Press Release

Development of a safe liver sinusoidal wall coating agent to significantly increase the efficacy of gene therapy drugs

Controlling the clearance of gene therapy drugs at the liver sinusoidal wall

- New technology to improve the efficacy and safety of gene therapy drugs was developed.
- A transient, selective, and safe coating of the liver sinusoidal wall was achieved. As a result, the clearance of gene therapy drugs was effectively prevented.
- Consequently, the gene transfer efficiency into cardiac muscle, skeletal muscle, and cancer tissue was boosted.
- This research will be published in Science Advances (IF = 12.804) on June 27 (JST).

5pm on June 26, 2020 – Kawasaki/Japan: The Innovation Center of NanoMedicine (iCONM), the National Institute for Quantum Science and Technology (QST), and the University of Tokyo jointly announced that a reagent for the selective and safe coating of the liver sinusoidal walls to control the clearance of gene therapy drugs was successfully developed. The contents of this research will be published in Science Advances by the American Association for the Advancement of Science (AAAS) at 2:00 pm on June 26, east coast of the United States (Japan standard time: 3:00 am on 27th): A. Dirisala, S. Uchida, K. Toh, J. Li, S. Osawa, T. A. Tockary, X. Liu, S. Abbasi, K. Hayashi, Y. Mochida, S. Fukushima, H. Kinoh, K. Osada, Kazunori Kataoka, ”Transient stealth coating of liver sinusoidal wall by anchoring two-armed PEG for retargeting nanomedicines”.

Recently, gene therapies have been successively approved in Europe, US, and Japan, and are expected to provide novel therapeutic options for cancer, chronic diseases, acquired and inherited genetic disorders. Whilst this is promising, in reality, when gene therapy drugs are systemically administered to living organisms, they are rapidly eliminated and metabolized in the liver, thus impeding the delivery of a sufficient amount to the target organs and raising the toxicity concerns. This elimination by the liver is caused by the adsorption of the gene therapy drugs to the vascular wall of the liver sinusoid, which is an intrahepatic capillary. To overcome this issue, we conceived to selectively coat the liver sinusoidal wall using polyethylene glycol (PEG). However, a long-term coating may impair the normal

physiological functions of the liver, and therefore the coating should be transient. In addition, coating needs to be selective for liver sinusoids, as coating the blood vessels throughout the body would not only cause adverse effects but also decrease the delivery amount of gene therapy drugs to target organs. Towards this end, we have developed a coating agent with two-armed PEG conjugated to positively charged oligolysine, which demonstrated the selective coating on the liver sinusoidal wall, the first-of-its-kind strategy in the world. Interestingly, the coating with two-armed PEG was excreted into bile within 6 hours after binding to sinusoidal walls, while the coating with single chain of linear PEG bound to oligolysine persisted in the walls for a long time. In this way, the precise molecular design was necessary to achieve a transient coating.

This coating was subsequently applied to boost the delivery efficacy of gene therapy drugs. Adeno-associated virus (AAV) is widely used for viral gene therapy drugs, and its serotype 8 (AAV8) targets myocardium and skeletal muscles. When AAV8 was administered after prior coating of two-armed PEG to the liver sinusoidal wall, the transfer of AAV8 to the liver was suppressed, and as a result, the gene transfer efficiency into the myocardium and skeletal muscles was improved by 2 to 4 times. This approach is promising for the treatment of muscular dystrophy. In addition, we expanded the use of our strategy to virus-free gene delivery systems, which allows more economically attractive and safe gene therapy. We have been working on non-viral gene therapy for malignant tumors using plasmid DNA-equipped smart nanomachine for over 10 years. When the coating agent was used for this system, the adsorption of nanomachines to the sinusoidal wall was suppressed, resulting in an approximately 10-fold improvement in DNA transfer efficiency to colon cancer. As described above, we have succeeded in boosting the activity of gene therapy drugs while ensuring safety by using the coating agent developed this time.

The above findings are summarized as follows:

- The coating agent with two-armed PEG selectively coated the liver sinusoid wall for several hours and was then excreted in the bile.
- The coating agent with single chain of linear PEG is not excreted in bile and coated the liver sinusoidal wall for more than 9 hours, which raises a safety concern.
- The coating agent with two-armed PEG had selectivity for the liver sinusoid wall, without coating the blood vessels in the connective tissues.
- The coating agent improved the gene transfer efficacy to the myocardium and skeletal muscles using the AAV vector by 2 to 4 times, and the gene transfer efficiency to colorectal cancer using DNA-loaded smart nanomachines by 10 times.
- As a result, our approach is expected to allow for improving the effect of gene therapy drugs and reducing their dose needed to obtain therapeutic outcome, which will lead to the reduction of medical cost and adverse event opportunities.

Innovation Center of NanoMedicine:

The Innovation Center of NanoMedicine (iCONM) is a leading facility of King Skyfront, that is a biotech and healthtech innovation cluster in Kawasaki City. iCONM started the operation in April 2015 with Kawasaki Institute of Industrial Promotion in order to drive "Center of Open Innovation Network for Smart Health (COINS)" as a part of Japanese governmental research program "Center of Innovation (COI) Stream". Designed for the purpose of promoting "open innovation" through industry-academia-government and medicine-engineering collaborations with state-of-the-art facilities and experimental equipment capable of conducting the R&D from organic synthesis and micro-processing to preclinical studies. This is a very unique research center that is hardly found in the world.

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

National Institutes for Quantum and Radiological Science and Technology:

The National Institutes for Quantum and Radiological Science and Technology (QST) was established in April 2016 to promote quantum science and technology in a comprehensive and integrated manner. The new organization was formed from the merger of the National Institute of Radiological Sciences (NIRS) with certain operations that were previously undertaken by the Japan Atomic Energy Agency (JAEA). QST's mission is to raise the level of quantum and radiological sciences and technologies through its commitment to research and development into quantum science and technology, the effect of radiation on humans, radiation emergency medicine, and the medical use of radiation. To ensure that research and development delivers significant academic, social and economic impacts, and to maximize benefits from global innovation, QST is striving to establish world-leading research and development platforms, explore new fields, and serve as a center for radiation protection and radiation emergency medicine.

https://www.qst.go.jp/site/qst-english/

Department of Bioengineering, Graduate School of Engineering, University of Tokyo:

In a society where the population ages and the birth rate declines with the sustainable development being longed for, the Department of Bioengineering aims to contribute to the promotion of health and well-being of the humanity. To achieve this goal, we promote the education and research of bioengineering, which is the multidisciplinary academic field integrating the existing disciplines of engineering and those of life sciences at their interface. The key features of bioengineering are to establish its theoretical basis by understanding and clarifying the interactions of materials and systems with living bodies, and to develop fundamental technologies that control these interactions based on the theory. The control of the interactions with living bodies renders materials and systems far more useful and compatible, promising the birth of groundbreaking medical technologies.

http://www.bioeng.t.u-tokyo.ac.jp/en/overview/index.html