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Padova, July 29 2025

Dear Editors,

We are pleased to submit our revised manuscript titled **“Redirecting the Route: Monocyte-Mediated Delivery of oHSV-1 Across a Human BBB-on-chip Model”** for consideration as a research article in **Materials Today Bio**.

In this study, we report the development and validation of a human microfluidic blood–brain barrier (BBB)-on-chip platform designed to evaluate cell-based delivery strategies for oncolytic virotherapy targeting glioblastoma (GBM), one of the most aggressive and treatment-resistant brain tumors. Our laboratory has a strong track record in engineering advanced *in vitro* models to investigate therapeutic dynamics in cancer and its microenvironment, particularly in the context of the central nervous system.

Using this platform, we demonstrate that human monocytes infected with a neuroattenuated oncolytic herpes simplex virus type 1 (oHSV-1) can successfully traverse the engineered BBB, migrate toward GBM spheroids, and selectively deliver the virus to tumor cells. Importantly, viral transfer is effective even in the presence of anti-HSV-1 antibodies and does not result in off-target infection of the BBB itself, an important advantage over free virus administration. Free oHSV-1 virions are also sequestered by the barrier and neutralized by circulating immunoglobulins before reaching the tumor compartment.

Our findings highlight monocyte-mediated OVs delivery as a promising, immune-evasive strategy for GBM therapy and the relevance of organ-on-chip technologies for evaluating next-generation cancer therapeutics.

We believe that this work will be of significant interest to the readership of Materials Today Bio, given its relevance and positioning at the interface of microfabrication, bioengineered disease models, immunotherapy, and viral oncology

We look forward to the reassessment of our revised and improved work and sincerely hope you will find our work suitable for publication in Materials Today Bio.

Sincerely,

A picture containing text

Description automatically generatedProf. Elisa Cimetta