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Mixed Monolayer and PEG Linker Approaches to Creating Multifunctional Gold Nanoparticles

Authors : D. Dixon, J. Nicol, J. A. Coulter, E. Harrison

Abstract : The ease with which they can be functionalized, combined with their excellent biocompatibility, make gold nanoparticles (AuNPs) ideal candidates for various applications in nanomedicine. Indeed several promising treatments are currently undergoing human clinical trials (CYT-6091 and Auroshell). A successful nanoparticle treatment must first evade the immune system, then accumulate within the target tissue, before enter the diseased cells and delivering the payload. In order to create a clinically relevant drug delivery system, contrast agent or radiosensitizer, it is generally necessary to functionalize the AuNP surface with multiple groups; e.g. Polyethylene Glycol (PEG) for enhanced stability, targeting groups such as antibodies, peptides for enhanced internalization, and therapeutic agents. Creating and characterizing the biological response of such complex systems remains a challenge. The two commonly used methods to attach multiple groups to the surface of AuNPs are the creation of a mixed monolayer, or by binding groups to the AuNP surface using a bi-functional PEG linker. While some excellent in-vitro and animal results have been reported for both approaches further work is necessary to directly compare the two methods. In this study AuNPs capped with both PEG and a Receptor Mediated Endocytosis (RME) peptide were prepared using both mixed monolayer and PEG linker approaches. The PEG linker used was SH-PEG-SGA which has a thiol at one end for AuNP attachment, and an NHS ester at the other to bind to the peptide. The work builds upon previous studies carried out at the University of Ulster which have investigated AuNP synthesis, the influence of PEG on stability in a range of media and investigated intracellular payload release. 18-19nm citrate capped AuNPs were prepared using the Turkevich method via the sodium citrate reduction of boiling 0.01wt% Chloroauric acid. To produce PEG capped AuNPs, the required amount of PEG-SH (5000Mw) or SH-PEG-SGA (3000Mw Jenkem Technologies) was added, and the solution stirred overnight at room temperature. The RME (sequence: CKKKKKKSEDEYPYVPN, Biomatik) co-functionalised samples were prepared by adding the required amount of peptide to the PEG capped samples and stirring overnight. The appropriate amounts of PEG-SH and RME peptide were added to the AuNP to produce a mixed monolayer consisting of approximately 50% PEG and 50% RME. The PEG linker samples were first fully capped with bi-functional PEG before being capped with RME peptide. An increase in diameter from 18-19mm for the ‘as synthesized’ AuNPs to 40-42nm after PEG capping was observed via DLS. The presence of PEG and RME peptide on both the mixed monolayer and PEG linker co-functionalized samples was confirmed by both FTIR and TGA. Bi-functional PEG linkers allow the entire AuNP surface to be capped with PEG, enabling in-vitro stability to be achieved using a lower molecular weight PEG. The approach also allows the entire outer surface to be coated with peptide or other biologically active groups, whilst also offering the promise of enhanced biological availability. The effect of mixed monolayer versus PEG linker attachment on both stability and non-specific protein corona interactions was also studied.

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