# Researchers Develop Ultra-Small Nanomedicines to Target Intractable Cancers

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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.

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## Main body

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: using chemically modified nucleic acids and 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.

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