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A slow, efficient and safe nanoplatform of tailored ZnS QD-mycophenolic acid conjugates for *in vitro* drug delivery against dengue virus 2 genome replication†

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Dengue is a major health concern causing significant mortality, morbidity and economic loss. The development of anti-dengue viral drugs is challenging due to high toxicity, as well as off-target/side effects. We engineered size tuned ZnS QDs as a platform for the efficient delivery of mycophenolic acid (MPA) against dengue virus serotype 2 (DENV2) to evaluate the drug efficacy and toxicity using the DENV2 sub-genomic replicon system in BHK21 cells. The results indicate that the Selectivity Index 50 (SI_{50}) of the ZnS QD-MPA conjugate was two orders higher than that of free MPA with lower cytotoxicity. The effect is attributed to the sustained release of MPA from ZnS QD-MPA. The conjugated MPA caused significant inhibition of the virus at the level of replication and viral protein translation. The study underpins the efficiency of the ZnS QD for the delivery of antiviral drugs against DENV2 with negligible toxicity and side effects.

Introduction

Viral infections are one of the leading causes of mortality worldwide, having a global negative impact on healthcare and socio-economic development.[1] However, the lack of selective inhibitors against a multitude of medically important viruses, with a prominence of emerging and re-emerging RNA viruses (*e.g.*: Dengue, Chikungunya, SARS-CoV, MERS-CoV, and SARS-CoV2) has aggravated the scenario. Although it is impractical to develop drugs against each of these viruses within a short duration, the development of novel treatment strategies is the key to resolve the issue.[2] The adverse side effects/toxicity due to prolonged use of drugs and the rapid development of drug resistance in patients to the existing therapies make it a more serious public health concern.[3]

In this context, nanomedicine based strategies using biocompatible nanomaterials can be considered as a powerful tool to enhance the efficacy of antiviral drugs with the possibility of a remarkable reduction in toxicity. Nanoparticles offer distinctive physical properties that can have associated advantages for drug delivery, mainly due to the small particle size, large surface area to volume ratio, and the tunable surface charge of the particle.[4] The possibility of drug encapsulation, as well as the capability of nanoparticles to handle large drug payloads, can be attributed to the above properties. Thus nanoparticulate drug delivery systems are attractive candidates to improve the therapeutic effects of drugs.[5,6] Several anti-cancer drugs including paclitaxel, doxorubicin, 5-fluorouracil, and dexamethasone have been successfully re-formulated using nano-material based delivery systems.[7–10] Nano-medicines with different types of nano-formulations against HIV have been approved and are currently undergoing investigation for the treatment of viral infections.[11] It was reported that glucose coated gold nanoparticles (GNPs) attached to the drugs abacavir and lamivudine can act as a multivalent drug against HIV.[12]

Importantly, quantum dots (QDs) are promising zero-dimensional materials that can be designed/engineered for tailored applications. The use of QDs in medicine, and cell and molecular biology is one of the fastest emerging and most interesting interfaces of nanotechnology.[13–15] The bio-distribution and the toxicity of QDs are determined by their surface coating and particle size.[16,17] Zinc sulfide (ZnS), which belongs to the semi-conductor class II–VI, is one of the most ideal QDs which can be explored for biological applications due to its low toxicity levels.[4] It has excellent potential for application in fields such as drug delivery, and bio-imaging and also

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