

S007 Polymer anticancer drug conjugates as nanomedicines:
from laboratory to clinic

Ruth Duncan

*Centre for Polymer Therapeutics, Welsh School of
Pharmacy, Cardiff University, Cardiff CF10 3XF, UK*

The concept of polymer anticancer drug conjugates was born in the 1970s with the realisation that the endocytic pathway might be useful for 'lysosomotropic drug delivery. Both lysosomal proteases and the reduced pH of endosomes and lysosomes have been used as a means to activate such macromolecular prodrugs. Optimisation of conjugate features including whole body and cellular pharmacokinetics, molecular weight, polymer drug linker and drug loading led us to the design of six anticancer conjugates based on N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers that have progressed into Phase I/II clinical trials, as well as the first polymer-based gamma camera imaging agents. Covalent drug conjugation to HPMA copolymers via a tetrapeptide linker (gly-phe-leu-gly) produced conjugates with reduced toxicity and anti-tumour activity in chemotherapy-resistant/refractory patients. Second-generation conjugates are being designed using novel dendritic architectures, biodegradable polymers and also as polymeric drugs that have the drug as an integral component of a biodegradable polymer backbone, and as a platform to deliver combination therapy. An HPMA copolymer carrying both an aromatase inhibitor and doxorubicin displays greatly enhanced in vitro cytotoxicity. As clinical trials progress it is increasingly apparent that lysosomotropic delivery is not only an opportunity for delivery, but malfunction can be a mechanism of resistance.