Combination Therapy: Opportunities and Challenges for Polymer-Drug Conjugates as Anticancer Nanomedicines

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The discovery of new molecular targets and the subsequent development of novel anticancer agents is opening new possibilities for drug combination therapy as anticancer treatment. Polymer-drug conjugates are well established for the delivery of a single therapeutic agent, but only in very recent years their use has been extended to the delivery of multi-agent therapy. This approach is now considered to be an important opportunity to enhance tumour response rates. The conjugation of two drugs within the same polymer mainchain confers clinical benefits as it is the only approach that can guarantee simultaneous delivery of both drugs to the same site of action, and with careful design, can enable synergistic effects. Additionally, a combination conjugate could be administered as single dose and therefore benefits would be also found in patience compliance and manufacturing. These early studies not only revealed the therapeutic potential of this application but raised new challenges (i.e. drug loading and drugs ratio, characterisation, development of suitable carriers) that need to be addressed for a successful optimisation of the system towards clinical applications [1].

We pioneered this field with the first endocrine-chemotherapy combination in the form of the model compound HPMA copolymer-aminoglutethimide (AGM)-doxorobucin (Dox) [2]. The conjugate containing both drugs showed markedly enhanced cytotoxicity compare with HPMA copolymer-Dox, a conjugate that has already show clinical activity in breast cancer patients , whereas mixtures of polymer conjugates containing only AGM or Dox did not show a synergistic benefit. A follow on study suggested that such increased activity could be due to a variety of factors, including drug release rate, conjugate conformation in solution and possibly, activation of certain molecular pathways. [2b] In order to further improve this construct, we have also proposed the use of a biodegradable and multivalent polymer poly(L-glutamic acid) (PGA) being able to increase drug loading capacity and conjugate Mw enhancing therefore its tumour targeting by the EPR effect. [2c]

Finally, proof of concept has been also achieved *in vivo* with combination conjugates including an antiangiogenic compound with chemotherapy also using PGA as polymer carrier, namely PGA-PTX-E-[c(RGDfK)$_2$] conjugate. [3]

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