Smart pH-responsive anti-fouling polymers to improve internalisation of cationic hyperbranched polymers into tumours

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A key function of nanomaterials in pharmaceutical formulation is to improve compound stability and pharmacokinetics. Low biofouling polymers such as polyethylene glycol (PEG), have been used to modulate the pharmacokinetics and biodistribution of nanomedicines by preventing destabilisation and elimination through serum protein biofouling and recognition by the mononuclear phagocyte system.[1] However, as PEG hinders interactions with biology indiscriminately, it has been increasingly scrutinised for its role in reducing interactions with target cells, thereby compromising the therapeutic capacity of loaded drugs.[2]

To address this dilemma, we have investigated mechanisms of 'switchable' or 'sheddable' PEG systems (Figure 1). Here, the synthesis of a sheddable hyperbranched polymer (HBP) comprised of a cationic dimethylaminoethyl methacrylate (DMAEMA) core conjugated to coronal $mPEG_{1000}$ via an acid-labile hydrazone bond is described. Here, hydrazone linkers exploit the acidity of the local tumour microenvironment so that PEG chains cleave off an accelerated rate compared to normal tissue. This 'shedding' decreases the bioinertness of the material, promotion cellular internalisation and endosomal escape.

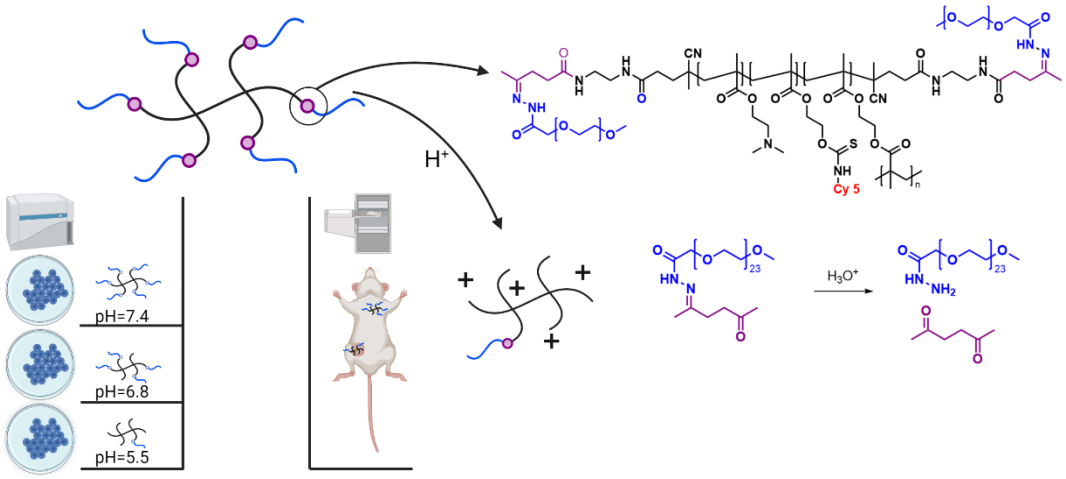

Figure 1: Schematic representation of the PDMAEMA hyperbranched polymer core that is decorated with $mPEG_{1000}$ on the corona via acid-labile linkages

References:

[1] Mills, J. A. Liu, F. Jarrett, T. R. Fletcher, N. L. Thurecht, K. J. *Biomater. Sci*. **2022**, *10* (12), 3029-3053.

[2] Fang, Y. Xue, J. Gao, S. Lu, A. Yang, D. Jiang, H. He, Y. Shi, K. *Drug Deliv*. **2017**, *24* (2), 22-3