# Phase 1, Dose Escalation, Nonrandomized, Open-Label, Clinical Trial Evaluating the Safety and Preliminary Efficacy of Allogenic Adipose-Derived Mesenchymal Stem Cells for Recurrent Glioblastoma: A Clinical Trial Protocol

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**BACKGROUND AND OBJECTIVES:** Despite standard of care with maximal safe resection and chemoradiation, glioblastoma (GBM) is the most common and aggressive type of primary brain cancer. Surgical resection provides a window of opportunity to locally treat gliomas while the patient is recovering and before initiating concomitant chemoradiation. The objective was to assess the safety and establish the maximum tolerated dose of adipose-derived mesenchymal stem cells (AMSCs) for the treatment of recurrent GBM. Secondary objectives were to assess the toxicity profile and long-term survival outcomes of patients enrolled in the trial. In addition, biospecimens will be collected to explore the local and systemic responses to this therapy.

**METHODS:** We will conduct a phase 1, dose-escalated, nonrandomized, open-label, clinical trial of patients with GBM who are undergoing surgical resection for recurrence. Up to 18 patients will receive intracavitary application of AMSCs encapsulated in fibrin glue during surgical resection. All patients will be followed for up to 5 years for safety and survival data. Adverse events will be recorded using the CTCAE V5.0.

**EXPECTED OUTCOMES:** This study will explore the maximum tolerated dose of AMSCs along with the toxicity profile of this therapy in patients with recurrent GBM. In addition, preliminary long-term survival and progression-free survival outcome analysis will be used to power further randomized studies. Finally, cerebrospinal fluid and blood will be obtained throughout the treatment period to investigate circulating molecular and inflammatory tumoral/stem cell markers and explore the mechanism of action of the therapeutic intervention.

**DISCUSSION:** This prospective translational study will determine the initial safety and toxicity profile of local delivery of AMSCs for recurrent GBM. It will also provide additional survival metrics for future randomized trials.

**KEY WORDS:** Human mesenchymal stem cells, Prospective, Stem cell, Stromal cell, Window of opportunity

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**ABBREVIATIONS: AMSC,** adipose-derived mesenchymal stem cell; **DLT,** dose-limiting toxicity; **INF,** interferon; **MCP,** monocyte chemoattractant protein; **MSC,** mesenchymal stem cell; **MTD,** maximum tolerated dose.

## GENERAL INFORMATION

**Protocol Title:** Phase 1, Dose Escalation, Nonrandomized, Open-Label, Clinical Trial Evaluating the Safety and Preliminary Efficacy of Allogenic Adipose-Derived Mesenchymal Stem Cells (AMSCs) For Recurrent Glioblastoma.

**Registry:** This study is registered in ClinicalTrials.gov (NCT05789394).

**Study Dates:** June 2023 to present.

**Sponsor/Funding Agency:** National Cancer Institute of the National Institutes of Health, Grant No. R01CA195503 & R01CA183827 and Center for Regenerative Biotherapeutics of the Mayo Clinic Florida.

**Institutional Approvals:** Mayo Clinic Institutional Review Board, IRB No. 21-004561 and U.S. Food and Drug Administration Investigational New Drug, IND No. 27651.

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## RATIONALE AND BACKGROUND INFORMATION

Glioblastoma (GBM) is the most common and aggressive form of primary brain cancer.[1] The yearly incidence rate of GBM in the United States is estimated to be 3.19 per 100 000 population.[1,2] Although current standard therapies, which include maximal safe resection, radiation, and concomitant adjuvant chemotherapy, have reduced mortality rates significantly, the median overall survival remains 15 months,[3-6] while progression-free survival post-treatment remains 4 to 6 months.[7-10] Despite the aggressive approaches, there is almost a 100% recurrence rate.[11] Such limitations have resulted in a surge of more directed aggressive approaches toward GBM.[12]

Surgery presents an opportunity to deliver local therapy and bypass the blood-brain barrier.[13-17] Although conventional therapy involves a waiting period of 4 to 6 weeks after resection before initiating chemoradiation, intraoperative treatment allows for immediate intervention. Furthermore, approximately one quarter of recurrent patients with GBM are eligible for a second surgical procedure,[4,18-20] creating a critical time frame to introduce targeted therapies that can improve outcomes at recurrence. Such timely intervention may potentially arrest disease or prolong survival outcomes.

