to include a diverse range of chemical and biochemical protocols, most of which seek to maximize both the rate of empirical information obtained and its associated value. Secondly, combinatorial methodology is now an accepted procedure that, through careful design, has now been successfully used in a variety of applications. Furthermore, through the development of new reagents and techniques, combinatorial methodology will play an increasingly important role in most scientific research programmes.

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Plastics in cancer therapy

Reducing the side effect profile and increasing the efficacy of anti-cancer therapies might be possible through attachment of anti-tumour agents to bulky polymer molecules, according to Ruth Duncan (School of Pharmacy, University of London, UK) speaking at the Royal Society of Chemistry's annual conference in Edinburgh (UK) on 10 September 1999. The idea behind this approach is to improve tumour targeting and reduce accumulation of the agents in healthy tissue.

Polymers and plastics have historically been reserved for medical appliances such as replacement hip joints and heart valves rather than used for pharmacology. However, as Duncan explained, water-soluble polymer–drug conjugates have an interesting property in that, after intravenous injection, they cannot cross the cell membranes of healthy tissues. This is because the tight endothelial gap junctions of normal blood vessels inhibit their entry. However, the newly formed blood vessels that supply tumour cells are much 'looser' in architecture so that bulky macromolecules, such as polymers, can cross the membranes into the tumour tissue. These 'leaky' blood vessels therefore provide a gateway for selective delivery.

Current approaches

The administration of chemotherapeutic agents without selective targeting wastes much of the drug and can cause cytotoxic damage to healthy tissues leading to the well-known symptoms of chemotherapy, such as nausea, diarrhoea and hair loss. Duncan also highlighted that secondary (metastatic) tumours that have spread from an original site of disease are notoriously difficult to locate and target using conventional agents. She believes the way to overcome these problems is to use an appropriate targeting mechanism.

Much effort has focused on a 'magic bullet' for tumour targeting, in particular, ones based on antibody technology and liposomes. However, these early approaches have had their own problems such as immunogenicity, poor stability or being difficult to synthesize. 'The design of tailor-made polymer conjugates allows the sophisticated use of chemistry to provide a synthetic approach that can overcome many of the early difficulties as well as being an inexpensive and industrially practical approach', says Duncan.

Polymer–drug conjugates

The idea of using polymeric macromolecules for carrying a drug directly to a tumour was first proposed in the mid-1970s by the polymer chemist Helmut Ringsdorf (University of Mainz, Germany) with whom Duncan collaborated during her PhD [Ringsdorf, H. (1975) *J. Polym. Sci., Polym. Symp.* 51, 135–153]. Duncan and her colleagues at the Centre for Polymer Therapeutics (London, UK) are now investigating several polymer–drug conjugates using anticancer agents such as doxorubicin and cisplatin [Duncan, R. *et al.* (1999) *Eur. J. Cancer* 35, 994–1002]. Preliminary clinical trials have so far produced promising results [Cassidy, J. *et al.* (1999) *Clin. Cancer Res.* 5, 83–94].

Water-soluble synthetic polymer conjugates based on *N*-(2-hydroxypropyl)-methacrylamide (HPMA) copolymers developed in collaboration with the Institute of Macromolecular Chemistry (Prague, Czech Republic) were the first to enter clinical trials. One such agent, PK1 (Fig. 1), is an HPMA–copolymer conjugate of doxorubicin with a peptidyl spacer cleavable by intracellular lysosomal cysteine protease enzymes, which are found at high levels in certain tumour types associated with poor prognosis such as colorectal, lung, breast and refractory cancers. After intravenous injection, PK1 selectively accumulates in tumour tissue because of the increased vascular permeability of this tissue. After internalization, the drug is cleaved from its polymer carrier inside the lysosomal compartment and is distributed within the tumour cells destroying them. Duncan highlighted that careful design of the spacer linking the cytotoxic agent to the polymer is vitally important as to minimize the exposure of healthy tissue to the drug, the linker must only be cleaved within the tumour.

