Press Release

Creating Smart Nanomachines to Detect Highly Invasive Cancer After Surgery and Prevent Recurrence – Cancer Metastasis and Recurrence Prevention

Summary:

- Matrix metalloproteinases (MMPs) is an enzyme required for cancer cells to metastasize/invade, and cancer cells with higher MMP activity have higher metastasis ability and progress quickly.
  In this study, we created polymersomes (smart nanomachines) that act specifically in tissues that overproduce MMPs, prevent cancer metastasis, and developed a method to remove residual tumor tissue that could not be visually confirmed after surgery.
- We simultaneously loaded the cell division inhibitor colchicine and the MMP inhibitor marimastat into MMPs-responsive polymersomes as an enzymatically transformable nanomachine designed to achieve transformation following dePEGylation by cleavage of the inserted substrate peptide by MMPs. The effect on malignant tumors with high MMPs activity was evaluated.
- During transformation, nanomachines with exposed guanidine residues easily penetrate into cells, and at the same time, by releasing the contained drugs, it exerts an anti-cancer effect.
- Evaluating drug uptake using HT1080 cells derived from human fibrosarcoma that overproduce MMPs, studying pharmacokinetic and nano-bio interaction using a confocal laser scanning biomicroscope and evaluating metastasis inhibitory effect using triple-negative breast cancer transplantation model, the results were published in Advanced Materials (IF = 30.849 in 2021).

J. Li, Z. Ge, K. Toh, X. Liu, A. Dirisala, W. Ke, P. Wen, H. Zhou, Z. Wang, S. Xiao, J. F. R. Van Guyse, T. A Tockary, J. Xie, D. G.-Carter, H. Kinoh, S. Uchida, Y. Anraku, and K. Kataoka, Advanced Materials, 2021.

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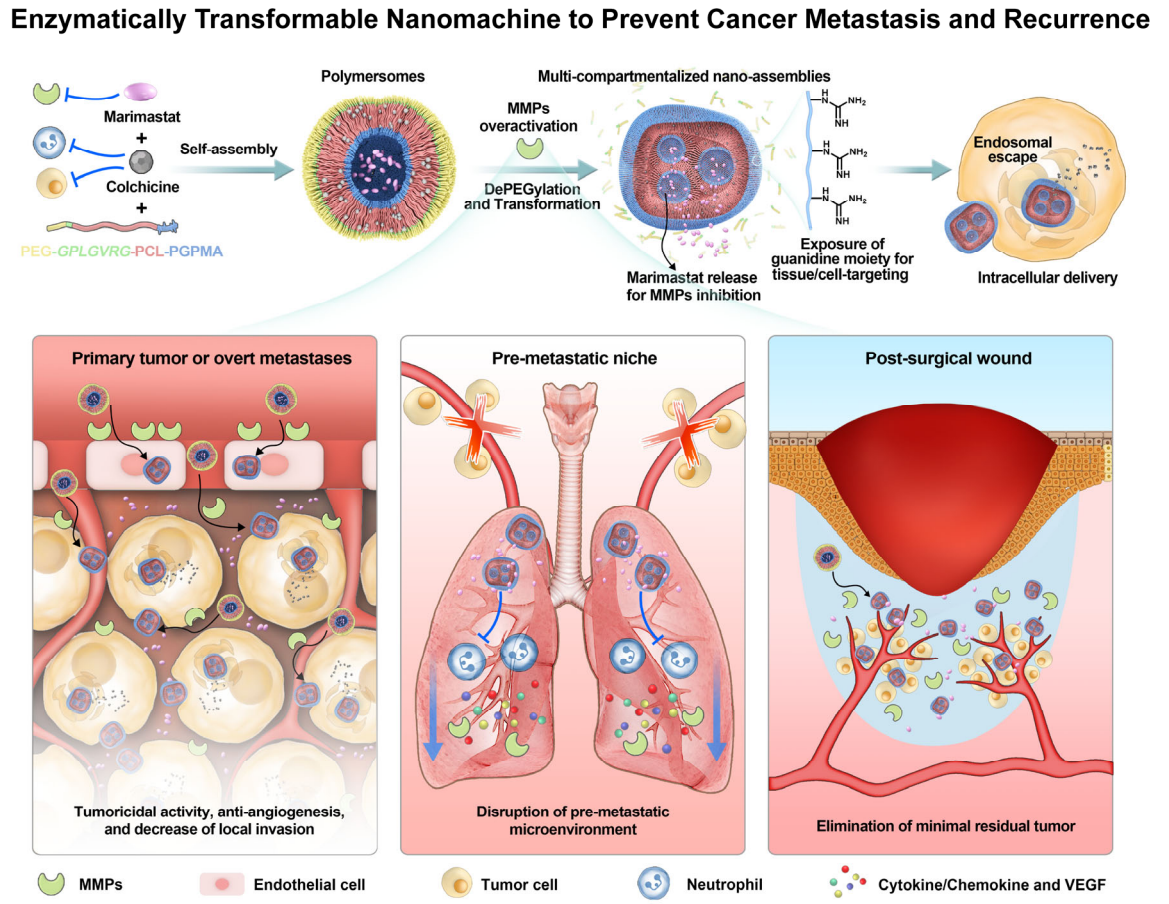
October 8, 2021, Kawasaki (Japan) and Hefei (China): The Innovation Center of NanoMedicine, Kawasaki Institute of Industrial Promotion (Director General: Kazunori KATAOKA, location: Kawasaki-ku, Kawasaki-City; abbreviated name: iCONM), in collaboration with the Chinese Academy of Science (CAS) Key Laboratory of Soft Matter Chemistry (USTC: University of Science and Technology), has created nanomachines that

