

# The progress of immunotherapy for glioblastoma

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Glioblastoma is the most common primary brain tumor in adults, accounting for about half of all primary brain tumors. Despite multiple therapeutic interventions such as surgical resection, radiotherapy, and systemic chemotherapy, the prognosis for glioblastoma remains poor. Due to the scientific community's enhanced understanding of the CNS immune system and significant achievements in tumor immunotherapy in recent years, immunotherapy has become a promising GBM treatment. In vaccine therapy, a number of clinical trials have achieved encouraging results. In antibody therapy, antibodies are used to target immune checkpoints such as ipilimumab and nivolumab. Bioengineering technology has also led to a new field of tumor immunotherapy, whereby genetically modified tumor-specific T cells are reintroduced into a patient's body.

## Introduction

Glioblastoma (glioblastoma multiforme, GBM) is the most common primary brain tumors in adults, accounting for about half of primary brain tumor.<sup>1</sup> Despite surgical resection, radiotherapy, and systemic chemotherapy, the median survival is only 14.6 months, and the 5-year survival rate is less than 10%.<sup>2-3</sup> As current glioblastoma treatment standard is not tumor specific and tumor cells are prone to resist radiotherapy and alkylating agent, treatment commonly results in inevitable recurrence and poor prognosis.

The rapid development of tumor immunotherapy in recent years brings out encouraging results in related clinical trials. Targeted vaccine of prostatic acid phosphatase Provenge was approved for the treatment of prostate cancer,<sup>4</sup> and the human CTLA-4 monoclonal antibody Ipilimumab approved for the treatment of a progressive melanoma in 2011.<sup>5</sup> Showing high efficacy in clinical and preclinical studies, immunotherapy is expected to become a new therapy beyond surgery, radiotherapy, and chemotherapy to treat gliomas.

## Basis of Cns Immunotherapy

CNS has traditionally been considered to be immune-privileged organ.<sup>6</sup> Recently, however, a variety of immune cells were

found in normal CNS. First of all, microglia is considered currently to have the function of the APCs, can migrate to the CNS inflammation area and be activated, then secrete a variety of cytokines and chemokine.<sup>7</sup> In addition, mononuclear cells can differentiate into macrophages and dendritic cells (DCs), which exist in perivascular, choroid and meningeal. And T lymphocytes can be transferred to the CNS through the blood-brain barrier after activation in the cervical lymph node.<sup>8</sup> All these facts above suggest the existence of immune function in the CNS.

However, gliomas have much immune escape mechanism so that the tumor can escape the immune system destruction: (1) tumor factors: glioma cells can secrete a variety of immunosuppressive cytokines, including TGF $\beta$ , PGE2, IL-10 and VEGF; (2) external factors: such as age, taking hormones and radiation and chemotherapy that reduce body immunity; (3) immune cells: the increase of regulatory T cells (Tregs), myeloid-derived suppressor cell (MODC) in the tumor microenvironment will suppress immune system.<sup>9</sup> It is because of these reasons that our body can hardly produce normal immune response to glioma cells and that enhancing the targeting of glioma cells of the immune system by various means has thus become an important anti-tumor method.

## Tumor Vaccination Therapy

Current immunotherapy can divide into active immunotherapy and passive immunotherapy.<sup>10</sup> Active immunotherapy refers to the use of foreign antigens to activate the body's tumor-specific immune system. We can either insert antigen directly into the body to activate DCs thus activating T lymphocyte cells, or insert DCs after they have been sensitized with antigen in vitro. Passive immunotherapy refers to the infusion of exogenous immune substances that surpass directly the tumor into the body, which don't require the activation of body's specific immune system. Passive immunotherapy includes antibody immunotherapy, adoptive immunotherapy, and other immune-modulatory therapy.

