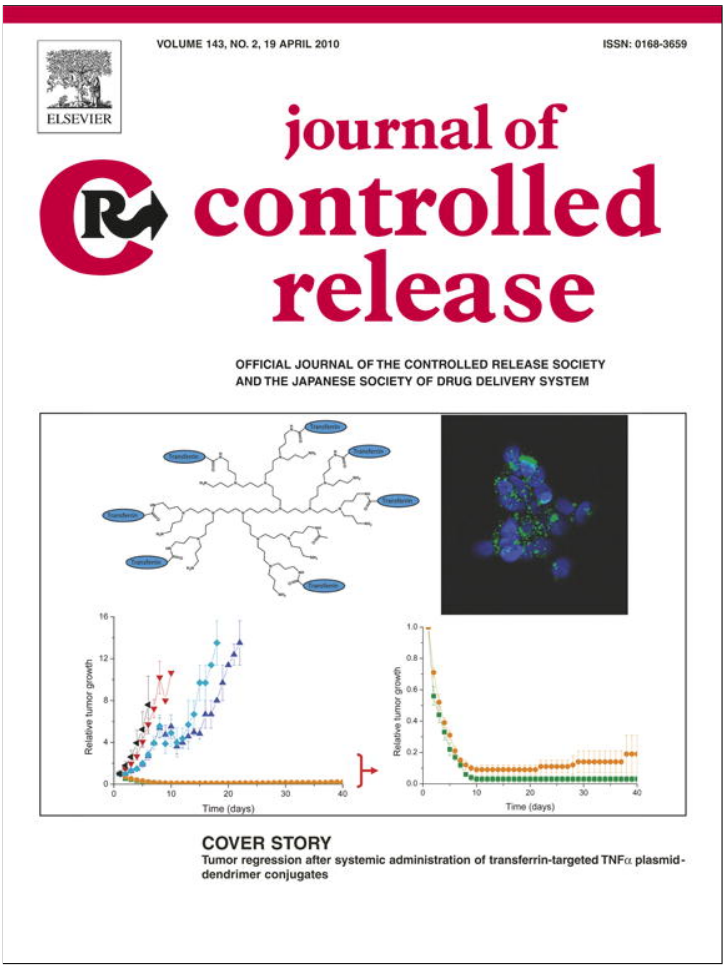

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Cover Story

Tumor regression after systemic administration of transferrin-targeted TNFα plasmid–dendrimer conjugates

With the rapid advancements in cancer genetics, gene therapy is becoming an increasingly promising strategy for the treatment of cancer. However, a major challenge for successful cancer gene therapy is the development of safe and efficacious delivery systems able to deliver therapeutic genes selectively to tumors by intravenous (i.v.) administration. In particular, non-viral gene delivery systems are most preferred. A wide range of cancer cells are known to overexpress the receptor for transferrin, an iron-binding glycoprotein, and naturally transferrin has been used as a targeting ligand toward cancer cells not only for gene delivery but also for drug delivery in general.

An article in this issue by Dr. Dufès' group investigated if the conjugation of a gene delivery system to transferrin could result in a selective gene delivery to the transferrin receptor (TfR) on tumors after i.v. administration [1]. The gene delivery system was based on the promising generation 3 diaminobutyric polypropylenimine. In this article, the authors demonstrated that the i.v. administration of the novel transferrin-bearing polypropylenimine polyplex resulted in gene expression mostly in the tumors. The gene expression levels in the liver, lung and other organs were significantly reduced compared to control polypropylenimine polyplex, thus confirming the targeting efficacy of transferrin to the tumors. As a result of this targeted delivery, the i.v. administration of the targeted delivery system complexed to a therapeutic plasmid encoding for tumor necrosis factor alpha (TNFα) resulted in a rapid and sustained tumor regression, leading to tumor disappearance for 90% of the animals and tumor regression for the remaining 10% of the animals. Furthermore, the treatment was well tolerated, with no apparent signs of toxicity.

The results reported by Dr. Dufès and her colleagues were highly remarkable and interesting for a few reasons. First, it is very rare to see disappearance of tumors in almost all animals tested by the targeted delivery of genes and drugs. Usually, the targeted delivery systems result in suppression of tumor growth, but they have seldom shown complete disappearance of tumors. Second, there is currently no gene medicine commercially available for the i.v. treatment of cancer. Thus, transferrin-bearing polypropylenimine is a highly promising gene delivery system for cancer therapy. Third, the current system could potentially become even better by using genetically modified transferrin with increased binding affinity to iron without affecting the binding affinity to TfR [2]. The genetically engineered transferrin is known to be retained longer within a cell, resulting in the efficacy of transferrin as a drug carrier to TfR expressing cancer cells.

The transferrin-bearing polypropylenimine will be further investigated by Dr. Dufès's group on various cancer models with different therapeutic strategies. There is no doubt that highly efficient gene delivery system will be developed soon for clinical applications, and for now Dr. Dufès seems to be at the forefront of achieving such a goal.

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Kinam Park
Purdue University,
Departments of Biomedical Engineering and Pharmaceutics,
West Lafayette, Indiana, USA
E-mail address: kpark@purdue.edu.

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