**Background** The therapeutic potential of the oncolytic virotherapy is severely restricted by multiple innate and adaptive immune barriers. To overcome this obstacle, we utilized adipose-derived stem cells (AD-MSC) loaded with tumor selective CAL1 oncolytic vaccinia virus to generate a new therapeutic agent called SNV1 (SuperNova-1). Intratumoral injection of SNV1 inhibited drastically tumor growth of multiple human cancer xenograft models at significant low virus titers. In syngeneic immunocompetent models, SNV1 showed a robust tumor growth inhibition and immune cell recruitment of both the local injected tumors and distant non-injected tumors.

**Methods** SNV1 was tested for its ability to resist humoral immunity-mediated virus inactivation in cell culture. In tumor-bearing mouse models, tumor growth inhibition of multiple human xenografts and murine syngeneic was examined by using either single or three dose regimens. Additionally, in bilateral tumor-bearing mouse models, immune profiles at different time courses of both treated and untreated tumors as well as lymph nodes were analyzed by flow cytometry. Antiviral and anti-tumor immunity was analyzed by ELISPOT.

**Results** Data showed that SNV1 was more resistant to rapid inactivation by humoral immune system as compared to naked CAL1 virus leading to a significant and robust improvement of oncolytic virus therapeutic efficacy in human melanoma (MeWo), head and neck (Fadu) and triple negative breast (MDA-MB-231) cancer cells. Furthermore, SNV1 significantly inhibited the growth of the tumors even at the very low dose of $1.5 \times 10^3$ cells containing $1.6 \times 10^4$ PFU. In a bilateral colon cancer tumor-bearing immunocompetent mouse model CT26, data showed both one (1) and three (3) administrations of SNV1 significantly inhibit tumor growth of injected tumors in comparison with the naked CAL1 virus or controls. However, significant systemic therapeutic efficacy was only achieved by three (3) but not one (1) intratumoral administrations of SNV1 suggesting multiple intratumoral administrations of SNV1 were required to induce robust systemic activation of the immune system. Furthermore, tumor infiltrating lymphocytes (TILs) from both treated and untreated tumors showed increased CD4 and CD8 T-cell infiltrations while suppressing frequency of Tregs. Early recruitment of innate populations was observed in tested models.

**Conclusions** The SNV1 stem cell-based platform protects and potentiates oncolytic vaccinia virus by circumventing humoral innate and adaptive immune barriers, resulting in enhanced anti-cancer effects in tumor-bearing mouse models. SNV1 provided instantly active viral particles for immediate infection in the injected tumors which help transforming tumor environment from “cold” to “hot” locally and systemically.