The etiology of treatment failure in GBM is complex. One significant factor contributing to this is the difficulty in achieving effective delivery of agents because of the blood-brain barrier.[21-23] Despite effective delivery, some tumors may develop mutational advantages that render them resistant to treatment.[3,12,24] This is further exacerbated by tumor-mediated immune evasion through multiple mechanisms, including indirect changes in the tumoral microenvironment and directed immune suppression imposed by the tumor itself.[25,26] Notwithstanding such complexities, the ability of these malignant cells to migrate and invade neural tissue remains a significant challenge. Studies have shown the presence of tumoral cells beyond the contrast-enhancing portion of the tumor (thus causing high rates of local recurrence)[27-29] and demonstrating an ability to migrate long distances into the contralateral side and recur distally to the primary site.[29-31] Hence, to effectively tackle the aggressive characteristics of GBM, a therapeutic with multimodal functions may counter the tumor's migrative, evasive, and immunosuppressive properties. One such emergent strategy is exploiting the potential use of

mesenchymal stem cells (MSCs) for the treatment of GBM.[32-37] Numerous studies have demonstrated the nononcogenic nature of MSCs in GBM models.[32,33,35-41] MSCs are a safe therapeutic option as they migrate and colocalize with tumor cells that remain in the tumor borders of those that have migrated distally.[33,35] Moreover, MSCs have been demonstrated to be hypoimmunogenic and possess immunomodulatory properties, which could potentially lead to clinical improvement in patients with GBM by reducing malignancy-induced inflammation.[38,42,43]

We hypothesize that the local delivery of AMSCs into the surgical cavity before surgical closure is feasible, safe, and could improve the long-term outcomes of recurrent GBM and posit that AMSC treatment may decrease the progression rate and invasiveness of malignant cells in these patients. The primary objective of this protocol was to assess the safety of AMSCs delivery to the surgical cavity of recurrent GBM. This study will collect data to assess the initial effectiveness of AMSC treatment, which will be used to complement further investigations. Correlative studies will also be conducted to gain insight into the mechanism of action underlying this approach.

## STUDY GOALS AND OBJECTIVES

### Primary Goals

1. To establish the maximum tolerated dose (MTD) of locally delivered AMSCs in patients with recurrent GBM.

### Secondary Goals

1. To assess the safety and toxicity profile of locally delivered AMSCs in patients with recurrent GBM.
2. To assess overall survival in patients with recurrent GBM treated with locally delivered AMSCs.
3. To assess progression-free survival in patients with recurrent GBM treated with locally delivered AMSCs.

### Correlative Research

1. To explore the systemic immune response after application of AMSCs through cytokine analysis on peripheral blood samples.
2. To explore the local changes on the brain parenchyma by analyzing tissue at recurrence.
3. To explore the presence of AMSCs on brain tissue at recurrence.

## STUDY DESIGN

This is a phase 1, open-label, nonrandomized, dose escalation, 3 + 3 design, clinical trial to evaluate the safety and preliminary efficacy of AMSCs for recurrent GBM applied to the resection cavity at the time of surgical resection (Figure 1). This study consists of 3 different dose levels (Level 1: $5 \times 10^6$ AMSCs, Level 2: $10 \times 10^6$, and Level 3: $20 \times 10^6$), and up to 18 patients will be enrolled in the trial. The selection criteria are presented in Table.

