Advanced glioblastoma immunotherapy: Attenuated herpes oncolytic virus armed with anti-PD-1 antibody and IL-12

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Lei Wang, Xusha Zhou, Xiaoqing Chen, Yuanyuan Liu, Yanxin Zheng, Runbin Yan, Yonghong Liu, Jing Zhao, Grace Guoying Zhou
ImmVira Co., Ltd, Shenzhen, China

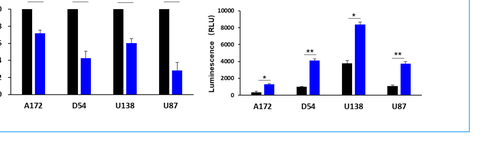
ImmVira 亦诺微医药

BACKGROUND

Glioblastoma (GBM), the most common and deadly primary brain tumor in adults, has limited treatment options with poor outcomes. The urgent need for innovative treatments has spurred research into immunotherapy and oncolytic virus therapy as promising alternatives. In this context, we have developed a new generation oncolytic herpes simplex virus (oHSV) named MVR-C5252, which is armed with IL-12 and an anti-PD-1 antibody, aiming to provide a synergistic anti-GBM efficacy for immune-oncolytic therapy. MVR-C5252 has obtained approval from both the FDA and NMPA for clinical trials in both the United States and China. Herein, we present preclinical data on MVR-C5252 developed for GBM treatment.

RESULTS

Characterization of oHSV MVR-C5252



C Expression of human IL-12 and anti-PD-1 Ab

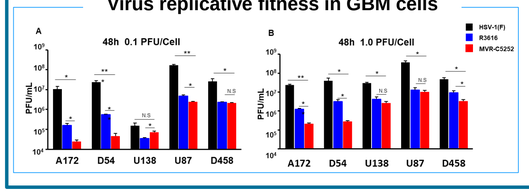
oHSV	Concentration (pg/mL)	
	IL-12 p70	Anti-PD-1 Ab
Mock	U	U
HSV-1(F)	U	U
R3616	U	U
MVR-C5252	401.69 ± 12.70	242.52 ± 5.55

*U: Undetectable

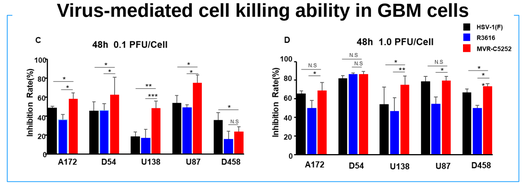
- Growth curves of the virus (A).
- Accumulation of viral protein (B).
- Expression of human IL-12 p70 or anti-PD-1 Ab from virus infected Vero cell culture medium (C).

MVR-C5252 is replication attenuated but with potent cell-killing activity in glioblastoma (GBM) cells

Virus replicative fitness in GBM cells

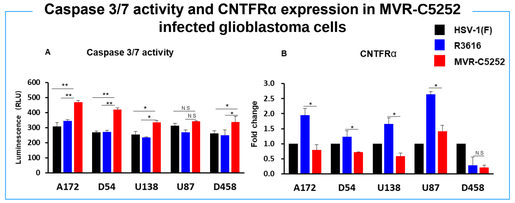


Virus-mediated cell killing ability in GBM cells

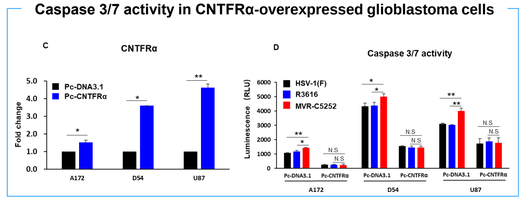


MVR-C5252 enhances apoptotic cell death via downregulation of CNTFRα expression

Caspase 3/7 activity and CNTFRα expression in MVR-C5252 infected glioblastoma cells



Caspase 3/7 activity in CNTFRα-overexpressed glioblastoma cells



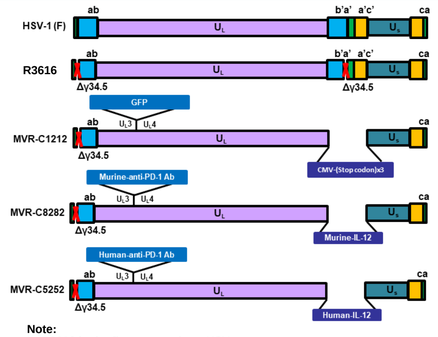
Caspase 3/7 activity in CNTFRα knockdown glioblastoma cells

- Compared to R3616 or wild-type HSV-1(F), MVR-C5252 infection reduced ciliary neurotrophic factor receptor α (CNTFRα) expression and increased caspase 3/7 activity in GBM cells (A,B).
- Transient overexpression of CNTFRα rescued caspase 3/7 activity in MVR-C5252 infected GBM cells (C&D).
- Knockdown of CNTFRα resulted in a significant increase of caspase 3/7 activity in GBM cells (E&F).

