## SUMMARY

**Title:** Antisense oligonucleotide coupled with drug delivery system as an effective treatment of glioblastoma

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**Abstract:** Glioblastoma (GBM) is the most common and lethal brain tumor. Although current comprehensive therapies include a tumor removal surgery and subsequent chemo and radiation therapies, the median over-all survival of GBM patients is about 14 months. Developing a novel drug for the treatment of GBM is highly desired. It's been increasingly demonstrated that Long non-coding RNAs (lncRNAs) affect the tumor progression via altering the chromatin structure, the microRNA (miRNA)-mediated gene regulation and the interaction with the multiple molecules. We recently showed that an lncRNA, TUG1, promotes self-renewal by sponging miRNA and recruiting polycomb to repress differentiation genes, indicating that it supports the stemness features of glioma cells. We then developed new antisense oligonucleotides (ASO) targeting at TUG1 combined with a new drug delivery system (AntiTUG1), which can be applied intravenously to provide efficient and selective delivery of ASOs to glioma cells at sufficient concentrations to acquire anti-tumor effects (PCT/JP2016/053960, PCT/JP2016/084328).

We established a strong and specific antitumor activity of AntiTUG1 towards a glioblastoma mouse model. It is highly innovative and promising to provide a novel treatment in this devastating disease. Since targeting lncRNAs is thought to act in different mechanisms than other anti-tumor drugs, our approach may provide a novel therapeutic paradigm not only for glioblastoma but also for other refractory cancers.

**Applications / Indications:** Glioblastoma
Pancreas cancer

**Advantages:**

- No effective drugs are currently available for glioblastoma.
- Our drug delivery system is highly specific to the tumor tissues.
- AntiTUG1 effectively inhibits cell growth of human glioma cell lines and

the other types of cancer cell lines (pancreas cancer and breast cancer), while it does not affect normal fibroblast growth.
- No adverse effects of antiTUG1 have been observed in the mouse xenograft model (>20 cases).
- There are no other drugs of the nucleic acid medicine against human glioma.

**Market Overview:**

- There are about 20,000 glioblastoma patients in the states, European countries and Japan.
- Four to six out of 100,000 people are annually diagnosed as glioblastoma.

**Stage of Development:**

- AntiTUG1 is currently in the preclinical stage.
- We will soon start to compile data required for starting a clinical trial, such as GLP toxicology studies with pharmacokinetic studies, and quality-controlled pharmacological studies.

**Patent Information & Publication:**

[Patent]

- PCT/JP2016/053960
- PCT/JP2016/084328
- U.S. Patent Application Serial No. 15/549,803

[Publication]

- Targeting the Notch-regulated non-coding RNA TUG1 for glioma treatment.
  Katsushima K, Natsume A, Ohka F, Shinjo K, Hatanaka A, Ichimura N, Sato S, Takahashi S, Kimura H, Totoki Y, Shibata T, Naito M, Kim HJ, Miyata K, Kataoka K, Kondo Y. *Nat Commun*. 2016; 7: 13616.

**Business Opportunity**

- We would to partner with a pharma company to conduct a Phase I study and further development.

**Contact to**

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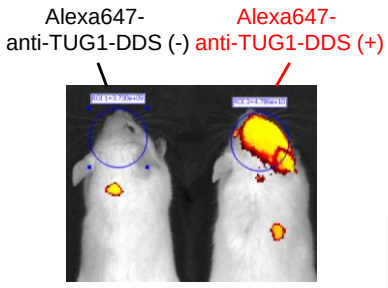
**Appendix:**

# Effects of antiTUG1-DDS in glioma xenograft model

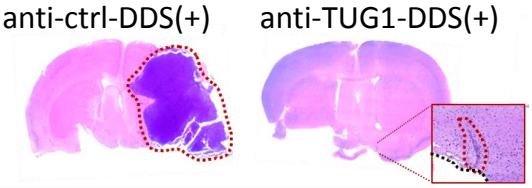



Human glioma stem cells were injected into the mouse brain (right hemisphere) before one month of treatment. Anti-TUG1 with and without DDS (anti-TUG1-DDS (+) and anti-TUG1-DDS (-), respectively), both of which were labeled with fluorescence (Alexa 647), were intravenously injected. After 9 hours, mice were analyzed by in vivo imaging system.

Anti-TUG1-DDS was efficiently accumulated in brain tumor, while it was accumulated in neither normal brain (left hemisphere), liver nor kidney.

Using this DDS, the following arm was performed:

- two times/week for a month
  1) anti-ctrl-DDS(+)（control oligo against luciferase gene）
  2) anti-TUG1-DDS(+)




We found anti-TUG1-DDS was effective as an anti-tumor agent in mouse xenograft model.
We validated this result in multiple animals and found the consistent results.
A mouse, which was not sacrificed, survived without recurrence more than a year.

(Katsushima K. et al., *Nat Commun.* 2016)