Press Release

Antibody Delivery Technology Empowers Immunotherapy against Glioblastoma and Suppresses Side Effects

Summary:

- An antibody delivery technology was developed based on multiple glucosylated polymers conjugated onto antibodies *via* linkers cleaving in tumor microenvironment.
- The delivery technology enhanced the accumulation of anti-PD-L1 antibody (Avelumab) in glioblastoma by 33-fold compared to unmodified Avelumab by recognizing Glucose Transporter 1.
- In orthotopic glioblastoma models, a single administration of the modified Avelumab at 15% of the standard dose achieved 60% complete response rate, with long-term immune memory.
- The delivery technology suppressed the immune-related adverse events of Avelumab.
- These results are published in Nature Biomedical Engineering (IF = 25.671) on October 12 (JST).
  DOI: 10.1038/s41551-021-00803-z

October 6, 2021, Kawasaki (Japan) and The University of Tokyo (Japan): 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 Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, has succeeded in efficiently delivering an immune checkpoint inhibitor (ICI) into the mouse brain, confirming its high efficacy and specificality in treating orthotopically transplanted mice with glioblastoma (GBM) (*1). The research was published in Nature Biomedical Engineering (*2), and a press briefing was held at 3:30 p.m., October 6. The details of the announcement are as follows:

Immune checkpoints are a normal part of the immune system with the role to prevent an immune response from being so strong that it destroys healthy cells in the body. Immune checkpoints engage when proteins on the surface of immune cells called T cells recognize and bind to partner proteins on other cells, such as some tumor cells. For this discovery, Professor Tasuku Honjo of Kyoto University was awarded the Nobel Prize in Physiology or

Medicine in 2018, with now six types of ICIs (*3) used in clinical practice for cancer treatment. However, while ICIs have shown excellent efficacy against a variety of cancers, they have not shown satisfactory efficacy in clinical trials against malignant brain tumors (including brain metastases). One of the reasons for this is that the blood-tumor barrier formed by the blood vessel walls of brain tumors suppresses the accumulation of immune checkpoint inhibitors in brain tumors. On the other hand, ICI formulations possess dose-limiting toxicity, eventually leading to life-threatening immune-related adverse events.

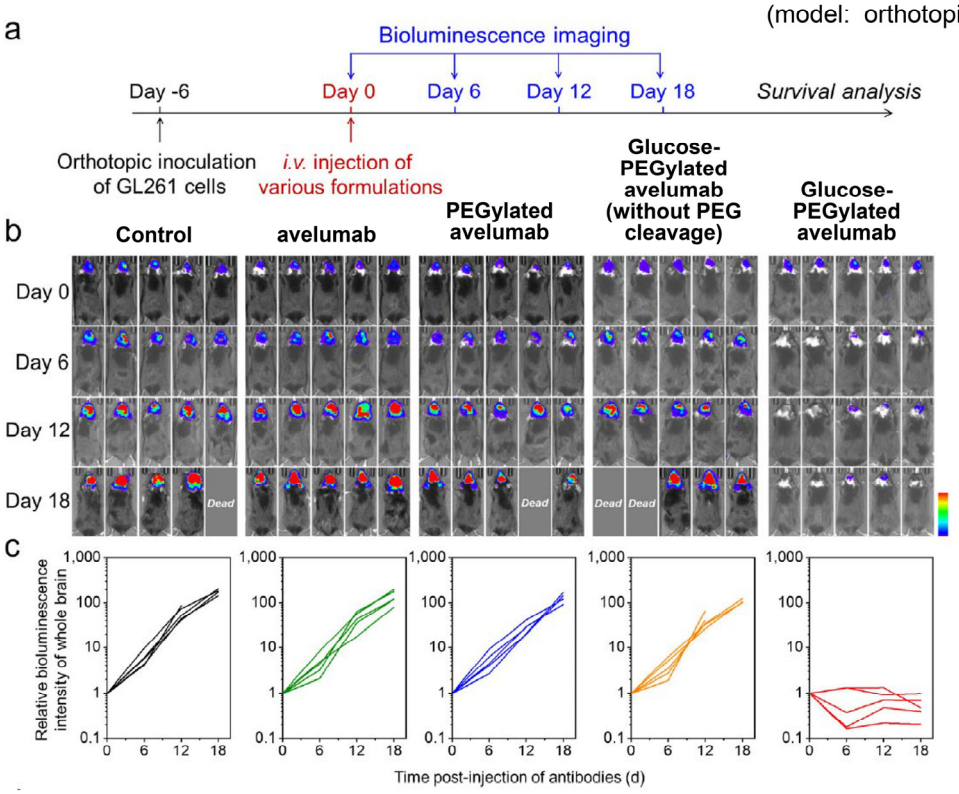
Hence, the goal of this study was to develop a technology to potently increase the accumulation of ICIs in brain tumors, and to achieve both therapeutic efficacy and safety. Avelumab (*4), which has been shown to be immunologically active in both humans and animals, was used as an ICI. As glucose transporter 1 (GLUT1) are over-expressed on brain capillary and GBM vasculature to support the sufficient energy uptake, the ICIs with properly configured glucose molecules smartly recognized the GLUT1 in GBM vasculature to promote access into GBM with ~20-fold accumulation amount as compared to native antibody. Furthermore, the amount of ICI accumulated in the brain tumor site was 33 times higher than that in normal brain tissue, indicating high brain tumor selectivity. Taking advantage of the reductive environment of GBM with elevated extracellular GSH or ascorbate levels that are up-regulated by GSH-dependent enzyme (e.g. glutathione-S-transferases) and hypoxic microenvironment, the specificity of Glc-ICIs was improved *via* introduction of disulfide bond as the linker. Our ICIs formulation retrieved their PD-L1 blocking ability in tumor tissues via PEG chain detachment, while their activity remained muted in healthy tissues. Through efficient delivery and specific immune response, the modified antibodies achieved potent anti-tumor efficacy against preclinical GBM model, which is a challenge for ICIs in a clinical setting (60% complete response rate in a mouse orthotopic GBM model). Furthermore, the drug was administered only once, with a low dose (1.5 mg/kg administered once in this study, compared to the standard drug dose of 10 mg/kg administered multiple times) found to be sufficient to achieve the desired effect.