## METHODOLOGY

### Study Agent

AMSCs will be produced in the human cell therapy laboratory (HCTL) at Mayo Clinic Florida following current good manufacturing practices.[44] In brief, lipoaspirates from a healthy female donor will be used to obtain the AMSCs. The adherent fraction of the lipoaspirate is expanded using the Quantum Cell Expansion System (Terumo BCT, Inc) to create an initial Master Cell Bank of cells that is fully characterized. The AMSC Product is generated by further expanding individual samples from the Master Cell Bank stock using the Quantum until the time of cryopreservation. Doses of the final cryopreserved product are formulated in 1 mL of CryoStor CS5 (Sigma-Aldrich). At the day of clinical use, cells will be thawed, washed, resuspended in 1 mL of lactate ringer solution (LRS, Baxter Healthcare Corp), and delivered directly to the operating room for application (Figure 2).

### Surgical Procedure

Participants will be screened for eligibility during outpatient consults. Once enrolled, all patients will undergo maximal safe resection for recurrent GBM. After resection is complete, while in the operating room before closure, cells will be encapsulated in Food and Drug Administration-approved fibrin glue (TISSEEL, Baxter Healthcare Corp) and applied locally to the resection cavity (Figure 2). The fibrin glue serves as an extracellular matrix to support cell survival. Viability and survival studies of the AMSCs will be published elsewhere once the study is complete. All patients will undergo implantation of an ipsilateral Ommaya reservoir (Natus Medical Inc) at the time of surgery to obtain cerebrospinal fluid (CSF) samples for correlative studies.

### AMSC + Fibrin Glue Mix Preparation

A prepackaged 4 mL fibrin glue (TISSEEL, Baxter Healthcare Corp) will be used. Under sterile conditions, the surgeon will remove 1 mL of thrombin (component 2) from the fibrin glue applicator (Figure 3A). Then, cell suspension (1 mL) will be injected into the thrombin barrel using an 18-gauge needle (Figure 3B). The fibrin glue applicator is then completed following the manufacturers' instructions (Figure 3C). This mixture will yield a final volume of 4 mL consisting of 2 mL fibrinogen + 1 mL thrombin + 1 m cell mixture.

### Correlative Research Studies

Participants will undergo a 10 mL blood draw within 24 h before surgical procedure, within 24 h after surgical procedure, 1 month after surgical procedure, and 2 months after surgical procedure. A complete blood count with differential and inflammatory cytokines (Interferon [INF]-γ, INF-a, TNF-a, IP-10, monocyte chemoattractant protein [MCP]-1, MCP-4, macrophage inflammatory protein-1b, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, and IL-15) will be measured.

Participants will undergo a 10 mL CSF aspiration through the Ommaya reservoir at the time of surgery and weeks 1, 2, 3, and 4 after treatment. Inflammatory cytokines will be measured (INF-γ, INF-a, TNF-a, IP-10, MCP-1, MCP-4, macrophage inflammatory protein-1b, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, and IL-15). Circulating tumor DNA will be quantified and measured. An exploratory bioinformatics analysis will be obtained to quantify the presence of AMSCs within the CNS through genetic material analysis.

All participants will be consented to provide mandatory tissue specimens for research at the time of surgery and at recurrence (either

