**The Use of Self-Immolative Polymers to Tune Nanoparticle/Biological Interactions**

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Introduction.Nanoparticle carriers have potential to enhance delivery of biological therapeutics by directing release to specific cells or tissue. However, nanoparticles are still limited by inefficient delivery to target regions within the cell. One of the key limitations for the delivery of biological therapeutics such as DNA or proteins is delivery to the cytosol. It is well known that nanoparticles are internalised into acidic, cellular compartments (lysosomes/endosomes) and need to efficiently escape from this region to be effective.1 To design such materials one interesting pH responsive polymer is poly(2-(diethylamino)ethyl methacrylate) (PDEAEMA), as it undergoes a transition from hydrophobic to hydrophilic in a pH range consistent with endosomal compartments. Nanoparticles using this polymer have shown the potential to facilitate endosomal escape based on pH induced change in the nanoparticle structure. Another emerging polymer with potential application in delivery systems is self-immolative polymers, which undergo depolymerisation after cleavage of a responsive end-cap. There are limited studies using such polymers as nanoparticle carriers and thus there is little information about endosomal escape capabilities. This presentation will report the synthesis of charge shifting nanoparticles and charge-shifting/self-immolative nanoparticles and investigate their response to pH. The interactions of the nanoparticles with their biological environment will also be discussed.

Results and Discussion. Charge-shifting nanoparticles were synthesised by the combination of a poly(ethylene glycol)-b-poly(2-(diethylamino)ethyl methacrylate (PDEAEMA) block copolymer with a random copolymer comprised of different mol ratios of charge shifting monomers, 2-(diethylamino)ethyl methacrylate (DEAEMA) and 2-(diisopropylamino)ethyl methacrylate (DPAEMA) (1:0, 3:1, 1:1, 1:3 and 0:1) using nanoprecipitation. It was shown the pH of disassembly could be tuned from pH 4.9 to pH 7.2 by the pKa of the random copolymer.2 In addition, an interesting trend of endosomal escape was observed across the particle library. Highest escape (>60%) was observed with nanoparticles that disassembled at either extreme of pH, e.g. DEAEMA particle (1:0) at pH 7.2 and the DPAEMA particle (0:1) at pH 4.9. In contrast there was minimal endosomal escape for 1:1 DEAEMA: DPAEMA (pH 6.2). To design nanoparticles that combined charge-shifting and self-immolative properties, the random copolymer that formed the core was replaced with a poly(ethyl glyoxylate) variant. It was shown that these particles disassembled and then depolymerised with a decrease in pH. It was also shown these hybrid materials demonstrated enhanced ability to release protein cargo compared to the charge-shifting nanoparticles. The endosomal escape properties of these nanoparticles were compared using the calcein assay. These modular and responsive nanoparticles combine tunable drug release with the ability to facilitate endosomal escape, thus they offer potential for the delivery of biological therapeutics.

Figure 1: Schematic representing the behaviour of hybrid charge shifting/self-immolative nanoparticles in response to a decrease in pH.

**References**

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2. Kongkatigumjorn, N., Smith, S. A., Chen, M., Fang, K., Yang, S., Gillies, E. R., Johnston, A. P. R. & Such, G. K (2018). Controlling Endosomal Escape Using pH-Responsive Nanoparticles with Tunable Disassembly. ACS Appl. Nanomaterials, 1, 3164-3173.