Upon examination of antitumor immune cells in brain tumors of mice treated with Glc-ICI, it was shown that the number of tumor-attacking natural killer (NK) cells and CD8+ T cells increased, along with the effective re-polarization of M2-like macrophages to M1-like macrophages (an antitumor state). Meanwhile, the immunosuppressive microenvironment was also reshaped with declined population of regulatory T cells (Treg) and bone marrow-derived immunosuppressive cells (MDSCs). In addition, effector memory T cells were found in the spleen of mice that responded to Glc-ICI and whose tumors disappeared within 60 days (complete response), leading to a total rejection of tumor relapse. Although GBM is a malignant tumor that recurs frequently, these results are expected to be applicable to the prevention of GBM recurrence.

Figure 1

COINS Therapeutic effect against glioblastoma

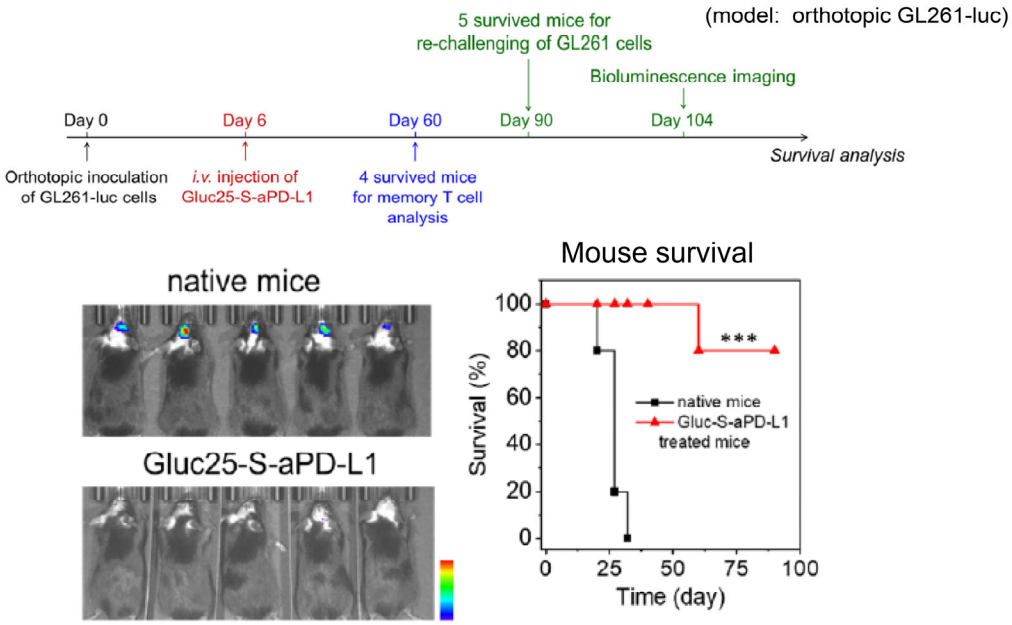
(model: orthotopic GL261-luc)



