Novel cancer therapy extends lives of terminally ill dogs, shows potential for use in human patients

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Dr. Sarah Ho prepares the engineered Mesenchymal Stem Cells. Credit: NUS Yong Loo Lin School of Medicine

Researchers from the Department of Biochemistry and NUS Centre for
Cancer Research (N2CR), at the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), have been pioneering a treatment using stem cell precision engineering technology, to deliver drugs directly to tumor sites in dogs and cats with late-stage cancer and no treatment options available.

To date, the treatment has been administered to nearly 100 dogs and cats with conditions such as perianal adenoma, lung metastasis, and sarcoma. Most animal patients showed signs of positive response, including full recovery, cancer remission and good quality of life.

Through the course of treatment on all the animal patients involved in the study, there were no significant side effects observed—possibly due to the localized presence of the therapeutic cells which remain within the tumor environment. For example, one of the dogs which had a tumor around its eye, did not lose its sight despite the treatment that destroyed the tumor—pointing to the localization of the treatment to the tumor site, which does not affect the function of surrounding organs.

While administering the treatment to the animal patients, the research team observed that some of the dogs with recurrent cancers did not experience any relapse nor side effects. This supports the idea that the engineered therapeutic cells, which were designed to have few side effects and help the body fight cancer, were working as intended.

The research team is piecing together information from important studies in the field to gather more evidence to explain their findings. Unlike traditional chemotherapy, which often has harmful effects limited by dosage, MSCs are engineered to deliver treatment directly to the affected areas in high concentrations, minimizing toxicity elsewhere in the body.

**About the treatment mechanism**
In the research led by Associate Professor Too Heng-Phon from the Department of Biochemistry and N2CR at NUS Medicine, the team modified MSCs, which can seek out cancerous tumors. These modified cells carry a potent "kill-switch" (cytosine deaminase) that produces a high, localized concentration of a cancer-killing drug (5-fluorouracil) in the tumor environment.

The "kill-switch" subsequently induces anti-cancer immunity—by activating the cancer's innate cGAS-STING and related pathways, which activate the immune response and suppresses the tumor.

The development of this therapy to treat canine patients led the team toward a better understanding of cancer treatments, as well as its use in human patients, as helping dogs with naturally occurring cancers provides valuable clues about human cancers.
The injectable engineered Mesenchymal Stem Cells are stored in a cooler box for transport to the operating theater where it will be administered to patients. Credit: NUS Yong Loo Lin School of Medicine

**Enhancing the treatment**

For late-stage cancers especially, the team found that there were still remnants of tumors that remained after a few rounds of the treatment. To target these remnants more precisely, the team set out to further enhance the treatment:

1. The mechanism was further enhanced by utilizing the MSCs' payload to accentuate the cGAS-STING and related pathways, which have recently been reported to be critical for the delivery of chemotherapy drugs, including 5-fluorouracil, in activating anti-cancer immunity.

2. The mechanism was enhanced with the expression of interferon beta—a cytokine that is known to recruit and facilitate T-cell activation for anti-cancer immunity. The expression of interferon beta can be tricky: too much of it in the blood can result in side effects, but a correct amount can be extremely powerful and efficient in targeting the cancer.

Assoc Prof Too said, "We are making the treatment more efficient by modifying cells that are like 'hunter killers' where they home in on the tumors and destroy only these tumors and not other healthy parts of the body. This explains why there are no side effects.

"Drugs in chemotherapy usually lead to some level of side effects. Our
treatment taps on the body's own biological system, which treats the tumor with no significant toxicity—this surpasses what drugs in chemotherapy can do."

"Exploring optimal disease treatments remains our ongoing endeavor, and the NUS Medicine technology for efficiently modifying stem cells serves as a 'future-ready' platform where recently identified therapeutic genes can be harnessed," he added.

Demonstration of the vial solution being transferred to the needle that will be used for injection into the tumor sites of patients with recurrent glioblastoma. Credit: NUS Yong Loo Lin School of Medicine
Preparing for human clinical trials

In January 2024, Assoc Prof Too led two senior research fellows from his team, Dr. Sarah Ho and Dr. Woo Jun Yung, to establish the AGeM Bio Pte Ltd. With the enhanced treatment, the research team is seeking validation for the manufacturing processes to prepare the treatment for use in human patients—estimated to be completed by the third quarter of 2025.

The team hopes to commence the first phase of human clinical trials in end-2025, where they will work with clinicians from the National University Hospital (NUH), to deliver intratumoural injections of the engineered MSCs to a small number of patients with recurrent glioblastoma—a debilitating form of brain tumor. After the first phase of the trials, the team will conduct subsequent trials with larger groups of patients over the next few years to collect data about its efficacy in human patients and enhance the treatment.

Dr. Ho said, "To act is to save—that is the mission of our corporation, AGeM Bio Pte Ltd, where AGeM refers to 'augmented gene modification.' With our research, we endeavor to fulfill the unmet need of engineering cells to save lives—a journey that we have undertaken for over a decade."

Dr. Yung added, "While there will be many phases of clinical trials spanning over several years before we can have a product that the world can use, we are excited about taking our research to the next level, which brings us a step closer to saving human lives."

Both Dr. Ho and Dr. Woo are from the Department of Biochemistry and N2CR at NUS Medicine, and co-founders of the AGeM Bio Pte Ltd.

The clinical trial will be led by Clinical Associate Professor Yeo Tseng.
Tsai, Senior Consultant, Division of Neurosurgery, Department of Surgery, National University Hospital.

He said, "Glioblastoma is a particularly aggressive brain tumor that often recurs after initial treatment. Unfortunately, there's no standard treatment protocol for such recurrent cases. This first phase of our clinical trial represents a significant step forward and will assess if a therapy demonstrably effective in animal models can be safely and effectively used in human patients with this condition."

Provided by National University of Singapore


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