



## Cover story

## True combination therapy using synergistic drug combination



Combination therapy has become a common practice in oncology during the last three decades. Combination therapy is likely to provide an alternative long-term solution for the treatment of metastatic and/or resistant neoplasms [1,2]. Even if synergistic drugs are co-administered, however, their pharmacokinetic (PK) profiles will be different. This may reduce the combined drug effect, if simultaneous presence of multiple drugs at the target site is required to maximize combination therapy. Even if multiple drugs are incorporated into the same vehicle, such as nanoparticles, liposomes, or polymer micelles, PK profiles of individual drugs will be different due to dissimilar physicochemical properties affecting the drug release kinetics as well as diverse elimination kinetics. Anticancer drugs can be conjugated to polymers to alter the PK profiles, but it still does not guarantee that both drugs will reach the same target cell around the same time. Different drug-polymer conjugates may still differ in their body distribution even if the drugs are conjugated to the same polymer. Different chemotherapeutic drugs have different mechanisms of action and toxicity profiles and distinct mechanisms for causing resistance. Thus, the optimal synergistic benefit of combination therapy may require different drug concentrations, necessitating delivery of drugs at a specific ratio.

In this issue, Professor Ronit Satchi-Fainaro and her team at Tel Aviv University demonstrated the advantage of a combined polymer conjugate bearing two drugs on the same polymer over a combination of drugs conjugated to separate polymer chains [3]. They report the rational design of combining two synergistic drugs, paclitaxel (PTX) and doxorubicin (DOX), on the same poly(glutamic acid) (PGA) backbone. Both drugs are used in the clinic as monotherapies or in sequential combination to treat various neoplasms. Drug combinations were first evaluated *in vitro* to find the optimal ratio of the two drugs. Then, the PGA-PTX-DOX conjugate bearing the two drugs at a synergistic ratio was synthesized to examine its activity and toxicity profiles *in vitro* and *in vivo*. The conjugate inhibited the proliferation and migration of cancer cells *in vitro*, and did not induce hemolysis or release pro-inflammatory cytokines. Most importantly, the conjugate exhibited a superior anti-

tumor efficacy and safety compared with a combination of free drugs as well as drugs conjugated to separate polymer chains at equivalent concentrations.

The polymer-based multi-drug conjugate allows for delivery of different drugs to the tumor at a predetermined ratio, providing an ideal platform for maximizing the benefit of combination therapy. Both drugs arrive at the target site simultaneously after a single injection to share similar pharmacokinetic profiles. A growing number of *in vitro* and *in vivo* studies involving drug combinations are confirming the potential of this exciting approach [4]. Combination therapy is certainly more complex and requires more attention than monotherapy. Drug combinations in an innovative polymeric vehicle, however, can yield significant benefits, such as administration of drugs at lower doses, potentially leading to reduced side effects and delayed development of drug resistance. The new formulation developed by the Satchi-Fainaro team is a sign that the targeted drug delivery field is maturing.

## References

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