detect MMPs (matrix metalloproteinases), a principal enzyme for cancer cells to invade normal tissue, and deliver anticancer drugs according to an announcement in the journal Advanced Materials (IF = 30.849). As it can target highly invasive cancer cells, it is expected to inhibit cancer metastasis and recurrence.

Cancer is known as a malignant tumor due to its characteristics of metastasis, recurrence, and invasion, and preventing them is one of the most effective ways for treatment. When cancer cells metastasize, they need to pass through (invade) normal tissues, and in doing so, they use extracellular proteases (proteolytic enzymes) called MMPs to destroy the fibrous tissue (matrix) that binds cells to cells and tissues to tissues. In this study, we focused on tissues and cells that overproduce MMPs and incorporated the cell division inhibitor colchicine and the MMP inhibitor marimastat into MMPs-responsive polymersomes as an enzymatically transformable nanomachine (ETN). The ETN was designed to possess an amino acid sequence that serves as a specific cleavage site for MMPs and thus be capable of releasing the PEG and exposing the guanidine residue after cleavage. In the drug uptake experiment using human fibrosarcoma-derived HT1080 cells, we found that the fluorescently labeled ETN (Cy5-ETN) had a 10-fold higher uptake than that of an inert vehicle without enzymatic transformation behavior. High cellular uptake enabled strong cytotoxicity of colchicine-loaded ETN with IC50 = 0.015 μM compared to the inert vehicle with IC50 = 0.402 μM.
Observation of mice treated with ETN using confocal laser scanning biomicroscopy showed no leakage out of blood vessels in the auricle and normal liver; strikingly, the nanomachines were found to extensively invade the tumor-associated tissues in breast cancer with high MMPs expression.

In pharmacological experiments with mice, we evaluated the antitumor effect for primary and secondary tumor using MDA-MB-231/LM2 (human) and 4T1 (mice) triple-negative breast cancer models. As a result, the ETN simultaneously encapsulating with colchicine and marimastat had a strong antitumor effect and prolonged survival in both triple-negative breast cancer models. In addition, on the basis of metastasis-prone phenotype of this model after orthotopic transplantation, the ETN was also confirmed to efficiently inhibit lung metastasis because of residual tumor targetability. Our results prove an applicable technology for not only to cancers but also to other diseases with high expression of MMPs.



Kawasaki Institute of Industrial Promotion (KIIP)

Kawasaki Institute of Industrial Promotion was established in 1988 funded 100% from Kawasaki City for the purpose of coping with the hollowing out of industry and changes in the demand structure. In order to realize a higher level of market development, transforming R&D type companies, training technological capabilities to support it, human resources development, understanding market needs, etc., by utilizing the functions of the Kawasaki, KIIP has been contributing to revitalize the local economy by promoting exchanges of local industry information, advancing technology and corporate exchanges with establishment of a R&D institutions, developing creative human resources through workshops and promoting businesses such as expanding sales channels through exhibition business.

https://www.kawasaki-net.ne.jp/

Innovation Center of NanoMedicine (iCONM)

Innovation Center of NanoMedicine (iCONM) started its operation in April 2015 as a core research center in life science field at King SkyFront on the request of Kawasaki city that KIIP utilized national policies as a business operator and proposer. It is a unique research center that the world has ever seen which is designed for the purpose of promoting open innovation through industry-academia-government/medical-engineering collaboration, prepared with state-of-the-art facilities and experimental equipment, that enables comprehensive research and development from organic synthesis / microfabrication to preclinical testing.

iCONM: https://iconm.kawasaki-net.ne.jp/en/index.html

University of Science and Technology of China (USTC)

The University of Science and Technology of China (USTC) is a public research university of China with scientific and technological research as core strength, under the leadership of the Chinese Academy of Sciences (CAS). Its foundation in 1958 was hailed as "A Major Event in the History of Chinese Education and Science.". USTC has three National Research Institutions and 6 State Key Laboratories and 18 Key Laboratories of the CAS. USTC actively promotes cooperation and exchange with around 100 universities and research institutions in more than 30 nations and regions. In recent years, USTC is ranked in the world's top 100 universities in the most-widely read university rankings.

USTC: http://en.ustc.edu.cn

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