→ Glucose-PEGylated avelumab prevented the growth of glioblastoma

Figure 2

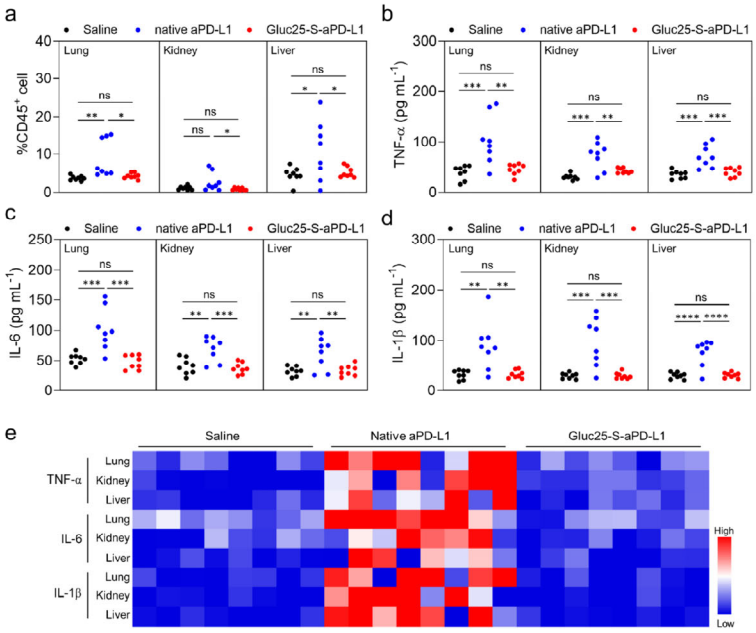
Tumor growth of rechallenged glioblastoma in the mice treated before



80% of the mice pre-treated with glucose-PEGylated avelumab rejected the growth of rechallenged glioblastoma.

Figure 3

Immune reaction in healthy organs



→ **Glucose-PEGylated avelumab increased neither the number of immune cells nor the secretion of proinflammatory cytokines in the lung, kidney, and liver.**

→ **Immune related adverse event (irAE) can be prevented.**

(*1) Glioblastoma: A brain tumor with extremely fast progression and poor prognosis (5-year survival rate: 10.1%), which greatly impairs one's QOL due to the various disabilities that accompany the rapid destruction of the brain. Although surgery is the first choice, it is either inoperable or, even if possible, extremely likely to recur. Although several compounds are in the process of clinical development as drug candidates, no drug therapy can significantly improve survival at present.

(*2) Nature Biomedical Engineering: A sister journal of the British scientific journal Nature, and a leading academic journal in the field of biomedical engineering. It has an impact factor of 25.671 (2020-2021). https://www.nature.com/natbiomedeng/

Thesis Title: Conjugation of Glucosylated Polymer Chains to Checkpoint-Blockade Antibodies Augment Their Efficacy and Specificity for Glioblastoma

Authors: Tao Yang, Yuki Mochida, Xueying Liu, Hang Zhou, Jinbing Xie, Yasutaka Anraku*, Hiroaki Kinoh, Horacio Cabral*, and Kazunori Kataoka

Underline indicates the corresponding author. Authors mark with * are with the Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, and the others are with the Innovation Center of NanoMedicine.

DOI: 10.1038/s41551-021-00803-z

(*3) ICIs approved in Japan: nivolumab (anti-PD-1), pembrolizumab (anti-PD-1), avelumab (anti-PD-L1), atezolizumab (anti-PD-L1), durvalumab (anti-PD-L1), ipilimumab (anti-CTLA-4)

(*4) Avelumab: An immune checkpoint inhibitor developed as a human anti-PD-L1 antibody. It has been approved in Japan under the brand name Baventio for the treatment of unresectable Merkel cell carcinoma, metastatic renal cell carcinoma, and urothelial carcinoma. Although it is a human-type antibody, it is shown to be activated by innate and acquired immunity in animal models.

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

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/

October 6, 2021

Media Contact:
Makoto Shimazaki / Mami Satake
COINS Research Promotion Support Office
Innovation Center of NanoMedicine (iCONM)
KAWASAKI INSTITUTE OF INDUSTRIAL PROMOTION
Email: jimukyoku-coins@kawasaki-net.ne.jp