May 13, 2025
Innovation Center of NanoMedicine
Toagosei Co., Ltd.

Toagosei and Innovation Center of NanoMedicine (iCONM) Announce the Conclusion of a Collaborative Research Agreement on an Innovative siRNA Medication for Triple-negative Breast Cancer Treatment

Summary of Disclosure

- Toagosei and Innovation Center of NanoMedicine (iCONM) concluded a collaborative research agreement on the development of a medication for the treatment of triple-negative breast cancer (TNBC) on May 1, 2025
- This collaborative research will combine Toagosei's siRNA design technology with iCONM's gene delivery technology
- TNBC, a typical example of unmet medical needs, is a breast cancer subtype with the poorest prognosis among all breast cancer types, for which limited treatment options are available
- We will develop an siRNA for TDP-43, a gene that plays a role in causing amyotrophic lateral sclerosis (ALS) as the first target and apply it to the treatment of TNBC
- We are planning to launch a clinical trial within five years
- This collaborative research is expected to not only become a springboard for the treatment of many intractable diseases but also lead to preventing another new virus pandemic

Innovation Center of NanoMedicine (Director General: Kazunori Kataoka; hereinafter "iCONM") and Toagosei Co., Ltd. (President, COO: Hidenori Kobuchi; hereinafter "Toagosei") have concluded a collaborative research agreement dated May 1, 2025 on the development of a small interfering RNA (siRNA) medication (Note 1) as a new treatment for triple-negative breast cancer (hereinafter "TNBC"). TNBC is a breast cancer subtype with the poorest prognosis among all breast cancer types, and is resistant to hormonal therapy and HER2 molecular-targeted drugs (Note 2), which are standard of care for common breast cancers.

TNBC is one of the breast cancer subtypes with the poorest prognosis and accounts for 10 to 15% of all breast cancers. TNBC is also characterized by its rapid disease progression, and its risk of recurrence within five years after diagnosis is higher than other types of breast cancers. There is also an issue that only few treatment options are available for the patients as TNBC is resistant to hormonal therapy and HER2 molecular-targeted therapy used for the treatment of common breast cancers. For that reason, the

development of an effective treatment for TNBC as a new modality (Note 3) is eagerly awaited.

It has been confirmed that an siRNA developed with Toagosei's original siRNA design technology to target the TDP-43 (TAR DNA-binding protein of 43 kDa) gene (Note 4) possesses cytostatic activity in vitro against TNBC cells (under article submission). Meanwhile, iCONM's nano-drug delivery system (DDS) technology using polymeric nano-micelles and unit poly-ion complex (uPIC) (Note 5) has caught the world's attention as a gene delivery technology and already been used in clinical trials for breast and other cancers. This collaborative research is aimed at developing an innovative, in vivo effective siRNA medication by combining Toagosei's siRNA design technology with iCONM's nano DDS technology and launching a clinical trial within five years.

Toagosei's siRNA design technology is to directly inhibit the abnormal expression of disease-causing genes. We therefore believe that this technology can be applied to address many unmet medical needs, including treatments for intractable diseases such as various refractory cancers, neurological diseases, and rare diseases, as well as prevention of rapid infection spread when a new virus pandemic occurs. In the meantime, iCONM's unique nano DDS technology is evolving every day. By combining this technology with innovative technologies, including those for penetrating interstitial barriers (Note 6) in the tumor microenvironment and for tissue-specific drug release system using nano-micelles (Note 7), which are key to overcoming refractory cancers, the minimum required amount of siRNA can be delivered to specific sites, which is expected to lead to offering treatments that have a favorable balance of efficacy and safety at reasonable costs.

Through the advancement of this collaborative research, we will offer TNBC patients a treatment option as a new modality and provide a process that promptly and accurately proceeds with the development of siRNA medications to address various global unmet medical needs, thereby contributing to the better future of medicine.

Reference 1: siRNA-related patents owned by Toagosei
・siRNA based on RNA sequence of SARS-CoV-2 and use thereof (Patent No. US 12,209,242)
https://patentimages.storage.googleapis.com/b5/3d/2c/0794836e3e4012/US12209242.pdf
Reference 2: siRNA-related patents applied for by Toagosei
・COMPOSITION AND USE THEREOF (PCT/JP2024/006139)
・COMPOSITION AND USE THEREOF (PCT/JP2024/006140)

Note 1 siRNA medications: Humans are equipped with a defensive mechanism called RNA interference (RNAi) that inhibits protein synthesis where exogenous mRNA, which has penetrated the cell through virus infection or other causes, is used as a template. siRNAs are 21-23 base pair double-stranded short-interfering RNAs involved in RNAi, and inhibit the expression of sequence-specific genes by degrading specific mRNA sequences. siRNA medications refer to nucleic acid medications that utilize the aforementioned nature of siRNAs and are designed for the treatment of specific diseases based on gene sequences relating to the expression of disease-causing abnormal proteins.