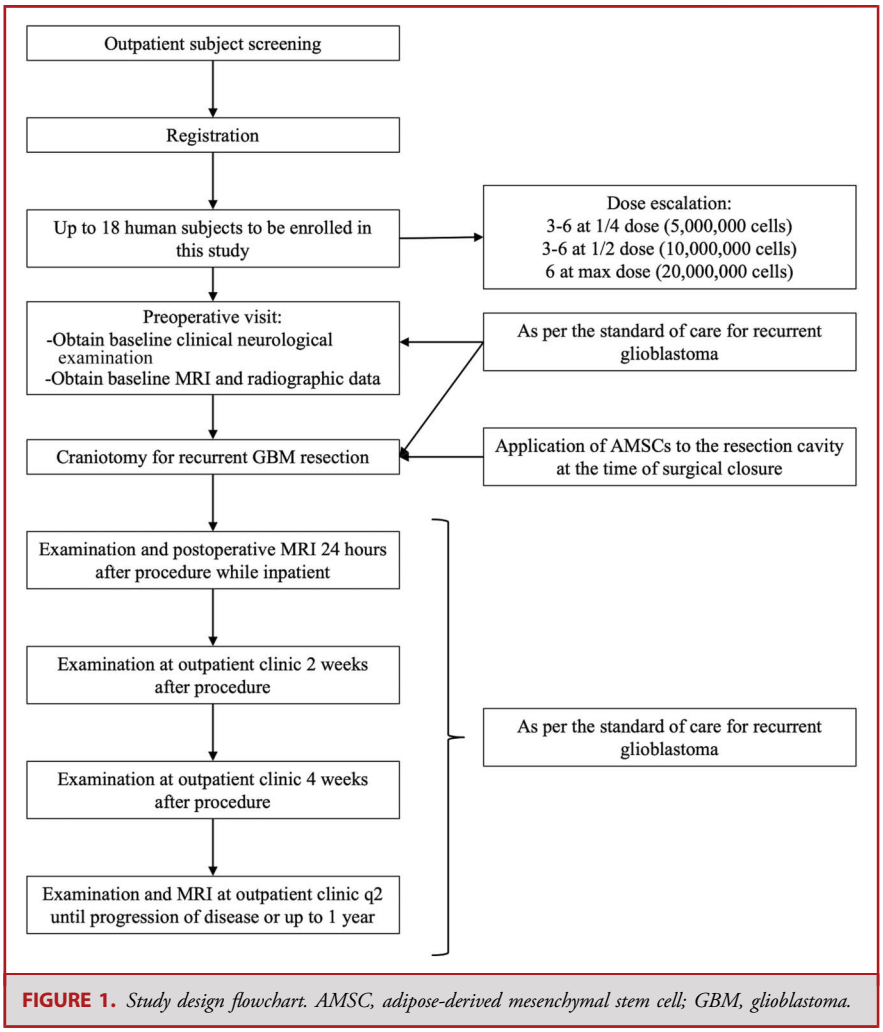


**FIGURE 1.** *Study design flowchart. AMSC, adipose-derived mesenchymal stem cell; GBM, glioblastoma.*

reoperation or postmortem). Postmortem samples will be processed at the MCF brain bank. Immunohistochemistry for immune infiltration ($CD4^+$, $CD8^+$, CD163+, PD1+, and Sox2+) will be assessed.

In addition, we will obtain clinical data along with tissue, blood, and CSF from institutional controls (IRB No.16-008485) enrolled in our brain tumor tissue biobank (Quiñones-Hinojosa, et al., unpublished data, 2023) to assess the effect of treatment with AMSCs vs untreated controls.

## DISCUSSION

This is a first in-human clinical trial evaluating intratumoral application of AMSCs for recurrent GBM. On study completion, the safety and MTD of intratumoral AMSCs for GBM will be established. The knowledge will enable the performance of late phase clinical trials to evaluate the efficacy of this therapy for recurrent GBM and potential design protocols for newly diagnosed disease. Moreover, the collection of preliminary efficacy data on long-term survival of these patients will allow for an adequate calculation of statistical power for future studies.

Ultimately, this study will offer valuable insight into the mechanism of action of AMSCs and streamline the development of targeted cellular biotherapeutics for future studies. The results from this study will corroborate prior preclinical research, by our group and others, which demonstrated the survival advantages of nanoengineered and virally transduced MSCs secreting bone morphogenic protein 4, TNF-related apoptosis-inducing ligand,[32,35,45] IL-12,[46] and further the work performed on nanoengineered and encapsulated MSCs in recurrent GBM (Al-Kharboosh et al., unpublished data, 2023) The outcomes of this work will empower future studies that leverage the AMSC's innate ability to migrate toward malignant glioma cells.

## TRIAL STATUS

This study is active and open for enrollment.

