Press Release

The ultra-small nanomedicines which can stably deliver oligonucleotides in the bloodstream for the therapy of refractory cancers.

・Ultra-small nanomedicines of approximately 18 nm were fabricated by dynamic ion-pairing between Y-shaped block copolymers and nucleic acid drugs, such as siRNA and antisense drugs.
・Chemically modified and double-stranded oligonucleotides dramatically enhanced the stability of the ultra-small nanomedicines in the blood circulation.
・The ultra-small size allows for high permeability in cancer tissues by slipping through the cracks in tumor vasculatures and stromal tissues.
・Clinical trials and preclinical studies using the developed ultra-small nanomedicines are proceeding for cancer therapy.
・Published in the website of Journal of Controlled Release on January 6.
https://doi.org/10.1016/j.jconrel.2021.01.001

January 19, 2021 – Kawasaki in Japan: The Innovation Center of NanoMedicine (Director General: Prof. Kazunori Kataoka, Location: Kawasaki-City in Japan, Abbreviation: iCONM) recently developed an ultra-small nanomedicines called Unit Polyion Complex (uPIC)* in collaboration with a group led by Prof. Kanjiro Miyata in Department of Material Engineering, Graduate School of Engineering, The University of Tokyo. uPICs with a diameter of about 18 nm have an excellent permeability in cancer tissues, and thus, they are expected to selectively deliver small nucleic acid drugs to intractable cancers, such as brain tumors with very narrow capillaries and pancreatic cancer coated with tissue called fibrous stroma.

Nucleic acid drugs**, such as messenger RNA (mRNA), small interfering RNA (siRNA), and antisense oligonucleotides (ASO), have the advantage of being easier to manufacture and less costly than antibody drugs. However, they are rapidly decomposed by nucleases when they are injected into human. Recently, a variety of nanomedicines are developed to overcome this drawback. In particular, lipid-based nanomedicines are highlighted as mRNA vaccines that prevent new coronavirus infections, even though lipid component-mediated adverse events, such as anaphylactic shock, remain to be further investigated. For the

nucleic acid delivery, we are focusing on the development of polymeric nanomedicines***, which are composed of non-biological components to avoid the risk of immunological responses.

uPICs are formed through an electrostatic interaction between "Y-shaped block copolymers (YBCs) comprising branched poly(ethylene glycol) and cationic polylysine" and "a single molecule of nucleic acid drugs". Since uPICs carry only one molecule of oligonucleotide, their size (~18 nm) can be adjusted to be dramatically smaller than that of existing nanomedicines using lipids (~100 nm). Another feature is that uPICs maintain a dynamic equilibrium with free YBCs,* allowing for the excellent stability of uPICs in the bloodstream. Due to these two features, ultra-small size and high stability, uPICs are able to deliver oligonucleotides to brain tumors equipped with the blood-brain tumor barrier. In the paper published in J. Control. Release on January 6, we focused on the structure of oligonucleotides in order to further enhance the stability of uPICs in the blood. As a result, we succeeded in significantly extending the blood half-lives of uPICs through two approaches: (1) using chemically modified nucleic acids and (2) changing oligonucleotides from single-strand to double-strand via hybridization. The obtained results show the great potential of nanomedicine for the oligonucleotide delivery. Clinical trials and preclinical research using uPICs have been already launched, and it is expected that excellent nanomedicines will be produced one after another in near future.

*uPIC（unit polyion complex）：Nanomedicines consisting of one molecule of oligonucleotide and one or two molecules of Y-shaped block copolymer(s), of which the size is approximately 18 nm and is in dynamic equilibrium with free Y-shaped block copolymers in human body. See the demonstration film => https://youtu.be/E90zF6_gL28

S. Watanabe, K. Hayashi, K. Toh, H. J. Kim, X. Liu, H. Chaya, S. Fukushima, K. Katsushima, Y. Kondo, S. Uchida, S. Ogura, T. Nomoto, H. Takemoto, H. Cabral, H. Kinoh, H. Y. Tanaka, M. R. Kano, Y. Matsumoto, H. Fukuhara, S. Uchida, M. Nangaku, K. Osada, N. Nishiyama, K. Miyata and K. Kataoka, ”In vivo rendezvous of small nucleic acid drugs with charge-matched block catiomers to target cancers” Nature Communications 10, 1894 (2019) (https://www.nature.com/articles/s41467-019-09856-w)

**Nucleic acid drugs：A drug that treats a disease by acting on the gene (DNA) that causes a specific disease and the mRNA transcribed from it by controlling the transcription and expression of genetic information. Various drugs are studied and developed, such as antisense drugs that bind to nucleic acids that serve as genetic information and inhibit the transcription, and siRNA that cleaves mRNA and causes it to lose its function.

See：http://www.nihs.go.jp/mtgt/section-1/related%20materials/0-19.pdf

***Polymeric nanomedicines：Micelles (nano-micelles) with a diameter of several tens of nm formed by associating amphipathic polymers with various functional molecules in water.

H. Cabral, K. Miyata, K. Osada, K. Kataoka, “Block copolymer micelles in nanomedicine applications” Chem. Rev.118 (14) 6844-6892 (2018) (DOI: 10.1021/acs.chemrev.8b00199)

Public Interest Incorporated Foundation KAWASAKI INSTITUTE OF INDUSTRIAL PROMOTION

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, KAWASAKI INSTITUTE OF INDUSTRIAL PROMOTION 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.

http://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 KAWASAKI INSTITUTE OF INDUSTRIAL PROMOTION 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.

https://iconm.kawasaki-net.ne.jp/en/

Center of Innovation Program (COI)

The COI program is a research and development program under the Ministry of Education, Culture, Sports, Science and Technology and the Japan Science and Technology Agency. The program employs the backcasting approach and set interdisciplinary and collaborative R&D themes that should be challenged at the present from the issues that are underlying in the future society. Eighteen centers have been established nationwide to realize radical innovation through industry-academia collaboration which cannot be accomplished by industry and academia alone.

The Kawasaki center is the only COI center managed by local governments, not universities, and the research projects carried out there are called COINS (Center of Open Innovation Network for Smart Health).

COI: https://www.jst.go.jp/tt/EN/platform/coi.html

COINS: https://coins.kawasaki-net.ne.jp/en/

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