Note 2 HER2 molecular-targeted drugs: HER2 is a cell growth factor overexpressed in 15 to 30% of breast cancer patients. HER2-positive breast cancer used to be regarded as a refractory cancer due to its resistance to hormonal therapy. However, the treatment outcome of breast cancer has greatly improved since the approval of Trastuzumab, which binds to HER2 proteins, as the world's first human monoclonal antibody therapeutic drug in the United States in 1998.

Note 3 Modality: In the pharmaceutical business field, modality refers to basic drug-discovery technology. Compared to the end of 20th century, when the main stream of modality was small-molecule medications, antibody drug and other bio-pharmaceutical technologies are now evolving remarkably. Nucleic acid medications, such as siRNA and mRNA, are currently capturing attention as a new drug discovery modality.

Note 4 TDP-43: TAR DNA-binding protein of 43 kDa (TDP-43) is a protein that mainly relates to neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). TDP-43 was identified as a protein binding to an RNA regulatory sequence called trans activation responsive region (TAR) that exists in the terminal repeat sequence of a human immunodeficiency viral (HIV-1) gene for the first time in 1995. In particular, in ALS, nerve cells are damaged by the abnormal accumulation and aggregation of TD-43, which is believed to promote disease progression. Moreover, recent cancer studies have uncovered new insights that TDP-43 enhances the steaminess of breast cancer stem cells, and that decreased expression of TDP-43 can interfere with the progression of TNBC.

Note 5 Unit poly-ion complex (uPIC): A uPIC is a technique developed by iCONM to stabilize nucleic acids in the human body. The technique has already been used in clinical trials for refractory breast cancer. In general, nucleic acids are negatively charged. A uPIC refers to a complex generated by binding positively charged basic amino acid polymers (e.g., ornithine, lysine) to polyethylene glycol (PEG) 2 to form a Y-shaped block, and then electrostatically binding the block to nucleic acids. The complex has a minuscule size of 10 to 20 nm, making it possible to be delivered to refractory cancer cells covered by interstitial tissue.

Note 6 Interstitial barriers: In the microenvironment of refractory cancer cells, a thick layer of fibrous tissue called interstitial tissue is developed to protect the cancer cells from being attacked by

immune cells. Since such interstitial matrix has a size of 20 to 30 nm, nanoparticles of less than 20 nm are required to penetrate the interstitial barriers.

Note 7 Tissue-selective drug release system: Nanocarriers and drugs included in such carriers are generally linked by chain organic compounds called linkers. When nanocarriers are delivered to the targeted tissue, linkers are cleaved under the specific environment to release the drugs.

■ About Innovation Center of NanoMedicine

Innovation Center of NanoMedicine (iCONM) was established by its operating body KAWASAKI INSTITUTE OF INDUSTRIAL PROMOTION at the request of Kawasaki City as a pioneering facility that plays a core role in the formulation of a life-science research base in King SkyFront in Tonomachi, Kawasaki City, and the center started its operations in April 2015. Equipped with the latest equipment and experimental tools that enable the center to cover end-to-end research and development, from organic synthesis, microfabrication to non-clinical study, iCONM is a very unique research center designed to promote open innovation through collaboration among government, industry, and academia as well as between medicine and engineering. This makes the center unrivaled anywhere else in the world.

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

■ About Toagosei

Toagosei develops and sells products that make life more fulfilling in broad areas, ranging from basic materials used in diverse industries, intermediate materials with various functions to end products like an instant glue Aron Alpha. As part of its biotechnology research initiatives, Toagosei, on the initiative of Institute for Advanced Sciences launched in Tsukuba City in 1991, is working together with universities and other research institutions to actively pursue research and development of nucleic acid and functional peptide design based on bioinformatics technology.

In 2024, Toagosei also launched Kawasaki Frontience R&D Center in King SkyFront in Tonomachi, Kawasaki City. With its favorable location, the center is promoting advanced research and development and early commercialization in growth areas such as medical care materials through collaborative development with neighboring research institutions.

https://www.toagosei.co.jp/english/index.html

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