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Polyvalent Multifunctional Nanoparticles: A Powerful Tool to Address Various Biomedical Challenges

Yuan Guo[1] and Dejian Zhou[2,*]
[1]School of Food Science and Nutrition, and Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds LS2 9JT, U.K. Email: y.guo@leeds.ac.uk.
[2]School of Chemistry and Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds LS2 9JT, U.K. Email: d.zhou@leeds.ac.uk.

Extended Abstract

A great healthcare challenge facing the society is to find solution to some of the most devastating diseases, such as viral infection, neurodegenerative diseases and cancer. We are pursuing a polyvalent multifunctional nanoparticle (PMN) strategy to exploit multivalency (greatly enhanced affinity and specificity), surface chemistry (maximising ligand accessibility and function) and integrate nanoparticles' unique chemical-physical properties to achieve multi-functionality in order to address this challenge. Herein I will introduce two aspects of our research.

(1) PMN-cancer nanomedicine. Owing to excellent biocompatibility, water-solubility, non-cytotoxicity, and universal high cell uptake, polyvalent DNA-gold nanoparticle conjugates (DNA-GNPs) are powerful probes for biomedical research.[1] However, lacking stimuli-response release and limited resistance against nuclease degradation and non-specific adsorption have significantly limited their real-world applications. To overcome such problems, we have introduced an *i*-motif DNA sequence which can produce rapid, pH-dependent conformational switches between single- and four- stranded structures [2] into DNA-GNP, and successfully achieved efficient intracellular acidic pH-triggered drug release inside cancer cells, leading to high anticancer efficacy.[3] We have developed a new PEGylation strategy by hybridizing terminally PEGylated complementary DNA strand onto DNA-GNP, affording it complete resistance against non-specific adsorption and greatly enhanced stability against nuclease degradation without compromising its DNA loading and cell uptake efficiency.[4] Furthermore, we have combined the *i*-motif DNA sequence and gold nanorod to harness their pH-responsiveness and near-infrared (NIR) photothermal effects, allowing us to achieve pH/NIR light dual-responsive drug release inside cancer cells and effectively overcome cancer multidrug resistance at the cellular level.[5]

(2) Glycan-PMN Probes. Multivalent lectin-glycan interactions (LGIs) are widespread and vital for viral infection.[6] Understanding the underlying structural mechanisms is key to develop glycoconjugates that can specifically block such LGIs to prevent infection. Unfortunately, the structures of two vitally important tetrameric lectins, DC-SIGN [7] and DC-SIGNR, which play a key role in facilitating the HIV, HCV, and Ebola virus infections, remain unknown, limiting our ability to design spatial-matched polyvalent glycans to target DC-SIGN/R specifically for therapeutic interventions. To address this challenge, we have pioneered the use of glycan-PMNs as structural probes for LGIs. We have developed a new glycosylation method using lipoic acid-PEG-glycan ligands which works robustly for both quantum dots (QDs) and GNPs.[8-10] By exploiting nanoparticles' unique fluorescence properties, we have developed two new LGI affinity quantification methods, *via* fluorescence resonance energy transfer with QDs [8,9] or fluorescence quenching with GNPs [10], revealing that glycan-PMNs can offer greatly enhanced binding affinity with DC-SIGN (*e.g.* ~1.5 million-fold) over the corresponding monovalent binding. Moreover, we show that glycan-PMNs can offer unprecedented >100-fold discrimination between DC-SIGN and DC-SIGNR, two-closely tetrameric lectins which were thought to be identical. We further discover that a subtle difference in binding site orientation afford DC-SIGN/R with distinct glycan-PMNs binding modes (simultaneous binding and inter-crosslinking for DC-SIGN and DC-SIGNR, respectively), resulting in glycan-PMNs only potently blocking DC-SIGN-, but not DC-SIGNR- mediated virus infection [10]. Finally, we show glycan-GNPs potently inhibit DC-SIGN mediated pseudo-Ebola virus infection of host cells (IC_{50} ~95 pM), making it the most potent glycoconjugate inhibitors against DC-SIGN-mediated Ebola virus infections.

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