SUMMARY

Title: Potent Inhibitor of LSD1 as a treatment of glioblastoma

Investigators: Yutaka Kondo, Professor, Nagoya University
Takashi Umehara, Unit Leader, RIKEN

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.

Lysine-specific demethylase 1 (LSD1/KDM1A) has been known as a key effector of the tumor-propagating cell (TPC) regulatory program. LSD1 suppression triggered cell death exclusively in TPCs. Therefore, LSD1 histone demethylase was identified as a therapeutic target in tumor-propagating cells. In 2010, we developed a small-molecular cell-permeable inhibitor designated as S2101 that selectively inactivates LSD1 by structure-guided drug design (Mimasu et al Biochemistry, 49, 6494, 2010). This compound is commercially available from Calbiochem, and widely used as one of benchmark LSD1 inhibitors. By modifying the chemical structure of S2101, we obtained several novel LSD1 inhibitors, such as S2172, which shows a higher inactivation activity toward LSD1 compared with S2101 (unpublished data; patent JP2017-134173 applied on July 7, 2017). We found that the treatment of glioma stem cell lines with S2172, or its analogue compounds, can result in loss of glioma stemness. We have been further developing LSD1 inhibitors which can highly target at glioma tissues. Since no effective drugs are currently available for glioblastoma, our approach may provide a novel therapeutic paradigm for it.

Applications / Indications: Glioblastoma

Advantages:

- No effective drugs are currently available for glioblastoma.
- [Advantages over other research groups] We developed several LSD1 inhibitors that show a 10-fold stronger activity to inhibit the growth of glioma stem cell lines as compared with other publicly-known compounds.
- [Status of other research groups] No specific LSD1 inhibitors (materials) have been developed for glioma/glioblastoma, except US20160116474 A1 (WO2014205266A2, A3) by Bradley Bernstein's lab where they filed

methods for detecting and treating glioblastoma (including utilization of S2101).

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:

- Basic Research
- FY2018 Plans: To obtain a proof-of-concept for the treatment of glioma stem cell-derived carcinogenesis in mouse xenograft model; and to develop LSD1 inhibitors which can highly target at glioma tissues.

Patent Information & Publication:

[Patent]
Title of the Invention: Compounds that inhibit lysine-specific demethylase 1
Application Country: Japan
Applicants: RIKEN, Nagoya City University and Jichi Medical University
JP Application Number: 2017-134173 (filed on July 7, 2017)
Inventors: Umehara, T., Sato, S., Koyama, H., Yamamoto, H. (RIKEN)
Kondo, Y., Katsushima, K. (Nagoya City University)
Furukawa, Y., Kikuchi, J. (Jichi Medical University)
Status: Filed
[Publication]
1. Mimasu, S. et al. Structurally designed *trans*-2- phenylcyclopropylamine derivatives potently inhibit histone demethylase LSD1/KDM1. Biochemistry, 49, 6494, 2010.
2. Niwa, H. and Umehara, T. Structural insight into inhibitors of flavin adenine dinucleotide-dependent lysine demethylases. Epigenetics 12, 340, 2017.
3. Osada, N. et al. Lysine-specific demethylase 1 inhibitors prevent teratoma formation of human iPS cells. Oncotarget, in press, 2018.

Business Opportunity:

[Outline of Business Plan] To develop candidate compounds for preclinical studies in the treatment of glioblastoma by academia side (RIKEN and Nagoya Univ), and to further conduct clinical trials with the candidate drugs (by a pharma company after licensing out).
[Desired Collaboration Style] Joint Collaboration (e.g. company side: chemical synthesis; academia side: evaluation including xenograft models and ADME) or Licensing only (after academia side develops candidate compounds suitable for preclinical studies)

Contact to:

[Nagoya University]
Division of Cancer Biology, Nagoya University Graduate School of Medicine
Yutaka Kondo, MD, Ph.D.
ykondo@med.nagoya-u.ac.jp
+81-52-744-2463

Center for Advanced Medicine and Clinical Research, Nagoya University Graduate School of Medicine
Hitoshi Fujita, Ph.D.
hitoshi-fujita@med.nagoya-u.ac.jp
+81-52-744-2942

[RIKEN]
RIKEN Center for Life Science Technologies (CLST)
Takashi Umehara, Ph.D.
takashi.umehara@riken.jp
+81-45(045)-503-9457

RIKEN Program for Drug Discovery and Medical Technology Platforms (DMP)
Tadayuki Yamauchi, Ph.D.
tadayuki.yamauchi@riken.jp
+81-45(045)-503-9151