### EGFRvIII vaccine

As the mutant of epidermal growth factor receptor (EGFR), EGFRvIII is only expressed in cancer cells but not in normal tissue, and it can directly lead to the growth of cancer cell. About 20-25% of patients with glioblastoma suffer from EGFRvIII excessive expression.<sup>11</sup> Earlier study of Heimburger et al. suggested that EGFRvIII is a negative prognostic factor for GBM patients.<sup>12</sup> Recent studies have shown that EGFRvIII expression does not have a significant relationship with patients' prognosis

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**Table 1.** Survival of EGFRvIII positive adult patient with GBM in 3 Phase II Rindopepimut trials

Trial	PFS(month)	OS(month)
ACT III (n=65)	12.3	24.6
ACT II (n=22)	15.2	23.6
ACTIVATE (n=18)	14.2	26

with the current standard of care.<sup>11</sup> The company Celldex in the United States has created the experimental immunotherapeutic vaccine targeting specifically EGFRvIII molecular against tumor called Rindopepimut, which is a kind of complex of polypeptide and immunogenic carrier protein. Clinical trials of Phase I and Phase II show that Rindopepimut can stimulate efficiently anti-tumor immunity in those EGFRvIII overexpression-caused GBM patients, thus prolonging their survival. In the 3 clinical trials of Phase II, the newly diagnosed GBM patients with EGFRvIII overexpression were given an intradermal injection of 500 µg Rindopepimut and 150 µg colony stimulating factor GM-CSF respectively 0, 14, 28 days after concurrent chemoradiotherapy. These patients were injected the same dose of Rindopepimut and GM-CSF on the 21st day in each standard adjuvant chemotherapy cycle until the tumor get further development or the patient cannot tolerate. No serious adverse reactions were found and the survival in this 3 Phase-II clinical trials is consistent, which show that Rindopepimut can significantly increase the median overall survival (OS) and progression-free survival (PFS) of EGFRvIII positive adult patients with GBM, as shown in Table 1.<sup>13</sup>

A randomized, double-blind Phase II clinical trial named “ReACT” (2011-2015, NCT01498328) concerning relapsed glioblastoma is being carried out by Celldex in order to clarify the influence of Rindopepimut & Bevacizumab combination on the OS and PFS of the recurrent glioblastoma patient with EGFRvIII overexpression. The preliminary result of the study is satisfactory, and it found that EGFRvIII antibody titer associated with survival. The median OS of patients with lower antibody titer is 10.6 months while it reaches more than 20 months for those with high EGFRvIII antibody titer, that’s why EGFRvIII antibody titer is recommended to be checked as a predictive marker in early examination.<sup>14</sup> Currently an ongoing Phase III clinical trial called “ACT IV Study” (2011-2016, NCT01480479) for newly diagnosed glioblastoma may make Rindopepimut be approved by FDA as the first kind of immunotherapeutic drug for primary brain tumors if the study gets positive result.

### DCs vaccines

As the most important antigen-presenting-specific cells, DCs can start body’s immune response by expressing high level of the MHC molecules and stimulating molecules such as B7-1 (CD80), B7-2 (CD86), CIM0. The ability to absorb all kinds of antigen and to secrete IL-2 enables DCs to activate naive T cells and initiate immune response. By mediating effectively the anti-tumor immune response of CD8+ and CD4+ T lymphocyte, DCs play a key role in the induction of an efficient and specific T cells immune response against the related antigens. Researchers cultured DCs and sensitized them with various types of tumor antigens both in vitro, and then injected them into the body to induce antigen-specific immune responses. The antigens used to sensitize DCs are mainly from surgically resected tumor cell lysates as well as the specific synthetic polypeptide, other special antigens include tumor stem cell antigen and cytomegalovirus antigen. Being currently hot in tumor immunotherapy research, DCs vaccine Phase I, II even III clinical trials are underway both at home and abroad, as shown in Table 2.<sup>15</sup>

