013, 7, 7011. [2] Cerroni B. et al, *Biomacromolecules* 2015, 16, 1753.