Reply to Cormode et al.: High-density lipoprotein mimicking synthetic nanoparticle

We thank Cormode et al. (1) for their interest and comments on our recent article in PNAS (2). We would like to emphasize that throughout our article, we call our nanoparticle as "synthetic high-density lipoprotein (HDL) mimic" not "HDL-like." The very definition of the term "synthetic mimic" implies that the nanoparticle, itself, imitates the actions of the natural source but is not exactly the same. We would like to stress that the goal of this work was to produce a synthetic HDL-mimicking particle, as evidenced from the title of the article. The rationale for creating a completely synthetic HDL-mimicking nanoparticle was to overcome problems associated with reconstitution of natural HDL, such as possible immune responses, and scale-up challenges.

We chose to make the nanoparticle ~120 nm, which is 10 times greater than that of natural HDL, to avoid rapid clearance by the kidneys or through extravasation and to allow for long circulation and favorable biodistribution. A poly(lactic-*co*-glycolic) acid (PLGA) copolymer was used because of its biocompatibility, biodegradability, and well-known use in Food and Drug Administration-approved therapeutic products. A lipid polyethylene glycol layer was incorporated to decrease biofouling and increase the blood circulation, which, in turn, allowed the nanoparticles a greater probability of reaching their final destination. The lipid layer also helps in retention of the quantum dots in the PLGA–cholesterol core. The 4F peptide was used because of the recent success with restoring vascular endothelial function and improving the HDL inflammatory index at low doses (3). With available literature, we were unaware that clinical trials for this mimic peptide were abandoned. Although we did not report the density of our nanoparticles, with all of the organic components used, we expect our nanoparticle density to be in the range of HDL. As clearly mentioned in our article (2), our preliminary data only indicate that the ratio of lipid to cholesterol is in the same range as HDL.

We stated clearly in our article that we used cationic stearyl lipid to target the mitochondria of macrophages (2). We do not have any additional comment to address the statement by Cormode et al. (1), "Despite the use of the 4F apoA-I mimetic peptide, binding to a nonnatural target, mitochondria, is shown, likely because of the cationic lipid used," because this is irrelevant.

Cormode et al. (1) comment that our formulation does not perform cholesterol efflux in macrophage cells. We do show efficacious in vitro natural cholesterol binding ability of our synthetic HDL mimic and cholesterol reduction in vivo in Sprague–Dawley rats.

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1 Cormode DP, Fisher EA, Stroes ESG, Mulder WJM, Fayad ZA (2013) High-density lipoprotein is a nanoparticle, but not all nanoparticles are high-density lipoprotein. *Proc Natl Acad Sci USA* 110:E3548.

2 Marrache S, Dhar S (2013) Biodegradable synthetic high-density lipoprotein nanoparticles for atherosclerosis. *Proc Natl Acad Sci USA* 110(23):9445–9450.

3 Sherman CB, Peterson SJ, Frishman WH (2010) Apolipoprotein A-I mimetic peptides: A potential new therapy for the prevention of atherosclerosis. *Cardiol Rev* 18(3):141–147.

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The authors declare no conflict of interest.

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