**TABLE. Selection Criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Participants ≥18 y <65 y of age | Patients who are undergoing biopsy only or noneligible for a surgical intervention |
| Karnofsky performance score ≥60 | Previous treatment with bevacizumab |
| Negative pregnancy test performed <7 d before registration, for persons of childbearing potential only | Radiographic evidence of leptomeningeal disease |
| Patients with a previous histological diagnosis of GBM that show recurrence at the same location, who are candidates to and will undergo a redo craniotomy for excision of recurrent tumor. | |
| Patients have undergone previous standard of care as outlined by Stupp et al (2004) which include maximal safe resection followed by concomitant radiation therapy and chemotherapy with oral temozolomide. | |
| Adequate organ function as assessed by the following laboratory values ≤3 wk before registration: | |
| a. Serum creatinine and urea ≤2 times the upper limit of normal | |
| b. ALT, AST, and alkaline phosphatase ≤3 times the upper limit of normal and bilirubin ≤2.5 mg/dL | |
| c. Prothrombin time ≤1.5 times upper limit of normal | |
| d. INR and PTT ≤1.5 times the upper limit of normal | |
| e. Hemoglobin ≥9 g/dL | |
| f. Platelets ≥100 × $10^9$/L | |
| g. ANC ≥1.5 × $10^9$/L. | |
| Willing to return to enrolling institution for follow-up (during the active monitoring phase of the study). | |
| Patient or legal guardian is able to fully understand and provide written and verbal consent for the protocol. | |
| Willingness to provide mandatory blood specimens for correlative research. | |
| Willingness to provide mandatory tissue specimens for correlative research. | |
| Willingness to undergo Ommaya reservoir placement and provide CSF samples for correlative research. | |

ANC, absolute neutrophil count; AST, adenosine transaminase; CSF, cerebrospinal fluid; GBM, glioblastoma; INR, International Normalized Ratio; PTT, partial thromboplastin time.

## SAFETY CONSIDERATIONS

All patients enrolled in this study will receive standard of care and supportive disease measures at the discretion of the treating neuro-oncologist. All adverse events will be collected on patients throughout the study. For adverse events, we will use the CTCAE v5.0. Toxicities will be assessed for 28 days after treatment and are defined as any grade ≥3 that has prolonged for more than 7 days and that is not expected from any of the established complications of a neurosurgical procedure. In case of any occurrence, the patient will remain under observation with supporting measures for at least 7 days or until the toxicity has resolved. The first 3 patients will be enrolled at the starting dose level. If no dose-limiting toxicities (DLTs) are seen, the next 3 patients will be enrolled at the next higher dose level. If at least 1 patient develops a DLT, 3 additional patients will be enrolled and treated at the same dose level. If a DLT is seen in at least 1 of these additional patients, the MTD will have been exceeded (MTD is defined as the dose of AMSCs at which ≤1 of 6 subjects experience a DLT) and further accrual will cease to this cohort. In case the MTD is exceeded, the dose will be de-escalated to the previous dose level where a DLT was not observed.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment that satisfy the following stopping rules:

