

Visish M. Srinivasan, MD

Institution: Baylor College of Medicine/MD Anderson Cancer Center

Award: 2016-17 AANS/CNS Joint Section on Cerebrovascular Research Fellowship Grant

Project Title:

Endovascular Delivery of Allogenic Human Mesenchymal Stem Cells Transfected with the Delta-24 Oncolytic Virus in a Canine Model of Glioblastoma

Abstract:

This project aims to determine the feasibility and efficacy of intra-arterial endovascular delivery of mesenchymal stem cells in a large animal model. Previous studies have shown that human bone marrow mesenchymal stem cells (hMSCs) exhibit tropism for gliomas.

A recent clinical trial using a tumor-selective oncolytic adenovirus, Delta-24-RGD showed positive results via intratumoral injection. However, intratumoral injection was limited by backflow and limited viral diffusion. I hypothesize that catheter-based endovascular injection, utilizing the tumor-tropic hMSCs as viral carriers, could offer minimally invasive, selective, and more effective delivery.

Although small animal studies have suggested that hMSC delivery of Delta-24 is efficacious, these models do not recapitulate the true clinical scenario; the feasibility and safety in patients is unknown. We propose to first assess the feasibility of endovascular delivery of MSCs transfected with Delta-24-RGD (hMSC-Delta-24) in a nontumoral healthy canine model. Optimal catheter type, location of intra-arterial injection, maximal dose, and systemic distribution of hMSC-Delta-24 will be determined. These parameters will then be applied in a tumor-bearing canine model to assess their impact on the tumor-tropism of hMSC-Delta-24. The results of this study will provide crucial preclinical data to support and guide a human clinical trial of endovascular delivery of Delta-24-hMSC.

This translational research regarding endovascular therapy for GBM is a unique opportunity for collaborative treatment between two neurosurgical subspecialties and is a promising new avenue of practice for cerebrovascular neurosurgeons.

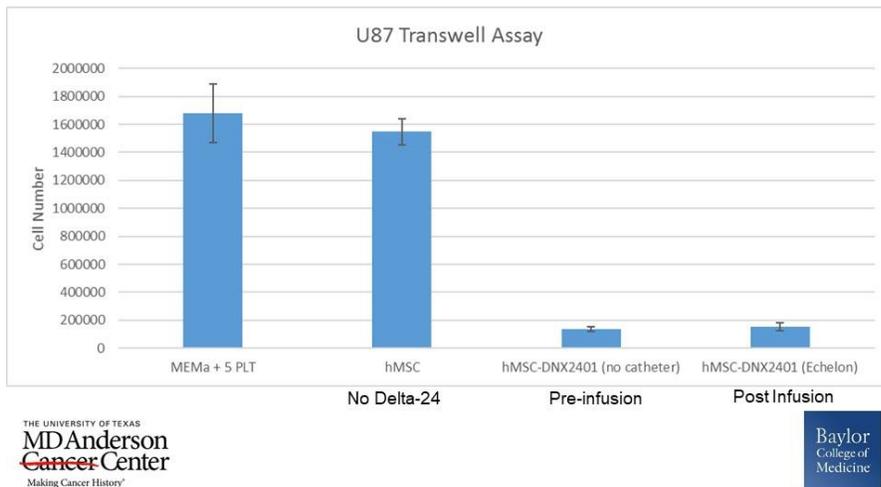
Progress:

Aim – Determine the optimal neuroendovascular technique, maximum tolerated dose (MTD), and safety profile injection of hMSC-Delta-24 in a healthy canine.

- 1.1 Determine the optimal microcatheter to use for endovascular injection of hMSC-Delta-24.
- 1.2 Identify the maximum tolerated dose (MTD) of hMSC-Delta-24.
- 1.3 Determine the optimal microcatheter location for endovascular injection of hMSC-Delta-24.
- 1.4 Assess the systemic/organ distribution and toxicity profile of hMSC-Delta-24 following endovascular injection.

