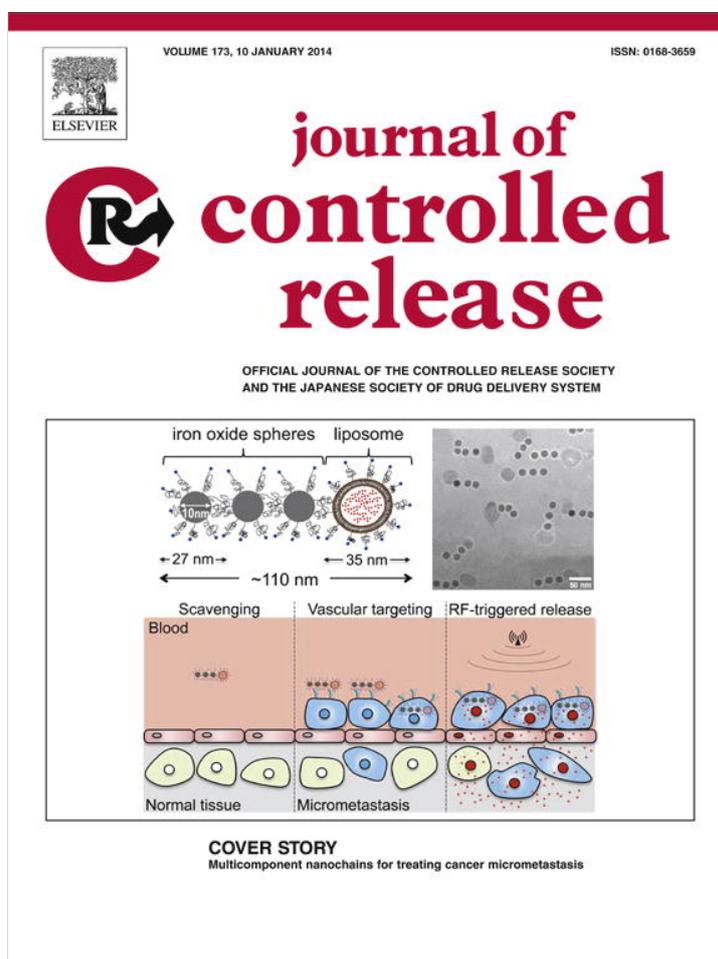


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## Cover Story

## Multicomponent nanochains for treating cancer micrometastasis

Cytotoxic drugs, most of which are extraordinarily potent, are randomly dispersed throughout the body in chemotherapy. This tends to result in suboptimal doses for eradication of micrometastatic disease. Recently, it was suggested that the drug delivery field takes aim at cancer metastasis [1]. This stems from the fact that most chemotherapy is designed to focus on primary tumors, although metastatic disease is responsible for the vast majority of cancer deaths. The current tumor-targeted drug delivery is mostly based on the so-called enhanced permeability and retention (EPR) effect of nanoparticles. Many recent publications, however, indicate that the impact of the EPR effect is marginal at best [2]. This explains the absence of any development of nanoparticle formulation in clinical applications. The results obtained from the mouse studies are disconnected from clinical practice. Typically, when a patient is diagnosed with cancer, the first-line treatment includes surgery to remove the primary tumor, followed by chemotherapy to eradicate any residual disease, including micrometastases at distant organs. Nanoparticle-based drug delivery may be useful in well-vascularized tumors with several millimeters in diameter. It is ineffective against micrometastases, which present small clusters of malignant cells dispersed within variable tissue types.

In this issue, Professor Efstathios Karathanasis and his colleagues report the design of a multicomponent nanochain which was specifically designed to consider the microenvironment of micrometastasis [3]. The nanochain particle was comprised of three iron oxide nanospheres and one doxorubicin-loaded liposome chemically linked into a linear, chain-like assembly. Contrary to traditional small-molecule drugs, the chain-like shape of the particles enabled them to specifically reach sites of micrometastasis *via* vascular targeting. The nanochain utilized a cyclic RGD peptide as a ligand to target the  $\alpha_v\beta_3$  integrin receptor, which is overexpressed on metastatic foci resident in blood vessels. The size, shape and flexibility of the nanochains encouraged the lateral drift and margination of the particles towards the blood vessel walls in microcirculation (*i.e.*, continuous scavenging of vascular walls), and targeting avidity of nanoparticles (*i.e.*, latching on vascular target) due to geometrically enhanced multivalent attachment on the vascular target. Within 2 h after injection, highly specific vascular targeting of the nanochains resulted in about 6% of the administered dose being localized in micrometastases in the lungs in a mouse model of metastasis. As expected, non-targeted liposomes or cRGD-targeted liposomes exhibited slightly less than 1% accumulation in lung micrometastases.

The subsequent event after successful targeting of nanochains to micrometastases is also essential. The drug molecules must spread to all the metastatic cancer cells, especially the hard-to-reach ones, resulting in widespread anticancer activity throughout the entire volume of micrometastatic sites. Two hours later, after nanochains slip from the blood stream and congregate in micrometastases, a "mild" radiofrequency (RF) field was applied outside near the body. The field caused the iron oxide nanospheres of the nanochain to vibrate, breaking

open the liposome spheres and spreading the drug to the entire volume of micrometastatic sites. The nanochains were tested *in vivo* using the murine 4T1-GFP-luc breast cancer cells, which represent a model of triple-negative breast cancer. For more careful recapitulation of clinical breast cancer settings, they surgically resected primary 4T1 tumors, developed in the mammary fat pad of mice, whose micrometastatic foci remained intact. Treatments were administered at a dose of 0.5 mg/kg doxorubicin, which is 10–20-fold lower than the typical clinical regimens of liposomal doxorubicin. Most importantly, while 100% of mice treated with various treatments died within 50 days, 57% of the nanochain-treated group was still alive after 140 days.

In another example of selective activation of anticancer drug delivery in this issue, Professor Basar Bilgicer and his colleagues present the synthesis of a series of photosensitive Pt(IV)-azide prodrugs derived from cisplatin [4]. These prodrugs were incorporated in self-assembling micelles. Upon UVA irradiation, the micelles rapidly released biologically active Pt(II). While small-molecule drugs exhibited negligible therapeutic benefits in the H22 murine hepatocarcinoma model, the application of UVA irradiation on animals treated with the micelles resulted in significantly improved efficacy.

Translation of the nanochain approach to clinical practice will undoubtedly require additional studies. For instance, application of a RF field in a specific area of the human patient will need to be better understood and optimized. But the work by the Karathanasis team indicates that the increased avidity resulting from multifunctionality provides an additional avenue to tackle the complexity of the aggressive forms of cancer facilitating enhanced treatment of hard-to-reach cancer sites.

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