

**P019** Transcriptional effects of delivery systems: the effect of dendrimer architecture on EGFR mRNA expression and on siRNA-mediated gene silencing activity

**Andrew Hollins, Yadi Omid, Mustapha Benboubetra and Saghir Akhtar**

*Centre for Genome-Based Therapeutics, Welsh School of Pharmacy, Cardiff University, Cardiff CF10 3XF, UK*

RNA interference (RNAi) is an evolutionary conserved process for regulation of gene expression. In mammalian cells, RNAi-induced via short (21-23nt) duplexes of RNA, termed small interfering RNA (siRNA), can elicit highly specific RNAi-mediated gene silencing providing the antisense strand of the duplex is incorporated into a multi-protein RNA-induced silencing complex (RISC). RNAi technology is being widely used in studies of gene function, drug target validation as well as being explored for potential therapeutic use in the clinic. Synthetic siRNA duplexes are polyanionic macromolecules that do not readily enter cells and typically require the use of a delivery vector for effective cellular gene silencing. Here, we show that separate from their effects on cell uptake, delivery systems can also exert changes in target gene expression that can significantly influence siRNA potency. Our results show that two PAMAM dendrimer DDS, differing only in their structural architecture, elicited many different gene expression changes in human cells including opposing effects on the expression of epidermal growth factor receptor (EGFR), a gene targeted for silencing by siRNA. Despite providing similar improvements in siRNA uptake, these two formulations led to a ~10-fold variation in anti-EGFR siRNA activity. These data show that gene expression changes induced by DDS, separate from their ability to enhance cell uptake, determine siRNA potency and offer the possibility of tailoring delivery system-siRNA combinations for additive or synergistic effects on gene silencing.