Genetically engineered Mesenchymal stem cells to express a suicidal cytosine deaminase gene for the treatment of brain tumor in combination with a prodrug, 5-fluorocytone

R&D Center
Ajou University

Contact Information

Korea Health Industry Development Institute	
Contact Point	Heajin Jung, Esq.
email	heajinjungattorney@gmail.com
Cell	+82 10 7215 3543

Industry Sector	Drug delivery, Phamaceutical
Therapeutic Area	Central Nervous System
Stage of Development	Preclinical

1. Summary

- Glioblastoma multiforme (GBM) is the most common form of malignant brain tumors in the central nervous system. Despite the effort to treat GBM, the most effective treatment, a combination of chemotherapy and radiotherapy following brain resection still remains as a palliative cure (Stupp et al., 2005; 2009).
- This anti-cancer pharmaceutical kit comprises mesenchymal stem cells carrying a suicide gene and administration of a prodrug.
- Bone marrow-derived mesenchymal stem cells (MSCs) were genetically engineered to express a bacterial cytosine deaminase (CD). After resection of tumor mass, MSC/CD will be transplanted the remaining brain parenchyma. Patients will be systemically administered 5-fluorocytosine (5-FC), a nontoxic prodrug. MSC/CD migrate toward micromass of remaining tumors and convert 5-FC to cytotoxic 5-fluorouracil (5-FU).
- As a result, the concentration of 5-FU is increased in brain area near tumors. 5-FU is highly permeable to cell membrane and induces cell dysfunction by incorporating to DNA and RNA in actively growing tumor cells. (bystander effects)
- Meanwhile MSC/CD also undergo cell death caused by suicide effects of 5-FU, which insures the long-term safety of this kit.
- 5-FC is an anti-mycotic drug that has been utilized for serious infections caused by *Candida* or *Cryptococcus neoformans*. 5-FU has been used as one of standard treatment of gastrointestinal cancers.

2. Applications

- This therapeutic agent is originally designed to treat the remaining tumor masses after surgery in firstly diagnosed brain tumor patients.
- This therapeutic agent can be effective to treat recurrent patients who received a standard treatment [surgery, radiotherapy, and chemotherapy of temozolomide].

- This therapeutics can be utilized after removal of cancer mass by surgery in order to ensures the cell death of remaining micromass of cancers in other types of organs.

3. Market Feasibility

- This therapeutic agent can be given to patients while waiting for recovery from surgery, thus does not compete with standard therapy or treatment which are already in market.
- MSCs have strong tropism toward cancer cells and can serve as cellular vehicles to deliver therapeutic gene (CD) near to tumor sites.
- Approximately 20,000 new cases of primary brain tumors are diagnosed per in US. This therapeutics can be applied to treatment other types of cancers following surgery. Thus, more patients will get benefit from this therapeutic agent
- The master cell bank (MCB) of this therapeutic agent was already produced in a GMP-compliant facility.
- This therapeutic agent will be filed to Korean FDA in 2 years, after performing toxicity/safety tests in GLP laboratories.
- Large quantity of clinical lots will be produced by simple amplification of MCB since CD gene is integrated to MSC host genome. Consequently the cost of quality control (QC) of clinical lot is relatively easy.
- This therapeutic agent will be formulated for multi-center clinical trials.

4. Type of Business Relationship Sought (include licensing availability)

- Technology transfer, or Collaboration

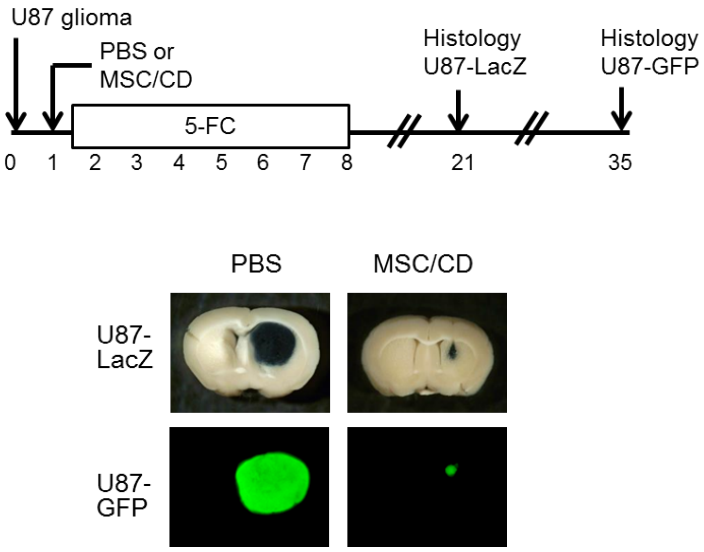
5. Technical Advantages

- Compared to other companies which use replicating virus (Toca 511, Tocagen, CA, USA) or neural stem cells (City of Hope Hospital, CA, USA), the efficacy of this therapeutic agent is higher with 4-8 fold lower IC_{50} value for 5-FC MSCs have strong tropism toward cancers.

