inhibits lysis of E-cadherin-expressing cells by NK cells (Ito et al., 2006, *Journal of Experimental Medicine* 203, 289-295). KLGRl is also an inhibitory receptor in T cells (Grundemann, *et al.* 2006, *J Immunol* l 76, 1311-1315). Besides its known function as a KLRGl ligand, E-cadherin is well known as a calcium dependent cell-cell adhesion molecule that cooperates with Nectin-1 in the formation of cell-cell adherens junctions (Tachiban et al., 2000, *The Journal of Cell Biology* 150, 1161-1176; Drees et al., 2005, *Cell* 123, 903-915). As a herpes virus entry receptor, Nectin-1 is crucial for HSV-1 infection. The binding of Nectin-1 and HSV glycoprotein D (gD) triggers viral entry of HSV. Loss of Nectin-1 expression in cells results in resistance or low susceptibility to HSV-1 infection (Akhtaret et al., 2008, *Investigative Ophthalmology & Visual Science* 49, 4026-4035; Xu et al., 2011, *Nature Biotechnology* 29, 735-741). E-cadherin junctions can recruit Nectin-1 to the cell surface, which may help to facilitate HSV-1 viral spread (Troyanovsky et al., 2015 *Journal of Cell Science* 128, 140-149). However, most GBM cells do not natively express E-cadherin (Lewis-Tuffin et al., 2010, *PloS one* 5, e13665).

[0007] Thus, there is a need in the art to develop oncolytic viral therapies, particularly oncolytic HSV therapies, that have improved virus spread within a solid tumor like GBM and that avoid depletion of virally infected cells by immune cells such as NK cells and T cells.

SUMMARY

[0008] This disclosure provides reagents and methods for oncolytic viral therapies, particularly oncolytic HSV therapies, that have improved virus spread within a solid tumor like GBM and that avoid depletion of virally infected cells by immune cells such as NK cells. In one aspect, provided herein is oncolytic herpes simplex virus (HSV) comprising a heterologous gene encoding E-cadherin.

[0009] In another aspect, the present disclosure provides use of an oncolytic herpes simplex virus (HSV) as described herein in the manufacture of a medicament for treating a subject having a tumor. In other examples, provided herein is a method for treating a subject having a tumor, the method comprising: administering to a subject in need thereof atherapeutic amount an oncolytic herpes simplex virus (HSV), comprising a heterologous gene encoding E-cadherin.

[0010] In another aspect, provided herein is a pharmaceutical composition comprising an HSV comprising a heterologous gene encoding E-cadherin and a

pharmaceutically acceptable carrier or diluent.

[0011] In some examples, the heterologous gene is operably linked to a HSV promoter sequence which is selectively active during HSV replication. In some examples, the HSV promoter is a HSV immediate early promoter.

[0012] In some examples, the HSV further comprises an ICP 6-inactivating mutation or deletion. In some examples, the HSV further comprises any γ 34.5inactivating mutation or deletion.

[0013] In some examples, the tumor is a solid tumor such as a glioblastoma, anovarian tumor or a breast tumor.

[0014] In some examples, the subject is a mammal. In some examples, themammal is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figures lA-lH show oncolytic viral-E-cadherin (OV-CDHl) infection introduces E-cadherin expression to infected GBM cells. Figure l(A) illustrates a schematic map of oncolytic viruses used in the methods disclosed herein. Specifically, the top portion of the Figure illustrates a genetic map of wild type HSV-I; the middle portion illustrates a map of control oHSV, parental oHSV (OV-Ql), with deletion of γ34.5, dysfunction of ICP6 and insertion of the green fluorescent protein (GFP) gene; and the bottom portion illustrates a map of OV-CDHl showing insertion of the humanCDHl gene (encoding E-cadherin) driven by the viral IE4/5 promoter. The genetic maps of OV-ΔCDHl shows the insertion of protein-coding sequence of mutant E- cadherin (IL-2Rα/E-cad), in which the original E-cadherin extracellular domain was replaced with the interleukin-2 receptor alpha chain (IL-2Rα) extracellular domain; the cytoplasmic domain remained intact. Figure l(B) illustrates immunoblotting performed with cell lysates from uninfected, OV-Ql- or OV-CDHl- infected GBM cells at 8 hours post infection (hpi). Figure l(C) illustrates immunoblotting performed with lysates from OV-CDHl- infected Gli36 or GBM30 cells at 0, 2, 4, 8, 12 hpi.

Figure l(D) illustrates flow cytometry performed with uninfected, OV-Ql- or OV-CDHl-infected GBM cells at 8 hpi. Figure l(E) illustrates immunoblotting performedwith cell lysates from OV-Ql, OV-CDHl and OV-ΔCDHl-infected U251 cells at 8 hpi using the antibody recognizing cytoplasmic domain of E-cadherin. Figure l(F) illustrates flow cytometry performed using OV-ΔCDHl infected U251 cells at 8 hpi using anti-CD25. Figure l(G) illustrates NK cell cytotoxicity measured by ^{51}Cr release from uninfected, OV-Ql-, OV-CDHl- and OV-ΔCDHl-infected Gli36 cells

WHAT IS CLAIMED IS:

1. An oncolytic herpes simplex virus (HSV) comprising a heterologous gene encoding E-cadherin.

2. The HSV of claim 1, wherein the heterologous gene is operably linked to a HSV promoter sequence that is selectively active during HSV replication.

3. The HSV of claim 2, wherein the HSV promoter is a HSV immediate early promoter.

4. The HSV of claim 1, wherein the HSV further comprises an ICP 6- inactivating mutation or deletion.

5. The HSV of claim 1, wherein the HSV further comprises an γ 34.5 inactivating mutation or deletion.

6. Use of an oncolytic herpes simplex virus (HSV) of any one of claims 1 to 5 in the manufacture of a medicament for treating a subject having a tumor.

7. The use of claim 6, wherein the tumor is a solid tumor.

8. The use of claim 7, wherein the solid tumor is a glioblastoma, an ovarian tumor or a breast tumor.

9. The use of claim 6, wherein the subject is a mammal.

10. The use of claim 9, wherein the mammal is a human.

11. The use of claim 6, wherein the tumor is a glioblastoma and wherein the medicament is to be administered intracranially, intraveneously, subcutaneously, via injection or infusion.

12. A pharmaceutical composition comprising an HSV comprising a heterologousgene encoding E-cadherin and a pharmaceutically acceptable carrier or diluent.

13. The pharmaceutical composition of claim 12, wherein the heterologous gene isoperably linked to a HSV promoter sequence which is selectively active during HSV replication.

14. The pharmaceutical composition of claim 13, wherein the HSV promoter is a HSV immediate early promoter.

15. The pharmaceutical composition of claim 12, wherein the HSV further comprises an ICP 6-inactivating mutation or deletion.

16. The pharmaceutical composition of claim 12, wherein the HSV further comprises an γ 34.5 inactivating mutation or deletion.