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New generation of oncolytic herpesviruses embodying immunotherapeutic genes encoding IL-12 and anti-PD-1 antibody

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ABSTRACT

We report here the properties of 3 families of oHSV expressing no immunomodulatory genes (T1 series), murine or human IL-12 (T2 series) and murine or human IL-12 and anti-PD-1 antibody (T3 series).

1) Insertion of the genes encoding PD-1 Ab and IL-12 significantly augmented the oncolytic activity of oHSV bereft of immune-stimulatory genes (T1 series).
2) In syngeneic mice the murine T3 oHSV induced significant intratumoral accumulation of IL-12, PD-1 Ab and IFN-γ and was effective against a variety of murine tumors. Thus T3 oHSV concentrates the immunomodulatory products in the environment of the tumors thereby reducing the risk of toxicity associated with systemic administration.
3) T3 oHSV injected into tumors was more effective than systemic administration of anti PD-1 Ab and IL12 alone or in combination with intratumoral injection of T1 oHSV. T3 induces local and systemic immune response characterized by cytokine signature.

The significant finding reported in this article is that the anti-tumor responses remain concentrated in the tumor environment.

OBJECTIVES

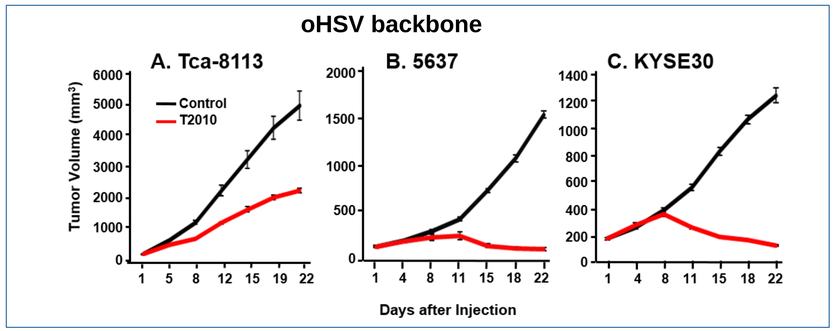
To test anti-tumor activities of new generation of oHSVs which reflect the marriage in a single therapeutic agent of three distinct cancer therapies by recombinant viruses: the targeting of cancer cells by the stimulation of immune system by IL-12 and the production of immunotherapeutic antibodies against PD-1.

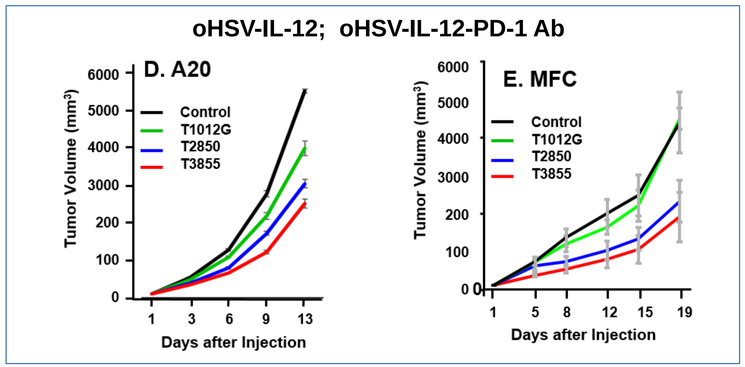
List of oHSVs in this study

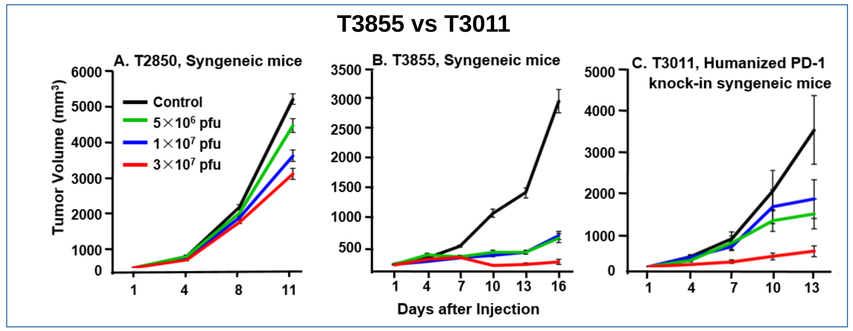
oHSV	Insertion
T1012G	GFP
T2850	Murine IL-12
T2010	Human IL-12
T3855	Murine IL-12 Murine PD-1 Ab
T3011	Human IL-12 Human PD-1 Ab

RESULTS

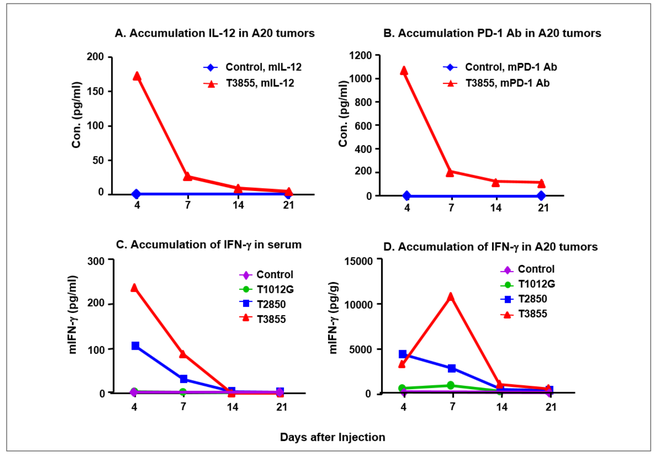
The oncolytic activity of oHSVs







Mechanisms of anti-tumor effects of oHSVs



Anti-tumor efficacy of oHSV, PD-1 Ab and IL-12

	Group (N=6)		D0	D3	D7	D10	D14
Average tumor volume (mm³)	1	Control	101±6.0	336±68	725±137	1025±212	2248±557
	2	Anti-PD-1 (1mg/kg)	109±8.1	307±53	585±87	1027±126	1836±200
	3	IL-12 (0.1μg/animal)	103±6.3	321±90	794±273	1228±398	2269±715
	4	Anti-PD-1+IL-12	105±7.4	131±42	241±106	400±179	1092±532
	5	T1012G	110±5.7	231±79	466±212	556±240	1393±736
	6	T3855	110±6.8	165±32	187±85	207±138	443±351
	7	T1012G+Anti-PD-1+IL-12	109±6.4	242±44	295±107	386±184	1050±624

Conclusion

T3011 is combination of three distinct cancer therapies: the targeting of cancer cells by oncolytic viruses, IL-12 and PD-1. antibody. The significant finding reported in this article is that the anti-tumor responses remain concentrated in the tumor environment.