ICT-107 is the autologous peripheral blood mononuclear cells (PBMC) sourced DCs which were sensitized by 6 kinds of synthetic peptide (tumor stem cell antigen MAGE-1, her-2, AIM-2, TRP-2, gp100, and IL-13Rα2). A Phase I clinical trial of ICT-107 on 16 newly diagnosed GBM patients resulted in 16.9 months as median PFS and 38.4 months as median OS.<sup>16</sup> Professor Patrick Y. Wen has released some preliminary test results (Abstract No. 2005) of a Phase II clinical trial at the 2014 ASCO meeting. Without significant difference in side effects between the treatment group and the control group, the result suggests that ICT-107 is rather safe and well tolerated. Median PFS has increased by 3 months (bilateral test  $p = 0.01$ , HR = 0.53), and OS has also increased by 3 months (bilateral test  $p = 0.40$ , HR = 0.79). That is the first randomized, controlled trial of immunotherapy for GBM treatment with positive results (Increase in PFS has statistical significance).

At the moment, another Phase III multi-center, randomized, controlled clinical research aiming to observe DCVax’s therapeutic effect for newly diagnosed GBM is being carried out by the company Northwest Biotherapeutics. 300 adult patients with newly diagnosed GBM are planned to be recruited for this research and to be randomly divided into 2 groups after standard of care, including surgery, concurrent chemoradiation and Temodar therapy, 2 out of 3 will additionally receive DCVax with the remaining one-third receiving a placebo. The primary endpoint of the study was PFS. (ClinicalTrials.gov identifier: NCT00045968).

**Table 2.** Main DCs-based Phase II, III clinical trials

Vaccine type	Phase	Experimental design	References
DCVax-Brain	III	2/3 vaccine, 1/3 placebo with option of crossover at disease progression	NCT00045968
Tumor lysate vaccine	II	Vaccine + standard therapy versus standard therapy alone	NCT01213407
Tumor lysate vaccine	II	DCs treated with PGE2 and TNF-, cervical lymph node injection	NCT00323115
Cancer stem cell vaccine, ICT-107	II	Six synthetic peptides associated with CSCs loaded onto autologous DCs	NCT01280552
Cancer stem cell vaccine	II	Autologous DCs loaded with stem cell-like antigens from irradiated GBM vs. placebo	NCT01567202
Alpha type I DC peptide vaccine	I/II	Four peptides loaded onto α type I DCs + poly-I:LC, included GBM and anaplastic glioma	NCT00766753

### Heat-shock protein-based vaccines

Using DCs as the vaccine carrier demands the culture of DCs *in vitro* and their sensitization with tumor antigen, which requires very specialized cell culture techniques. While the application of tumor-derived heat shock proteins (HSPs) as tumor antigen carrier can make use of DCs' antigen-presenting function without requiring the culture of DCs *in vitro*.<sup>16</sup> Belonging to a protein family whose main physiological function is to promote the mechanism of peptide folding by interacting with polypeptides, HSPs express at a higher level in case of fever, infection, hypoxia, cancer and other conditions. In addition, HSPs can be combined with the DCs and transfer the bound polypeptide antigens into them, thus activating CD4+ and CD8+ T cell response in tumor immunotherapy.

Bloch et al. has reported an open-label, single-arm, Phase II clinical trial of using autologous tumor-derived heat-shock protein peptide complex-96 (HPSC-96) vaccine in the treatment of recurrent GBM.<sup>17</sup> Between 3rd Oct. 2007 and 24th Oct. 2011, there are 41 patients with recurrent GBM that received an average of 6 doses of HPSC-96 vaccine intradermal injection, among which only one has encountered 3-degree adverse reaction related to vaccine. The 6-month survival rate of the patients is 90.2% (95% CI: 75.9-96.8), 12-month survival rate is 29.3% (95% CI: 16.6-45.7) and the median OS is 42.6 weeks (95% CI: 34.7-50.5).

In July 2014 Agenus Inc. published a randomized, single-arm, Phase II clinical trial of using HPSC-96 vaccine in the treatment of newly diagnosed GBM patients. The addition of HPSC-96 vaccine to the standard of care in this research resulted in an increase of 9.6 months in median OS and 26% in 2-year survival rate. By contrast, the median survival was 14.6 months and 2-year survival rate was 26% in the case of standard treatment.<sup>2-3</sup> It was also found in this study that patients with low-expression of PD-L1 protein react significantly to HPSC-96 vaccine, indicating that the joint use of vaccine and other Anti-PD-L1 immunotherapeutic drug may improve the anti-tumor efficiency in the future.

