

8.7 Dr S E Matthews, School of Chemical Sciences and Pharmacy, University of East Anglia *Synthetic Vectors in Gene Therapy and Medical Care*

The use of synthetic vectors, based on both linear polymers and dendrimers for gene (DNA and RNA) delivery is an area of intense research but is still to reach fruition in gene therapy and medical care. Dendrimers, due to their defined synthetic route, offer the advantage of a fixed structural architecture which enables characterization and evaluation of binding efficacy to be more readily determined than with linear polymers.

We have recently developed a new class of dendrimers, based on multi-calixarene cores that feature between 16 and 64 points for surface functionalisation and demonstrated their ability to bind to DNA and introduce DNA into cells. Binding and transfection has been shown to be dependent on a range of factors including the nature of the surface functionality of the dendrimer, with aliphatic amines proving more effective, and the shape of the dendrimer and how this aids co-operativity between the binding groups.¹ These results indicate the potential of our system to be tailored further to allow cell-specific targeting of gene delivery.

Cell viability studies, in a range of cell types, have shown the multicalixarenes dendrimers to be of very low toxicity however before these materials can be developed further for clinical use their behaviour in cells e.g how they taken up and their ultimate fate, needs to be further investigated. Thus, as part of our programme for the development of synthetic vectors for the delivery of DNA and RNA based on multicalixarenes we have developed novel fluorescent derivatives of simple calixarenes and investigated, for the first time, how these molecules are handled by cells.² Confocal microscopy has shown, through co-incubation with uptake inhibitors, that uptake is, importantly, not through the common clathrin coated pits or caveolae (lipid raft) endocytic pathways and that the calixarene derivative localizes within the cytoplasm and does not enter the nucleus of the cell.

Not only do these results aid the development and understanding of our gene transfection vectors but also demonstrate the power of fluorescent labeling for investigation of interactions between calixarenes and biological systems and the potential for calixarene based intracellular imaging agents.

The EPSRC National Mass Spectrometry Service has been valuable in allowing this work to progress through the use of MALDI-ToF Mass Spectrometry to provide the final confirmatory characterisation of complex novel dendritic systems, in particular on the level of surface functionalisation, and the fluorescently labelled derivatives, prior to their biological evaluation.

¹ R. Lalor, J. L. DiGesso, A. Mueller, S. E. Matthews, Efficient Gene Transfection with Functionalised Multicalixarenes, *Chem. Commun.*, 2007, 4907-4909

² R.Lalor, H. Baillie-Johnson, C. Redshaw, S. E. Matthews, A. Mueller Cellular Uptake of a Fluorescent Calix[4]arene Derivative, *J. Am. Chem. Soc.*, 2008, accepted for publication