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Stimuli-sensitive combination nanopreparations of siRNA and chemotherapeutic drugs to treat multidrug resistant cancer

Vladimir Torchilin
Northeastern University, USA

Tumor therapy, especially in the case of multidrug resistant cancers, could be significantly enhanced by using siRNA down-regulating the production of proteins, which are involved in cancer cell resistance, such as Pgp or survivin. Even better response could be achieved is 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. 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 have been developed. Additionally, these nanopreparations can be loaded into their lipidic core 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, it was made 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, it was possible to make the systems specific in delivering biologically active agents in tumors, which resulted in significantly improved therapeutic response.

Biography

Vladimir Torchilin is University Distinguished Professor and Director, Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston. He has published more than 350 original papers, more than 150 reviews and book chapters, wrote and edited 10 books and holds more than 40 patents. He is Editor-in-Chief of *Current Drug Discovery Technologies* and of *Drug Delivery*. He is a Member of European Academy of Sciences, Fellow of AIMBE, AAPS and CRS, and received many important national and international awards including the 2013 Blaise Pascal Medal in Biomedicine from EAS. In 2005, he was a President of the CRS and in 2011, Times Higher Education ranked him number 2 among top world scientists in pharmacology for 2001-2010.

v.torchilin@neu.edu