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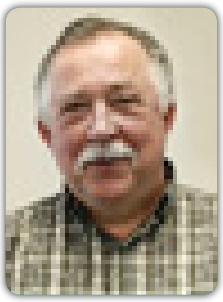

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Stimuli-sensitive nanopreparations for multidrug resistant cancer

Tumor therapy, especially in the case of multidrug resistant cancers, could be significantly enhanced by down-regulating the production of proteins, which are involved in cancer cell resistance, such as Pgp or survivin. This can be achieved by using corresponding siRNA. Even better response could be achieved if such siRNA could be delivered to tumors together with chemotherapeutic agent. This task is complicated by low stability of siRNA in biological surrounding. Thus, the delivery system should simultaneously protect siRNA from degradation. We have developed several types of lipid-core polymeric micelles based on PEG-phospholipid or PEI-phospholipid conjugates, which are biologically inert, demonstrate prolonged circulation in the blood and can firmly bind non-modified or reversibly-modified siRNA. Additionally, these nanopreparations can be loaded into their hydrophobic compartments with poorly water soluble chemotherapeutic agents, such as paclitaxel or camptothecin. In experiments with cancer cell monolayers, cancer cell 3D spheroids, and in animals with implanted tumors, it was shown that such co-loaded preparations can significantly down-regulate target proteins in cancer cells, enhance drug activity, and reverse multidrug resistance. In order to specifically unload such nanopreparations inside tumors, we made them sensitive to local tumor-specific stimuli, such as lowered pH, hypoxia, or overexpressed certain enzymes, such as matrix metalloproteases. Using pH-, hypoxia-, or MMP2-sensitive bonds between different components of nanopreparations co-loaded with siRNA and drugs, we were able to make the systems specifically delivering biologically active agents in tumors, which resulted in significantly improved therapeutic response. We have also developed approaches to target individual intracellular organelles to initiate the apoptosis in resistant cancer cells.

Recent Publications

1. Salzano G, Costa D F, Sarisozen C, Luther E and Mattheolabakis G, et al. (2016) Mixed nanosized polymeric micelles as promoter of doxorubicin and miRNA-34a co-delivery triggered by dual stimuli in tumor tissue. Small 12(35):4837–4848.
2. Salzano G, Navarro G, Trivedi MS, De Rosa G and Torchilin V P (2015) Multifunctional polymeric micelles co-loaded with anti-survivin siRNA and paclitaxel overcome drug resistance in an animal model of ovarian cancer. Molecular Cancer Therapeutics 14:1075–1084.
3. Essex S, Navarro G, Sabhachandani P, Chordia A and Trivedi M, et al. (2015) Phospholipid-modified PEI-based nanocarriers for *in vivo* siRNA therapeutics against multidrug-resistant tumors. Gene Therapy 22:257–266.
4. Torchilin V P (2014) Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. Nature Reviews Drug Discovery 13:813–827.
5. Perche F, Biswas S, Wang T, Zhu L and Torchilin V P (2014) Hypoxia-targeted siRNA delivery. Angewandte Chemie International Edition 53:3362–3366.

Biography

Vladimir P Torchilin, PhD, DSc, is a University Distinguished Professor of Pharmaceutical Sciences and Director at Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston. His interests include drug delivery and targeting, nanomedicine, multifunctional and stimuli-sensitive pharmaceutical nanocarriers, biomedical polymers and experimental cancer therapy. He has published more than 400 original papers, more than 150 reviews and book chapters, wrote and edited 12 books, and holds more than 40 patents. Google Scholar shows more than 50,000 citations of his papers with H-index of 100. He is Editor-in-Chief of *Current Drug Discovery Technologies*, *Drug Delivery*, and *OpenNano*, Co-Editor of *Current Pharmaceutical Biotechnology* and on the Editorial Board of many other journals. He received more than $30 M from the governmental and industrial sources in research funding. He has received multiple honors and awards and in 2011, Times Higher Education ranked him number two among Top World Scientists in Pharmacology for the period of 2000-2010.

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