Collateral tumor damage

By Tracey Baas, Senior Editor

Australian researchers are taking a new approach to attacking brain cancer—raising T cells against antigens from the cytomegalovirus frequently found in gliomas rather than against tumor targets.¹ The approach has shown efficacy in patients, and the next steps include applying the method to larger cohorts and identifying the best cytomegalovirus epitopes to be used to activate T cells.

Glioblastoma multiforme (GBM) is an aggressive malignancy, with median survival of less than 15 months and a 5-year survival rate below 10%.^{2,3} Standard care includes surgical resection, radiotherapy and chemotherapy.

The link between GBM and virus surfaced more than a decade ago, when researchers reported that cytomegalovirus (CMV) was found in a majority of human gliomas. The presence of virus was first considered an opportunistic infection because of the immunosuppressive environment of the tumor, but mounting evidence suggested that it contributed to disease progression.⁴⁻⁶

CMV was unlikely to be a causal agent, as placing the virus in culture with healthy cells did not give rise to gliomas.

In 2008, a team at the **University of California, Los Angeles** reported that a patient vaccinated with autologous dendritic cells pulsed with tumor lysate experienced a robust expansion of CMV-specific but not tumor-specific T cells.⁷ The patient's glioblastoma tissue was later shown to be infected with CMV.

The study suggested that an immune response against a viral antigen was more easily accomplished than inducing an immune response against tumor antigens.

Four years later, a team at the **QIMR Berghofer Medical Research Institute** decided to treat GBM using T cells that target CMV antigens isolated from patients' tumor-infiltrating lymphocytes. The institute was previously known as the Queensland Institute of Medical Research (QIMR).

In the group's one-patient, proof-of-concept study, *ex vivo* expansion of the patient's endogenous, CMV-specific T cells, which were then returned to the patient in combination with temozolomide, led to long-term, disease-free survival.⁸

“One of the advantages of using immunotherapy—T cells or vaccines—to target CMV antigens in tumors is that it is not requisite that the viral antigen is a driver of tumor biology or that the virus is undergoing a productive replicative life cycle for the immune system to attack and kill a tumor cell expressing the targeted antigen.”

—Duane Mitchell,
University of Florida College of Medicine

Now, the researchers have data from a larger cohort of patients.

The team collected and expanded CMV-specific T cells from 13 patients with recurrent GBM undergoing standard therapy. Two patients died from disease before receiving adoptive T cell therapy. In the 11 patients who received infusions of autologous, CMV-specific T cells plus radiotherapy, temozolomide and other standard treatments, median overall survival was about 57 weeks. Of the 11 treated, 4 were progression free at the end of the study and remain so to date, which is now between 10 months and over 4 years after T cell therapy.

However, the number of CMV-specific T cells did not correlate with overall or progression-free survival (PFS).

Thus, the researchers set out to identify T cell expression profiles that might provide prognostic value. To do so, the group compared profiles from patients with short vs. long PFS.

Seven genes were found with significant expression differences, including T cell transcription factors, cytokines such as interferon- γ (IFNG; IFN- γ), chemokines and checkpoint markers such as CTLA-4 (CD152).

Results were published in *Cancer Research*. The QIMR Berghofer team was led by Rajiv Khanna, a professor and director of the institute's Centre for Immunotherapy and Vaccine Development.

One bird, two stones

Khanna's team is starting a Phase II trial of autologous, CMV-specific T cell therapy to treat primary glioblastoma. The primary endpoints of the trial are the safety and tolerability of the adoptive transfer of CMV-

specific, cytotoxic T cells and PFS. Secondary endpoints include overall survival.

In the long term, Khanna said, a therapeutic vaccine based on the CMV epitopes may be a better approach than using engineered T cells because the latter are more cumbersome.

“We have an ongoing CMV vaccine program based on our IP that has successfully completed preclinical studies, and now the CMV vaccine is moving toward a Phase I clinical trial,” he added.

Regardless of modality, other researchers wanted to see data in larger groups of patients.

“Their exciting results will now have to be confirmed in larger trials, as well as in patients with newly diagnosed tumors who have a better chance of extended survival with this therapy than recurrent glioblastoma patients,” said Cecilia Söderberg-Nauclér, a professor of medicine at the **Karolinska Institute**.

Söderberg-Nauclér also suggested further examination of the CMV-specific epitopes that may be able to activate CMV-specific T cells in nonresponders. “It is possible that special cancer-associated CMV strains are present in these GBM patients and that the antigenic epitopes are

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driver of tumor biology or that the virus is undergoing a productive replicative life cycle for the immune system to attack and kill a tumor cell expressing the targeted antigen,” said Duane Mitchell, co-director of the Preston A. Wells Jr. Center for Brain Tumor Therapy, director of the University of Florida Brain Tumor Immunotherapy Program and an associate professor in the Department of Neurosurgery at the **University of Florida College of Medicine**.

“A central question with respect to CMV-directed immunotherapy is whether the low levels of viral antigens expressed within these tumors will be sufficient to mediate clinically meaningful responses in a significant number of patients,” noted Mitchell. “Additional clinical

different from those known to be produced by well-characterized CMV strains found in normal tissues,” she noted. “Thus, CMV strains in glioblastoma need to be defined in more depth.”

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studies are needed to address this issue, but I believe this is a promising area for future research.”

The findings have been patented by QIMR Berghofer and the IP, which includes CMV epitopes and the strategy for T cell-based adoptive immunotherapy, is available for licensing for its potential application in CMV-associated diseases including glioblastoma.

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Contact: Rajiv Khanna, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
e-mail: rajivk@qimr.edu.au
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COMPANIES AND INSTITUTIONS MENTIONED

Karolinska Institute, Stockholm, Sweden

QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia

University of California, Los Angeles, Calif.

University of Florida College of Medicine, Gainesville, Fla.