*Note: * p<0.05 ** p<0.01*

RESULTS

Schematic representations of MVR-oHSVs genome

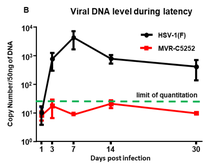


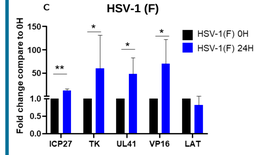
Note:
- R3616 is the first generation oHSV.
- MVR-C8282 is the murine surrogate of MVR-C5252 used for evaluating anti-tumor activity in immunocompetent mice.

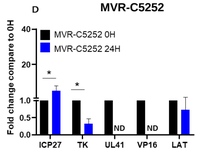
The safety evaluation of MVR-C5252 *in vivo*

A

Virus	PFU/mouse	No. of dead mice/total no. of mice (End of study Day14)	LD_{50}(PFU)	LD_{50} ratio compared with HSV-1(F)
MVR-C5252	1.5×10^5	1/8	$>1.5\times10^5$	>798
	1.5×10^4	0/8		
	1.5×10^3	0/8		
	1.5×10^2	0/8		
R3616	1.5×10^5	0/8	$>1.5\times10^5$	>798
	1.5×10^4	0/8		
	1.5×10^3	0/8		
	1.5×10^2	0/8		
HSV-1(F)	1.5×10^5	8/8	1.88×10^2	-
	1.5×10^4	3/8		
	1.5×10^3	1/8		
	1.5×10^2	0/8		



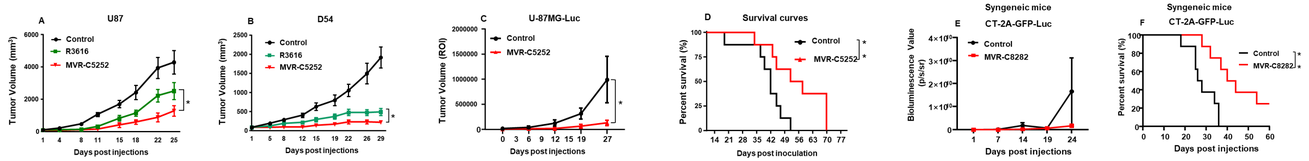




- LD_{50} test of oHSVs via intracranial injection route (A).
- Quantification of viral DNA expression in mice trigeminal ganglion (TG) during latency (B).
- Quantification of viral mRNA expression in mice TG during reactivation (C.D).
- MVR-C5252 has a lower toxicity and diminished ability to establish latency and reactivate in the brain, which makes it a safe candidate for the treatment of glioblastoma.

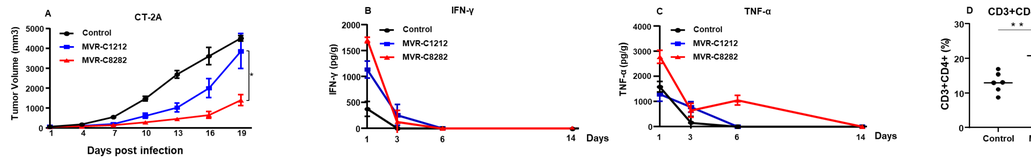
In Vivo anti-tumor efficacy of MVR-C5252

Anti-tumor efficacy in subcutaneous and orthotopic glioblastoma model



- The anti-tumor activity of MVR-C5252 in vivo was evaluated in U87 or D54 subcutaneous xenografts via intratumoral injections (A& B) and U-87MG-Luc orthotopic model via intracerebrally injection (C&D).
- The anti-tumor activity was validated in an immunocompetent orthotopic mouse model of murine GBM CT-2A treated with murinized MVR-C8282 virus. (E&F).
- MVR-C5252 significantly inhibited the progression of glioblastoma and prolonged the survival of the tumor-bearing mice.

Immune activation against tumors in immunocompetent glioblastoma model



- MVR-C5252 significantly reduced tumor volume in the CT-2A GBM syngeneic model compared to backbone virus MVR-C1212 (A).
- MVR-C5252 induced higher levels of IFN-γ and TNF-α compared to the MVR-C1212 and with a longer induction of TNF-α (B&C).
- MVR-C5252 induced remarkable CD8+ and CD4+ T cell infiltration in tumor bed (D&E).
- MVR-C5252 induced strong immune response against GBM.

CONCLUSION

- MVR-C5252 is highly replication attenuated but with higher cell-killing activity in GBM cells compared to the first-generation oHSV.
- Mechanistic studies demonstrated that MVR-C5252 specifically induces cell apoptosis by caspase 3/7 activation via reducing CNTFRα expression.
- MVR-C5252 shows superior anti-tumor activity and immune activation over the backbone virus.
- MVR-C5252 has a remarkable safety profile, which is unable to establish latency or reactivate.
- With the unique combination of safety, potent anti-tumor activity, and immune-stimulatory properties, MVR-C5252 makes it a big potential candidate to address the pressing need for effective treatment strategies for GBM.

grace.zhou@immviragroup.com

www.immviragroup.com