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Dear editors,

it is my pleasure to submit our new manuscript titled **“Redirecting the Route: Monocyte-Mediated Delivery of oHSV-1 Across a Human BBB-on-chip Model”** for publication as a research article in your journal **Small**.

In this study, we present the development and validation of a human microfluidic blood–brain barrier (BBB) model designed to assess the potential of cell-based delivery strategies for oncolytic virotherapy targeting glioblastoma (GBM), an aggressive and largely intractable brain tumor. Our laboratory has a long-standing interest in engineering advanced in vitro models to study the therapeutic dynamics of cancer and its surrounding microenvironment, particularly in the context of the central nervous system.

Here, we show that human monocytes infected with a neuroattenuated oncolytic herpes simplex virus type 1 (oHSV-1) can successfully traverse the engineered BBB-on-chip, migrate toward GBM spheroids, and deliver the virus selectively to tumor cells. Notably, the viral delivery 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. These findings position monocyte-mediated OV delivery as a promising, immune-shielded strategy for GBM therapy and underscore the relevance of organ-on-chip technologies for testing advanced therapeutic platforms.

We believe our manuscript provides impactful insights at the intersection of microfabricated devices, bioengineered models, immunotherapy, and viral oncology, and will be of broad interest to readers of your journal.

We look forward to the review process and sincerely hope you will find our work suitable for publication in **Small**.

Sincerely,

Prof. Elisa Cimetta