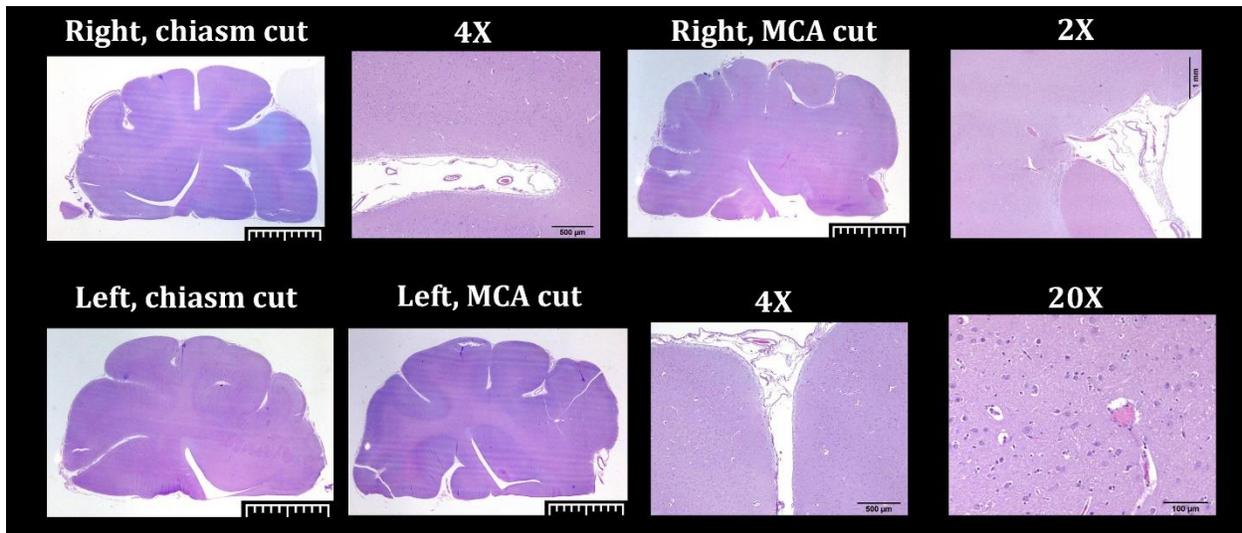
We tested multiple catheters for compatibility injection timing, catheter tortuosity, and medication compatibility. Some data are provided below. We found that none of these affected the viability of our hMSCs loaded with Delta-24. Further, we found that the hMSCs were able to deliver the virus successfully and the virus retained its oncolytic capability.

Result 4: Catheter-infused cells maintained anti-glioma activity



We then tested this in healthy non-tumor-bearing canines. This served to validate our technique in a large animal with endovascular characteristics similar to humans. While we had initially planned to use a tumor-bearing model, ultimately we determined this to be too costly and raised too many ethical concerns for a survival model in which stroke was possible or likely. As a result we have secured follow-up funding to validate this in a tumor-bearing rabbit model (see below).

Instead, we tested canines in this procedure and performed MRI and pathological testing to determine technical/procedural outcome and safety. We found no major complications and no strokes up to our highest concentration.



Subject	Age	Weight	Injected Concentrations and Volumes	Cell injection Duration & Location	Control Injection Duration & Location	Outcomes
Canine 1 (112918)	10 mo. 13 days	35kg (77lbs)	2x10 ⁶ cells/20mL	32 min; L ICA	17 minutes; R ICA	No stroke, no complications
Canine 2 (120139)	8 mo. 6 days	27.5kg (60.5lbs)	1x10 ⁷ cells/20mL	40 min 50 sec; L ICA	15 min 28 sec; R ICA	No stroke, no complications
Canine 3 (119700)	9 mo. 22 days	28.3kg (61.8lbs)	2x10 ⁷ cells/20mL	22 min 21 sec; L ICA	20 min 34 sec; R ICA	No stroke, no complications
Canine 4 (117936)	10 mo. 26 days	28.8kg (63.5lbs)	1x10 ⁸ cells/20mL	21 min; R ICA	17 min; L ICA	No stroke, no complications
Canine 5 (122450)	8mo. 22 days	33.1kg (72.9lbs)	1x10 ⁸ cells/20mL	21 min 34 sec; L PCA	18 min; R PCA	No stroke, no complications
Canine 6 (121462)	9 mo. 14 days	32.7kg (72.1lbs)	1x10 ⁸ cells/10mL	11 min 26 sec; L PCA	10 min 12 sec; R PCA	Basal cistern/perivascular SAH, no stroke or other complications
Canine 7 (127486)	8 mo. 15 days	27.6kg (60.8lbs)	Positive stroke #1	R PCA stroke	L PCA no injection	Basal cistern/perivascular SAH, no stroke or other complications
Canine 8 (122158)	9 mo. 27 days	33.6kg (74.1lbs)	Positive stroke #2	R ICA	No injection	Numerous particles found in vessels of the meninges and brain on both hemispheres.
Canine 9 (128882)	8 mo. 20 days	26.0kg (57.3lbs)	1x10 ⁸ cells/10mL Survival	R ICA	L ICA	No stroke, no complications
Canine 10 (133265)	9 mo. 2 days	29.3kg (64.6lbs)	1x10 ⁸ cells/10mL Survival #2	L ICA	R ICA	No stroke, no complications

Abstracts:

1. **Srinivasan VM**, Gumin J, Camstra KM, Lang FF, Kan P. (2017, February). Microcatheter Delivery of Neurotherapeutics: Compatibility with Mesenchymal Stem Cells. Oral presentation at: AANS/CNS Section on Cerebrovascular Surgery Annual Meeting; Houston, TX