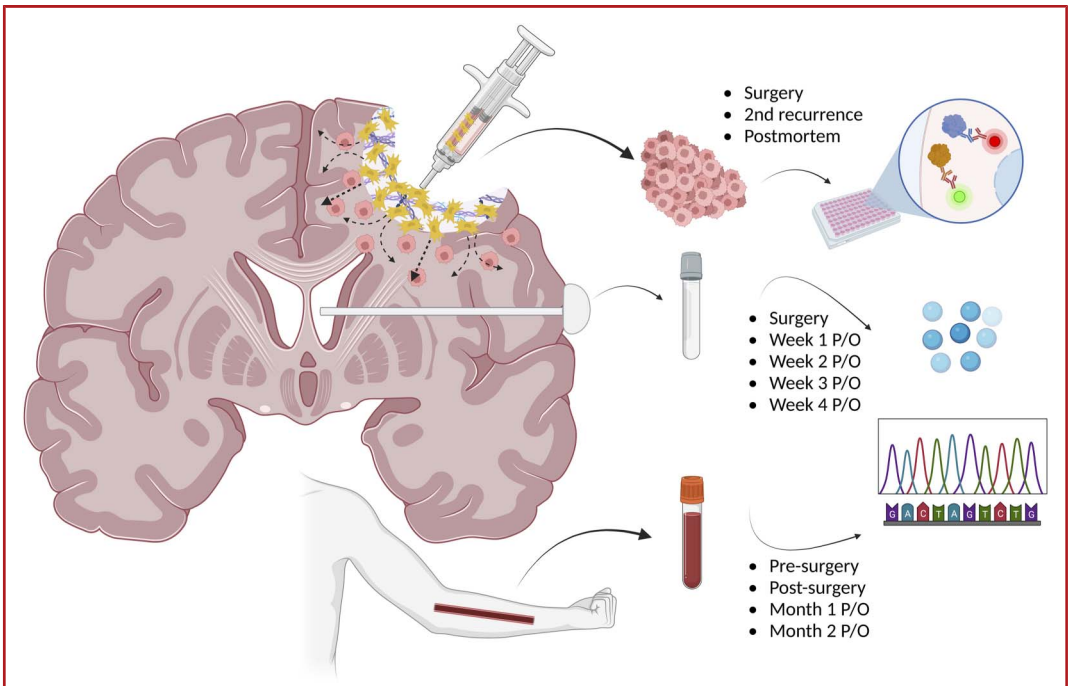


**FIGURE 2.** *Visual schematic of study procedures and correlative research (with time points). Patients will undergo intraoperative delivery of AMSCs encapsulated in fibrin glue to the resection cavity immediately after tumor excision. An ipsilateral CSF reservoir will also be placed at the time of surgery and will be used to collect CSF samples throughout the study. Tissue will undergo immunohistochemistry to evaluate immune infiltration and the long-term presence of AMSCs within the tissue. An inflammatory cytokine profile and next-generation sequencing will be performed in all CSF and blood samples. AMSC, adipose-derived mesenchymal stem cell; CSF, cerebrospinal fluid.*

1. >1 death within 7 days of AMSC application that is at least possibly related to the study agent across all treated subjects.
2. >1 serious adverse event that is at least possibly related to the study agent occurring in 2 or more patients in a single dose level.
3. >3 serious adverse events that are at least possibly related to the study agent occurring in a single dose level.

## FOLLOW-UP

Patients will be seen 24 h (±24 h) after the surgical procedure to obtain relevant medical history and adverse event collection. A postoperative MRI will be taken, while the patient is hospitalized within 24 hours (±24 h) of the procedure. Patients will then be seen as outpatient 1 week (±4 days), 2 weeks (±4 days), 3 weeks (±4 days), and 4 weeks (±4 days) after the procedure to obtain relevant medical history, adverse event collection, and biospecimen samples. Patients will then be seen for follow-up every 2 months (±7 days) until progression of disease as defined by iRANO or until 1 year from registration. Patients will then be followed for survival. Other therapies for recurrent GBM will not be restricted and will be dictated at the discretion of the treating neuro-oncologist or radiation oncologist.

## DATA MANAGEMENT AND STATISTICAL ANALYSIS

Data collection for this study will be performed exclusively through the Medidata Rave clinical data management system (Medidata Solutions Inc). All the relevant results pertaining to toxicity, MTD, response, timed end points, and laboratory correlates will be examined in an exploratory and hypothesis-generating fashion.

A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% ($1 - [1 - 0.25]^6$).

## QUALITY ASSURANCE

Mayo Clinic Florida is a National Cancer Institute Designated Comprehensive Cancer Center, and all patients will undergo a multidisciplinary approach by neurosurgery, neuro-oncology, and radiation oncology throughout the study. Patient confidentiality will be kept throughout the study, and data will be kept in an encrypted database following federal standards.