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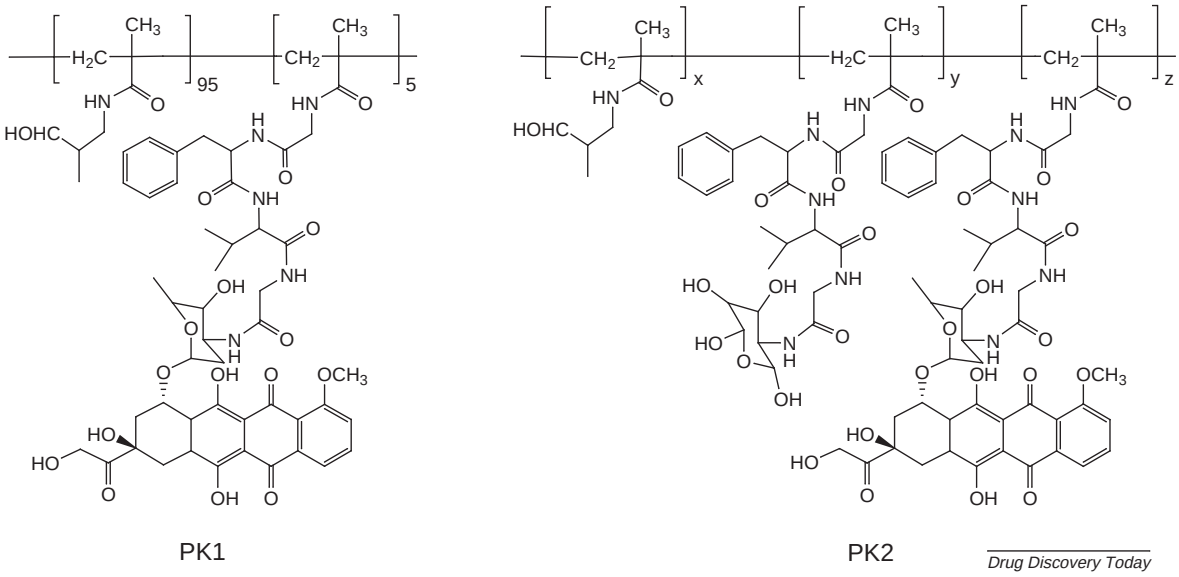

Figure 1. *Structure of PK1 (an HPMA–copolymer conjugate of doxorubicin with a peptidyl spacer) and PK2 (the doxorubicin-containing copolymer with added galactosamine).*

Clinical studies

Four conjugates based on the HPMA copolymer have entered clinical trials. The first trials with PK1 were supported by the Cancer Research Campaign (Glasgow, UK) and carried out by James Cassidy and colleagues (University of Aberdeen, UK). When given once every three weeks, PK1 greatly reduced toxicity compared with free doxorubicin, while being active in chemotherapy refractory patients. The maximum tolerated dose was 320 mg m^{-2} (doxorubicin-equivalent), which is 4–5-fold higher than the usual clinical dose of free doxorubicin (60–80 mg m^{-2}). In the Phase I trial, there was no evidence of PK1-related cardiotoxicity, despite individual cumulative doses of up to 1680 mg m^{-2} (doxorubicin-equivalent). The dose-limiting toxicity was found to be bone marrow suppression. PK1 is currently undergoing Phase II evaluation for the treatment of breast, colon and non-small cell lung cancer. This doxorubicin-containing copolymer with added galactosamine to mediate liver targeting (PK2; Fig. 1) and a paclitaxel-containing HPMA copolymer are currently in Phase I/II trials and preliminary reports suggest both have antitumour activity in humans. A fourth compound that has recently started Phase I evaluation is an HPMA copolymer conjugate containing a camptothecin analogue. 'If the trials work well, within 3–5 years we may well have a product in the marketplace', Duncan told the RSC conference. For a more in-depth review, please see Duncan, R. (1999) *Pharm. Sci. Technol. Today* 2, 441–449.

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