- Unlike replicating virus, MSC/CD cells undergo cell death via suicide effects after delivery of CD gene near cancer sites, which ensures the safety of this therapeutic agent and minimizes immune responses.
- Despite that it is allogeneic cells, this therapeutic agent can be repetitively utilized to patients without immune rejection, since MSCs have intrinsic immune suppressive functions. This agent also will benefit to alleviation of local brain edema after brain surgery.
- Additionally 5-FC is an antimycotic drug which will promote of healing after the surgery
- Since simple amplification ensures quality controlled production of large quantity, the cost of this agent will be competitive compared to other stem cell- and gene-based therapy.

6. Technical Highlighted Summary

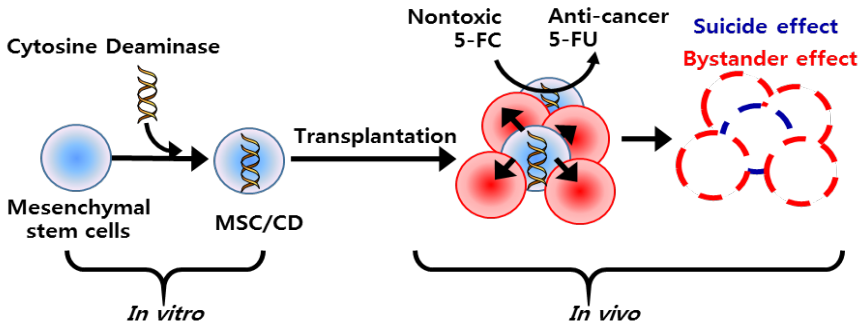
- Clinical lot of MSC/CD is being produced by simple amplification of MCB that was already established. After performing safety/toxicity tests in GLP institutes, this therapeutic agent will be filed to Korean FDA for IND in 2 years.



- **Figure 1. Anti-cancer effects in the brain.** U87 glioma cells were modified to express reporter genes such as β-galactosidase (LacZ) or green fluorescence protein (GFP) and

then stereotaxically transplanted into brain parenchyma. Next day MSC/CD was transplanted and 5-FC were systemically given for 5 days. Animals were sacrificed at indicated time and subject to histological analysis. Tumor volume was markedly reduced in animals treated with MSC/CD compared to the vehicle control (PBS).

7. Mechanism (MOA)



- 5-FU is highly permeable to plasma membrane. 5-FU is converted to FUTP and FdUTP inside the cell and then incorporated into RNA and DNA, leading to dysfunctions of the cell cycle progression.
- 5-FU has been utilized to treat gastrointestinal cancers but prohibited for CNS cancers due to high neurotoxicity.

8. Patent Information and Status

9. Patent Number(s)

Title	Country	Patent Application No.	Original Assignee	Filing Date	status	Inventors
Use of mesenchymal stem cells genetically modified to express a suicide gene for treating a cancer	Korea	2005-0091155	Ajou R&D Center	Filed:05.09.29 Registered:11.03.08	Registered	Hae Young Suh et al.
Use of mesenchymal stem cells genetically modified to express a suicide gene for treating a cancer	China	2006-80035727	Ajou R&D Center	Filed:06.09.29 Registered:12.01.04	Registered	Hae Young Suh et al.

Use of mesenchymal stem cells genetically modified to express a suicide gene for treating a cancer	Singapore	200801837-6	Ajou R&D Center	08.03.05	Registered	Hae Young Suh et al.
Use of mesenchymal stem cells genetically modified to express a suicide gene for treating a cancer	EP	06799011	Ajou R&D Center	06.09.29	Filed	Hae Young Suh et al.

10. Key Words

Mesenchymal stem cell, suicide gene, bystander effects, prodrug, cytosine deaminase, 5-FC, 5-FU, brain tumor, glioblastoma, glioma, cancer

11. Company Description

Ajou University R& D center