Role of nano-particles in ischemia-reperfusion therapies

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Ischemic heart disease is the leading cause of death world-wide. Many strategies have been devised to reduce ischemia-reperfusion injury but none has translated successfully to the clinic. One possible cause for this has been an inability for therapy to reach the target site. The application of nanotechnology has revolutionised the way drugs are delivered to their targets. Nanoparticles may facilitate the transport of drugs across cell membranes, enabling the release of the drug in a controlled manner and reducing the risk of toxicity.

We have previously demonstrated that nanoparticle (NP)-assisted delivery of a peptide derived against the alpha-interacting domain (AID) of the L-type calcium channel (AID-tethered NP), decreases myocardial damage associated with reperfusion after ischemia in guinea-pig hearts *ex vivo*. We designed branched synthetic polymers (dendrimers) to facilitate increased delivery of novel peptides into the heart. Here we assessed uptake of fluorinated *versus* non-fluorinated dendrimers into C57BL/6J mouse cardiomyocytes. Changes in fluorescence of tetramethylrhodamine (TAMRA)-labelled generation 4 and 5 dendrimers were monitored over a period of 65 minutes following addition to the cardiomyocytes (G4 and G5 respectively; G = number of branches). Maximal fluorescence was reached within 35 min and 50 min following application of non-fluorinated G4 (n=8) and G5 (n=5) dendrimers respectively, and within 25 min for fluorinated G4 (G4f) and G5 (G5f) dendrimers. Biodistribution of G5f was measured in heart, kidney and liver using CRi Maestro 2 multispectral imaging system at 24, 48 and 72 hours following *in vivo* treatment in *Hfh11nu* (nude) mice under light isoflurane anaesthetic. Dendrimers were taken up efficiently into the heart and demonstrated clearance from the liver at 72 hours.

We conclude that fluorination of the dendrimers results in rapid uptake into cardiomyocytes and may prove an efficient and safe mode of drug delivery.