NOVEL ANTICANCER POLYMER CONJUGATES DESIGNED TO TREAT HORMONE-DEPENDANT CANCERS AND CIRCUMVENT RESISTANCE

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Introduction: Over the last decade "polymer therapeutics" have emerged as first-generation nanomedicines. The ability of polymer anticancer-drug conjugates to decrease drug toxicity and improve antitumour activity is now well established pre-clinically and several conjugates show promise in clinical trials (1-4). So far those conjugates that have entered clinical development all carry well-known chemotherapeutic agents including doxorubicin (4), platinates (1) and paclitaxel (5). Designed for lysosomotropic delivery (Figure 1), their whole body and cellular pharmacokinetics brings advantages of passive tumour targeting due to the hyperpermeability of tumour vasculature, and the ability to bypass some resistance mechanisms (reviewed in (1)). Polymer-drug linkers are often designed for cleavage by lysosomal thiol-dependent proteases (e.g. cathepsin B) or the reduced pH of endosomes and lysosomes to facilitate intracellular drug liberation. It is becoming clear that inappropriate trafficking and/or malfunction of enzymatic activation can lead to new mechanisms of clinical resistance.

This presentation reviews our latest research which is trying to develop polymeric drugs, polymer-protein conjugates and polymer-drug combination therapy that will provide new opportunities of improved anticancer activity and circumvent new and classical resistance mechanisms. In addition, we have been trying to develop strategies to tackle hormone dependant cancers particularly breast and prostate cancer. The use of polymeric carriers to deliver endocrine therapy is largely unexplored. Like other solid tumours, breast and prostate cancer, are treated by surgical removal, radiotherapy and chemotherapy. In this case hormone therapy is also widely used as first line therapy, or in both neoadjuvant and adjuvant settings.

Results and Discussion

Polyacetal-diethylstilboestrol: We have recently described a polymeric drug designed for pH-triggered activation in endosomes and lysosomes (6). A 'ter'-polymerisation approach was used to incorporate the non-steroidal oestrogen diethylstilboestrol (DES) into the main-chain of water-soluble polyacetals using PEG\(_{3400}\) as co-monomer to give a polymer of Mw 43,000 g/mol, and a DES loading 4.7 wt%. The DES-polyacetal displayed greater cytotoxicity than DES against MCF-7 human breast cancer and B16F10 murine melanoma cells. Such conjugates can also be prepared with higher molecular weight to maximise their EPR-mediated targeting, thus they have considerable potential for further evaluation as a treatment for metastatic prostate cancer.

![Figure 1. Lysosomotropic delivery](image)

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In addition, many polymer-drug conjugates currently undergoing clinical trial, e.g. HPMA copolymer-doxorubicin and platinates, rely on peptidyl linkers designed for cleavage by lysosomal cathepsin B for activity. This enzyme is also responsible for the degradation of polyglutamic acid (PGA) conjugates (the polymer backbone itself) carrying paclitaxel in XYOTAX\textsuperscript{TM} an exciting new treatment for non small cell lung cancer. Recent preclinical and clinical studies have shown that low cathepsin B levels may compromise conjugate activity and therapeutic potential. Importantly, polymeric drugs like DES-polyacetals circumvent the need for activation by lysosomal enzymes.

HPMA copolymer-aminoglutethimide-doxorubicin: Tamoxifen brought a 28% reduction in mortality of breast cancer patients, but even so, the prognosis for
patients with metastatic breast cancer is still poor. The survival rate at 5 years being < 20% due to the mixed antagonist/agonist activity of tamoxifen, and acquired resistance that can develop long-term. To circumvent this problem aromatase inhibitors are being used, and recent clinical trials showed that letrozole and anastrozole were more effective in treating oestrogen receptor positive breast cancer than tamoxifen. We have recently described the first polymer conjugates to contain a combination of endocrine therapy and chemotherapy (7-9). HPMA copolymer conjugates containing both aminoglutethimide (AGM) (a first-generation aromatase inhibitor) and doxorubicin were synthesised as a model (7), and interestingly HPMA copolymer-Dox has already shown activity in chemotherapy refractory breast cancer patients (4).

HPMA copolymer-aminoglutethimide-doxorub-icin showed greater cytotoxicity against MCF-7 breast cancer cells in vitro than either of the individual conjugates alone, or a simple mixture of them (7,9). Activity correlated with aromatase levels in the cells. HPMA copolymer-AGM has shown the ability to inhibit aromatase (8) and mechanistic studies suggest that the enhanced activity is due to the kinetics of lysosomotropic drug liberation leading to enhanced apoptosis (9). Given that acquired drug resistance is a particular problem for many of the new molecular targets, this new concept provides an interesting opportunity to provide a platform for delivery of two or more drugs (potentially at different rates) that might act synergistically to block multiple cellular pathways simultaneously.

**Dextrin-phospholipase A2:** Our recent studies have been investigating a new concept that uses polymer conjugation to mask protein activity, that can then be regenerated slowly (or site-specifically) following triggered polymer degradation. Dextrin (degraded by amylase) has been developed as one such model (10). As the phospholipase A2 (PLA2) Crotoxin is showing promise as an anticancer agent, but its use is limited by non-specific neurotoxicity, we decided to prepare dextrin-PLA2 as novel anticancer agents with potential for use as membrane active agents for the treatment of breast cancer (11). The conjugate synthesised retained 36 % enzyme activity compared to free PLA2 and retained toxicity towards MCF-7 cells.

**Conclusions:**
Polymer anticancer conjugates are showing promise in clinical trials (1) and the exciting data emerging from Phase III clinical trials of XYOTAX™ in patients (particularly women) with non small cell lung cancer are to be used to support first market approval filing of an anticancer conjugate. Recent clinical data have underlined the complexity of the pharmacokinetics of polymer conjugates. Further studies are certainly needed to better understand pharmacokinetic-pharmacodynamic relationships of polymer conjugates in vivo, and genomic/proteomic profiling of patients would help select those that are best candidates for polymer therapy. The second generation conjugates currently emerging are using new polymer platforms, polymer-bound combination therapy, and new molecular targets in an attempt to further enhance activity and circumvent resistance. Not only are polymer therapeutics reaching clinical use in cancer, but a wide range of novel polymer chemistries and therapeutic indications are being explored (12).

**References:**


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