### Antibody-Based Immunotherapy

Antibody-based immunotherapy activates the immune system to eliminate tumor cells through the specific interaction between antibodies and antigens. Some suitable immunotherapy targets for glioma have been identified with the clarification of the pathological mechanisms of glioma, especially the mechanism of immunosuppression. Additionally, advances in bioengineering make the preparation of monoclonal antibodies increasingly simple. Current antibody-based immunotherapy mainly consists of the redirection of immune effector cells to interact with tumor mutations by means of bispecific monoclonal antibody-redirection, the antibody drug targeting negative immune regulatory molecules and the activation of anti-tumor immune by providing costimulatory signals,<sup>18</sup> among which the most promising is the immune checkpoint blockade. The immune checkpoint refers to some inhibitory regulatory molecules in the immune system that

make tumor escape immune destruction by inhibiting T cell activity. Ipilimumab, the antibody of Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), is the first immune checkpoint-targeted drug approved by FDA. Other immune checkpoints, such as programmed death protein-1 (PD-1) and its ligands have also been proven to be able to induce the remission of a wide variety of tumors. Targeting immune checkpoints has a broad application prospect in anti-tumor immunotherapy.

#### Anti-PD1/PD-L1 therapies

Programmed cell death factor-1 (PD-1) is a type I transmembrane glycoprotein belonging to the immunoglobulin superfamily, which exists on the cell surface in the form of a monomer. It can, after binding to the ligand (PD-L1), phosphorylate the downstream molecules, transduce negative signals, inhibit T cell proliferation and cytokine production and induce T cell apoptosis. Some preclinical trials on animal tumor model have demonstrated that tumor microenvironment can promote tumor's expression of PD-L1 which induces the apoptosis of T lymphocytes, while PD-1/PD-L1 antibody can save T cells by blocking PD-1 /PD-L1 pathway thus enhancing the anti-tumor immunity.<sup>19</sup> Recent clinical trials of anti-PD-1, such as MDX-1106, show its good tolerance and anti-tumor activity for the patients with solid tumors.<sup>20</sup> In Sep. 2014, the anti-PD-1 drugs Keytruda was approved to treat advanced melanoma. As to the clinical applications in GBM treatment, a related study was reported at the ASCO 2014 annual meeting. A randomized, open-label, Phase - clinical trial (Abstract number: TPS2101) is about to begin for the treatment of recurrent glioblastoma with monoclonal antibody of PD-1, aiming to evaluate the efficacy and safety of treating recurrent glioblastoma with nivolumab (Human PD-1 monoclonal antibody) alone or together with Ipilimumab.

#### Anti-CTLA-4 therapy

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), also known as CD152, is a kind of leukocyte differentiation antigen. As a transmembrane receptor on T cells, CTLA-4 can inhibit the immune reaction of effector T cells by competing with CD28 on the same cell for the B7 family immune molecules on the surface of APC. Pre-clinical trials demonstrated that CTLA-4 can inhibit tumor immunity by activating Tregs and that CTLA-4 antibodies inhibit tumor growth. Being a human-sourced monoclonal CTLA-4 antibody, Ipilimumab can promote the activation and proliferation of T cells by blocking the interaction of CTLA-4 with its ligand CD28 after binding to it, thereby promoting the anti-tumor effect. Despite the fact that Ipilimumab has been proved to be able to improve significantly the prognosis in melanoma treatment and have good anti-tumor effect in animal glioma models, its effect in the treatment of GBM has not been verified.<sup>21-22</sup> Two studies on treating recurrent GBM with Ipilimumab (Abstract number e13026 and e13010), reported at the ASCO 2014 annual meeting, resulted in significant curative effect on some patients and none serious side effect. Clinical trials on the treatment of GBM with Ipilimumab will begin shortly.

