

Reverse Pharmacology of Sceletium Tortuosum

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Abstract

Tumor therapy, especially in the case of multidrug resistant cancers, could be significantly enhanced by using siRNA downregulating the production of proteins, which are involved in cancer cell resistance, such as Pgp or survivin. 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 surroundings. 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 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, 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.

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