Comment on "Short Ligands Affect Modes of QD Uptake and Elimination in Human Cells"

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Received for review June 15, 2011

Published online October 25, 2011
10.1021/nn2021953

■ In a recent study, Al-Hajaj *et al.*[1] presented interesting data for uptake and elimination of four different quantum dots (QDs) labeled with various short ligands. The inhibition of cellular uptake by using an inhibitor of an amino acid transporter (X-Ag cysteine transporter) was interpreted as evidence for the direct uptake of one of these QDs (QD-Cys) *via* this transporter into cytosol. The effects obtained using an inhibitor or activator of P-glycoprotein were interpreted as evidence for elimination of QDs from cytosol (their Figure 1). It is very surprising and interesting if a QD with hydrodynamic diameter of 8−10 nm (measured in absence of proteins) should be able to pass through an amino acid transporter.[2] Thus, it is important that all necessary control experiments are performed to draw the conclusion that QDs can enter cytosol *via* this route. Whether QDs are present in cytosol or contained within intracellular organelles is a very important issue regarding the intracellular targets that can be reached.

In our opinion, the following information is lacking in order to draw the conclusions shown in Figure 1: (a) Confocal microscopy or electron microscopy should demonstrate the presence of QDs in cytosol and also changes in amount of cytosolic QDs after the use of inhibitors/activator. Confocal microscopy data are shown only for two of the QDs studied and not for the QD-Cys stated to end up in cytosol. Moreover, the confocal pictures shown indicate that all internalized QDs are localized within intracellular organelles, that is, possibly endosomes/lysosomes. (b) Control experiments should be performed using the inhibitor of the amino acid transporter and the three other QDs studied.

For such studies, it is essential to know if the QDs are entering the cells or if they are just adsorbed to the cells. If there is adsorption during incubation at 37 °C and an inhibitor reduces this adsorption, this would appear as decreased uptake. It is not possible to discriminate between these possibilities for the analyses performed. The upper picture of Figure 3C in the study by Hajaj *et al.*[1] shows particles that seem to be adsorbed to the cell only. There are many pitfalls in studying cellular uptake of nanoparticles. We have recently discussed endocytic uptake of nanoparticles and provided a toolbox for studies of cellular uptake and intracellular localization to guide nanoparticle scientists and avoiding wrong conclusions.[3]

REFERENCES AND NOTES

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