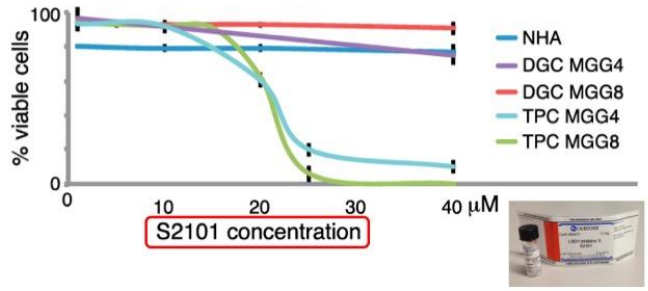
Appendix:

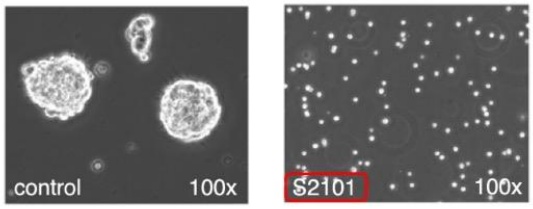
Specific histone lysine demethylase-1 (LSD1) inhibitor as a treatment of glioblastoma

Cell

Reconstructing and Reprogramming the Tumor-Propagating Potential of Glioblastoma Stem-like Cells

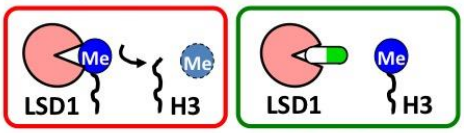
- So far, AML is the major target (Oryzon/Roche & GSK).
- Glioma (and brain tumors) are candidate diseases.
  → Blood-Brain Barrier Permeability is required.

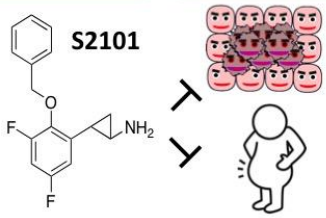




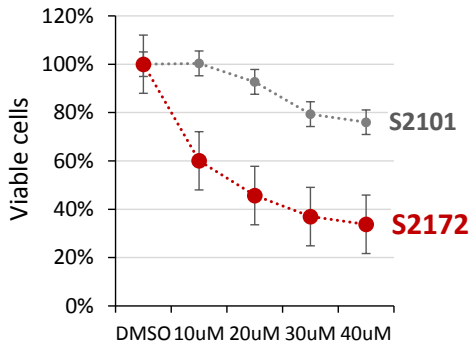
Suva et al. used in Cell 157, 580 (2014)

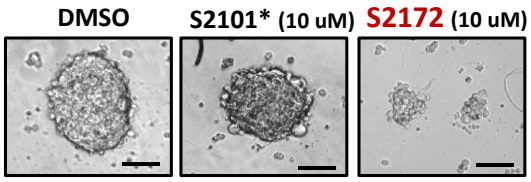
Developed LSD1 Inhibitor (S2101)





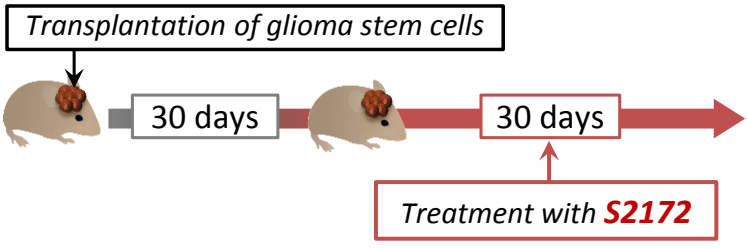
Mimasu et al. Biochemistry 49, 6494 (2010)
Hino et al. Nature Commun. 3, 758 (2012)
Yatim et al. used in Mol. Cell 48, 445 (2012)
Konovalov et al. used in J. Ovarian Res. 6, 75 (2013)
Schooley et al. used in J. Cell Sci. 128, 3466 (2015)
Li et al. used in Neuroreport 26, 539 (2015)
Hirano & Namihira used in Stem Cells (2016)
Di Stefano et al. used in Nat. Cell Biol. 18, 371 (2016)

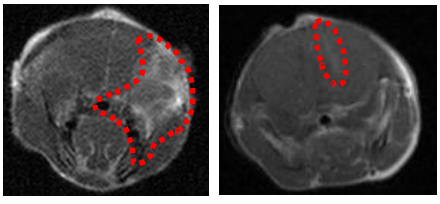




(Bars = 100 um)

S2172 effectively inhibited glioma stem cell proliferation *in vitro*.
*, Glioma stem cells lost viability in the presence of LSD1 inhibitor S2101 (Suva M et al. Cell 2014).





(·····Tumor area)

S2172 showed anti-tumor effect on glioma stem cells *in vivo*.