Safety Delivery of Camptothecin: From Prodrugs to Nanomedicines

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Introduction. 20-(S)-camptothecin (CPT) is a natural planar pentacyclic quinolone (Fig. 1) with strong antitumor activity against a wide spectrum of human cancers.[1] Unfortunately, CPT presents some major limitations with regards to therapeutic application, like poor water solubility and the rapid lactone ring hydrolysis at physiological pH, which gives rise to the inactive carboxylate form.[2] In addition, CPT is extremely insoluble in biocompatible solvents, which makes impossible conventional administration routes. To overcome these issues two strategies have been pointed out: i) structural analogues, in which the CPT molecule is chemically modified for increased solubility and stability in biological fluids; and ii) nanomedicines, wherein CPT is incorporated by physico-chemical methods to nanoparticles which act as stable carriers for drug delivery. We here present some of the most advanced and recent achievements in the design, synthesis and development of CPT analogues and nanomedicines.

Results. Most structural derivatives of CPT have been obtained through modifications of the quinolone A-B ring [1]. This include substitution at C9, C10 or C11 by amine or hydroxyl group, to give compounds with more antitumoral activity, whereas substitution of positions 9 and 10 by halides or other electron-rich groups and substitution of position 11 with fluorine or cyano groups increase the DNA topo I inhibition ability. Conversely, modification of the E-ring, mostly at C20 position, increases lactone stability. On the other hand, CPT nanoplatforms present major advantages as improved solubility, lactone ring stability, half-life extension, biocompatibility and control drug release rates.[3] Some of the most successful systems we have tested in preclinical research are: (i) fully inorganic core-shell nanoparticles obtained by coating gold nanoclusters with a mesoporous silica layer; (ii) redox sensitive derivatives of CPT coupled by disulfide bridge over complex silica nanoparticles containing a non-porous core and a mesoporous shell; and (iii) hybrid organic-inorganic silica nanoplatform with CPT linked by ester bond.

Discussion. Therapies merely relying on single, small molecules seem now out of step, due to their limited efficacy and unacceptable toxicities. For this reason, future seems good for those systems which are able to selectively discharge CPT at the target cells under a specific stimulus (stimuli-responsive), with no previous release.

References

[1] Beidler, D.R.; Chang, J.Y.; Zhou, B.S.; Cheng, Y.C. *Cancer Res.* 56 (1996), 345.
[2] Basili, S.; Stefano, M. *Expert Opin. Ther. Pat.* 19, (2009), 555.
[3] Rivero, E.; Botella, P. *J. Control. Release* 247 (2017), 28.

Figures

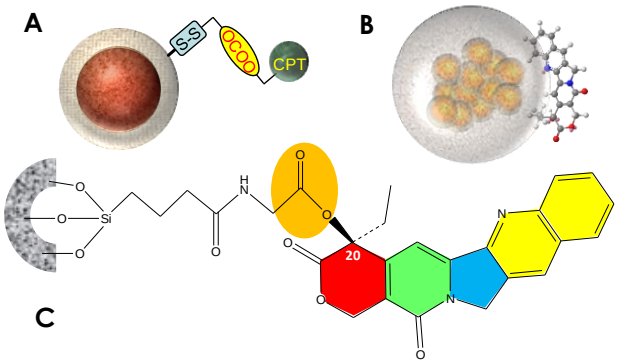

Figure 1: (A) Core-shell nanoparticles of gold nanoclusters coated with a mesoporous silica layer with CPT. (B) Redox sensitive derivative of CPT coupled by disulfide bridge dense core-porous shell silica nanoparticles; (C) Organic-inorganic silica nanoplatform with CPT linked by ester bond.