**Table 3.** Clinical trials of adoptive immunotherapy of CNS tumor

Tumor type	Phase	Note	References
GBM	I	CMV-activated T cells alone or combined with a DC-based vaccine	NCT00693095
Malignant glioma	I	Autologous CD8+ T cells expressing inducible suicide fusion protein and an IL-13 chimeric immunoreceptor	NCT00693095
Medulloblastoma And PNET	I/II	Tumor-specific T cells alone or combined with a DC-based vaccine	NCT01326104

## Adoptive Immunotherapy

Adoptive immunotherapy refers to the infusion of activated immune effector cell into tumor patients so as to make use of its anti-tumor immunity directly. Immune effector cells include lymphokine-activated killer (LAK) cells, natural killer (NK) cells, T cells, tumor-infiltrating lymphocytes (TILs), cytotoxic T lymphocyte (CTLs), tumor antigen-specific TCR-transgenic T cells and chimeric antigen receptors-modified T cells (CART). The first 3 kinds of cells are tumor antigen-specific and may attack normal cells with high nerve toxicity. TILs are tumor-specific, but they need to be extracted from the tumor tissues, and their proliferation is difficult. Currently, the most used in adoptive immunotherapy are CTLs, including CD4+ and CD8+ T lymphocytes. TCR transgenic T cells, as well as CART, are still mainly at the laboratory stage. By such means of genetically modifying T cells and prolonging their survival time, the effect of specific T cells could be enhanced.<sup>23-24</sup> Additionally, the reinfusion of the T cells proliferated in vitro back into the body can correct lymphopenia and improve immunosuppressive environment,<sup>25-26</sup> thereby enhancing tumor immunity.

Internationally, TCR transgenic T cells and CART are currently hot spots for adoptive immunotherapy. In Feb. 2014, researchers from US Sloan-Kettering Cancer Institute,<sup>27</sup> reported on "Science Translational Medicine" that they first removed T cells from the patient's body, and then transformed them with genetic engineering by making them be able to identify CD19 proteins contained in leukemia cells. The cells amplified in vitro can help to destroy leukemia cells in vivo after their reinfusion back into the body. In this experiment, a total of 16 relapsed or refractory B-cell acute lymphoblastic leukemia patients were treated, resulting in complete remission of 14 people. In the trials of animal glioblastomas, EGFRvIII-specific CART also showed good therapeutic effect.<sup>28-29</sup> At present, a number of clinical

trials concerning the adoptive immunotherapy of central nervous system tumors are underway, as seen in Table 3.<sup>30</sup>

## Outlook

Despite surgical resection, radiotherapy, and systemic chemotherapy, the prognosis for GBM remains poor. Therefore it's urgent to find a new alternative or adjuvant therapy. With the re-understanding of the CNS immune system and the significant achievements in the tumor immunotherapy in recent years, immunotherapy has become a kind of GBM treatment with big potential. Specificity of immunotherapy and memory characteristics of immune cells may have great significance in inhibiting tumor recurrence. In the vaccine therapy, a number of Phase II clinical trials have achieved encouraging results. Particularly, 2 Phase III clinical trials of the vaccines DCVax-Brain and Rindopepimut are very expected. With respect to antibody therapy, Ipilimumab has been proven to be able to improve significantly the survival and has been authorized for clinical use. The antibodies of CTLA-4 and PD-1 /PD-L1, such as Ipilimumab, nivolumab, etc. are being tested in clinical trials for their application in the treatment of GBM. By means of bioengineering technology, the reinfusion of genetically modified tumor-specific T cells back into the body has a unique advantage comparing with active immunotherapy, and the reinfusion of adoptive T cell has created another new field in tumor immunotherapy. There is no doubt that, with the development of the immunotherapy, new breakthroughs will take place in glioblastoma treatment shortly.

## Disclosure of Potential Conflicts of Interest

None of the authors has any conflicts of interest to disclose.

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