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The great escape-using biosensors to understand endosomal release of siRNA formulations

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RNA interference (RNAi) is a naturally occurring pathway found in eukaryotes for gene silencing. Since the Nobel Prize winning discovery of RNAi in 1998 scientists have been attempting to manipulate the pathway to selectively silence disease causing genes. In theory, successful implementation of RNAi-based therapeutics will present the exciting prospect of silencing any disease-causing gene. The development of antisense therapeutics has been hampered by problems associated with delivery. A key problem is that short interfering RNA (siRNA), the effector molecules in many therapeutic strategies, are incorporated into acidic intracellular vesicles called endosomes and lysosomes. Moreover, inadequate tools for quantifying release from endosomes and lysosomes are limiting the development of strategies aiming to improve the efficiency of intracellular trafficking. We have used advances in nanotechnology to develop an analytical tool for following the path of formulations inside a cell by monitoring changes in pH. We have used a micro-emulsion polymerisation technique to synthesise ratiometeric polyacrylamide based pH-sensitive biosensors, maximally fluorescent in endosomes and minimally fluorescent in the cytoplasm. Fluorescence microscopy in conjunction with flow cytometry has shown positively charged biosensors internalise to endosomes and lysosomes of MRC-5 fibroblast cells. Quantitative analysis of fluorescence intensities has been used to make pH measurements, which can be used to monitor endosomal release in a model system. The successful application of these biosensors will accelerate the development of more effective siRNA formulations.

Biography

Arpan Desai is a currently a final year PhD student at the AstaZeneca Centre for Doctoral Training in Targeted Therpautics in the School of Pharmacy at the University of Nottingham, UK. He received his BSc(hons) in Biotechnology from the University of Edinburgh. His research interest is in cellular uptake and intracellular transport of siRNA formulations.

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