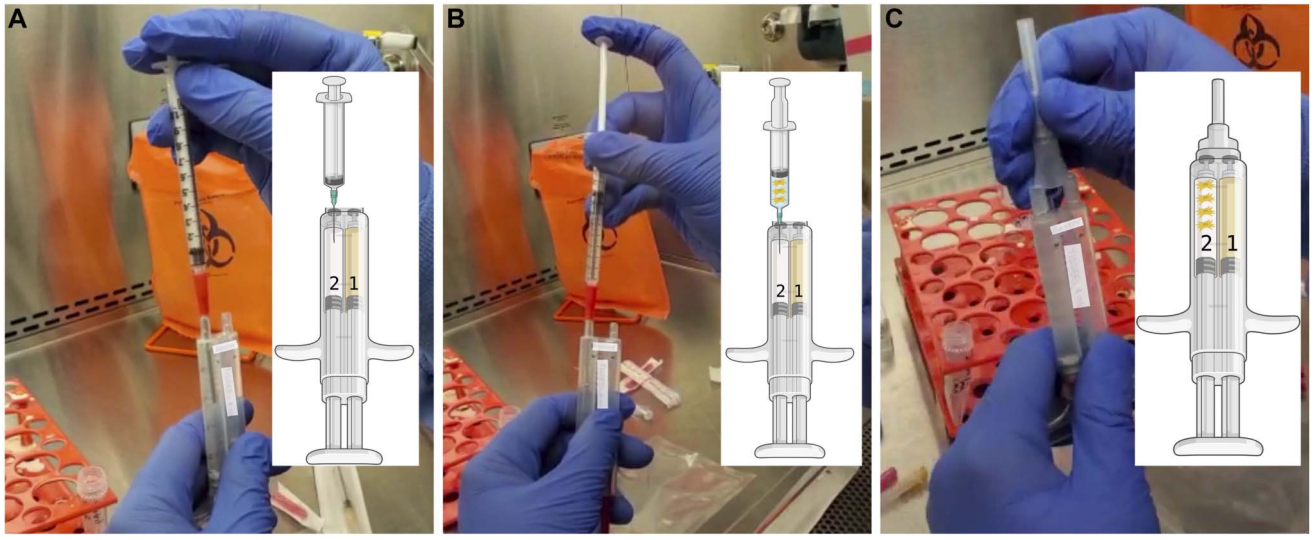


**FIGURE 3.** *Fibrin glue + AMSC mixture preparation.* **A**, *Under sterile conditions, the surgeon will remove 1 mL of thrombin (component 2) from the fibrin glue applicator.* **B**, *Then, cell suspension (1 mL) will be injected into the thrombin barrel using an 18-gauge needle.* **C**, *The fibrin glue applicator is then built following the manufacturers' instructions. This mixture will yield a final volume of 4 mL consisting of 2 mL fibrinogen + 1 mL thrombin + 1 m cell mixture. AMSC, adipose-derived mesenchymal stem cell.*

The study underwent thorough review for safety by the Food and Drug Administration through an investigational new drug application, by multiple neuro-oncology and cell therapy cancer center subcommittees, scientific review by the neuro-oncology committee, and finally by Institutional Review Board to ensure appropriate scientific procedures.

## EXPECTED OUTCOMES

We expect to find the MTD of AMSCs for the treatment of recurrent GBM to establish the safety of this therapy for GBM. At the same time, we intend to find a preliminary sign of efficacy to power and design a larger phase 2 study. Furthermore, the correlative research will allow us to further understand the effects and the antibrain cancer mechanisms of AMSCs.

## DURATION OF THE PROJECT

We expect to complete enrollment within the first 6 months after activation, and patients will be followed until progression of disease or until 1 year after treatment.

## PROJECT MANAGEMENT

Trial oversight will be maintained by the study principal investigator as well as with oversight from the Mayo Clinic IRB, DSMB, and the Mayo Clinic Comprehensive Cancer Center.

## ETHICS

This study protocol, informed consent, and preclinical data were reviewed and approved by the Mayo Clinic Institutional Review Board and the Food and Drug Administration through an investigational new drug application. Before enrollment, all patients will undergo informed consent and can withdraw from the study at any point.

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### Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Alfredo Quiñones-Hinojosa and Jordan J. Green are cofounders with equity and Managers of the startup company Dome Therapeutics.

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