Supramolecular assembly of enzyme-responsive nanoparticles with targeted antimicrobial activity

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The increasing number of multidrug resistant bacteria is a major threat to humans worldwide.[1] Due to the limited pipeline of new antibiotics,[2] known antimicrobials must be re-studied and formulated in a way that maximises their activity to fight the generation and spread of resistances. In this regard, antimicrobial polymers shown a remarkable broad spectrum and minimum capacity to generate resistances, yet their clinical application is still limited by their toxicity to the host.[3] We have prepared a polymeric nanoparticle from the self-assembly of the antimicrobial polymer poly(ethylene imine) (PEI) and an enzyme-responsive peptide (**P1$_{SH}$**) that can reduce the toxicity of PEI by 90%. The size, charge and stability of these nanoparticles could be tuned during the formulation step. Within the sequence of **P1$_{SH}$**, we included a region recognised by a protease (LasB) released by *Pseudomonas aeruginosa* during infection. These nanoparticles were specifically degraded when exposed to *P. aeruginosa's* elastase over other relevant elastases, ultimately displaying a pathogen-specific antimicrobial effect.[4]

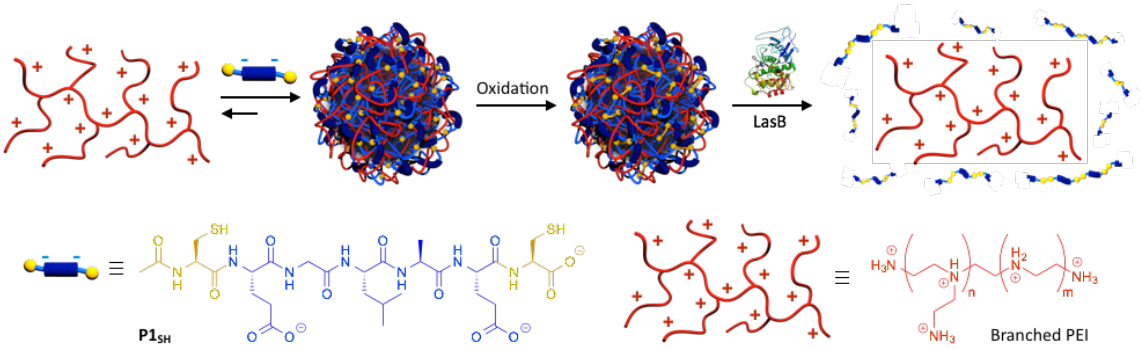

Fig 1 Self-assembly and degradation by bacterial elastase (LasB) of nanoparticles from an enzyme-responsive peptide (**P1$_{SH}$**) and the antimicrobial poly(ethyleneimine) (PEI).

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2 M. A. Cooper, M. Shlaes, *Nature*, **2011**, *472*, 32.
3 R. W. Scott, W. F. DeGrado, G. N. Tew, *Curr. Opin. Biotech.*, **2008**, *19*, 620-627.
4 I. Insua, E. Liamas, Z. Zhang, A. F. A. Peacock, A. M. Krachler, F. Fernandez-Trillo, *Polym. Chem.*, **2016**, *7*, 2684-2690.