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

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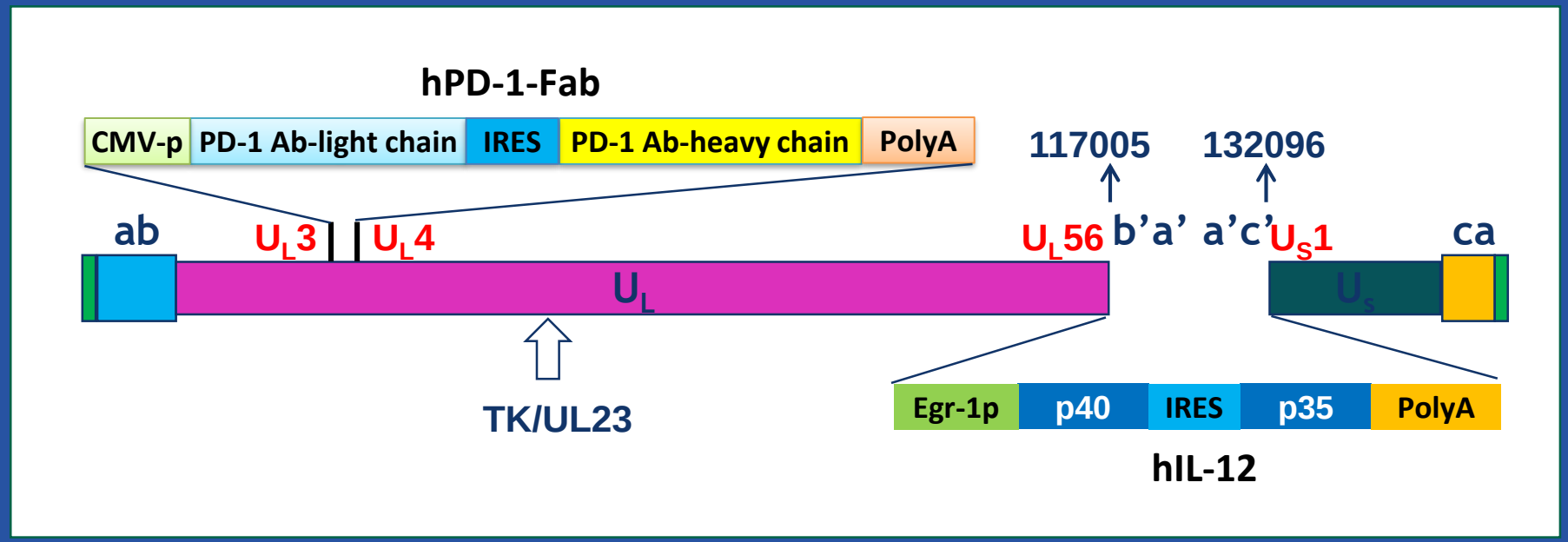
Outline of the presentation

1. Structure and characterization of the oncolytic virus (oHSV-T3011)
2. The oncolytic activity of T3011
3. The mechanisms of anti-tumor effects of T3011
4. Combination of T3011 with exosome carries miRNA against CTLA-4

Structure and characterization of the oncolytic virus (oHSV-T3011)---(1)

T3011



In-house discovery with 100% worldwide IP

Grace Zhou, Xiaoqing Chen, Xianjie Liu. (PCT/CN2016/080025)

Structure and characterization of the oncolytic virus (oHSV-T3011)---(2)

Expression of IL-12 or PD-1 Ab from T3011 infected Vero cell culture medium

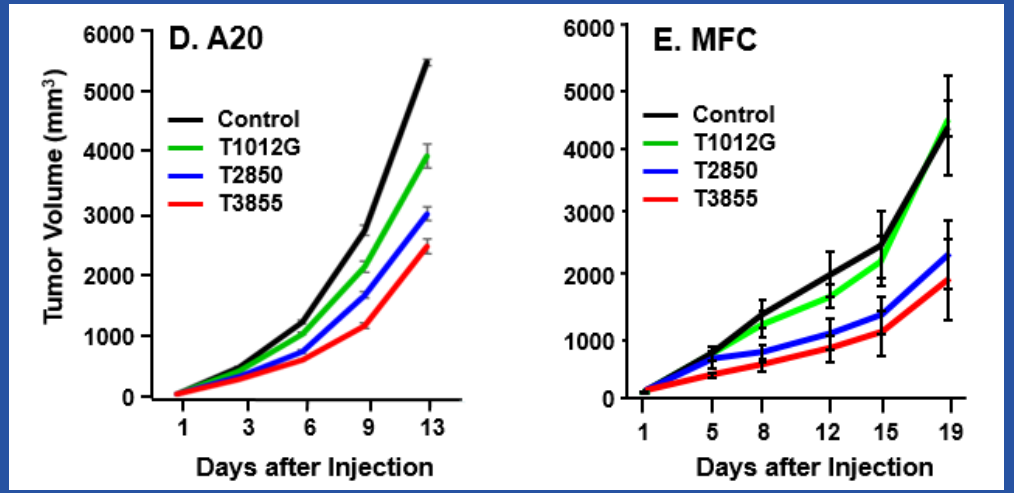
	IL-12 p70 concentration (pg/ml)		Mean ±SD
T3011	289.91	293.76	291.83 ±2.72

	PD-1 Ab concentration (pg/ml)		Mean ±SD
T3011	1146.76	1142.43	1144.60 ±3.06

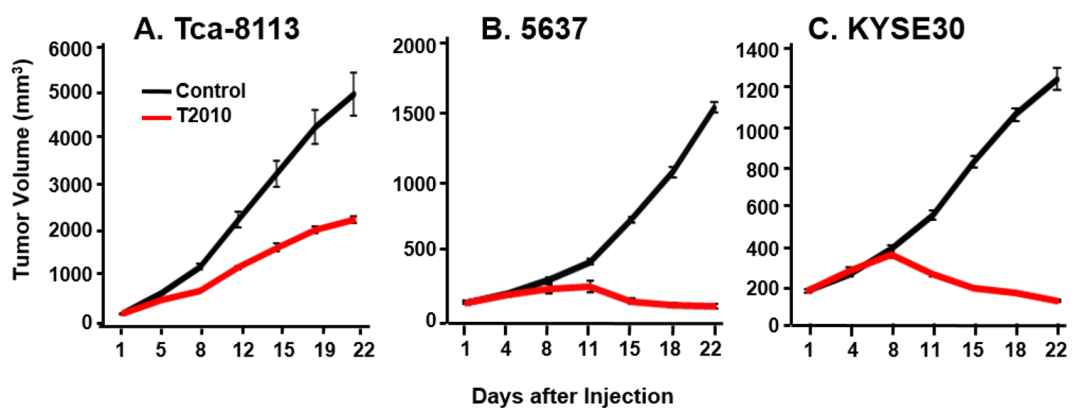
The oncolytic activity of T3011---(1)

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

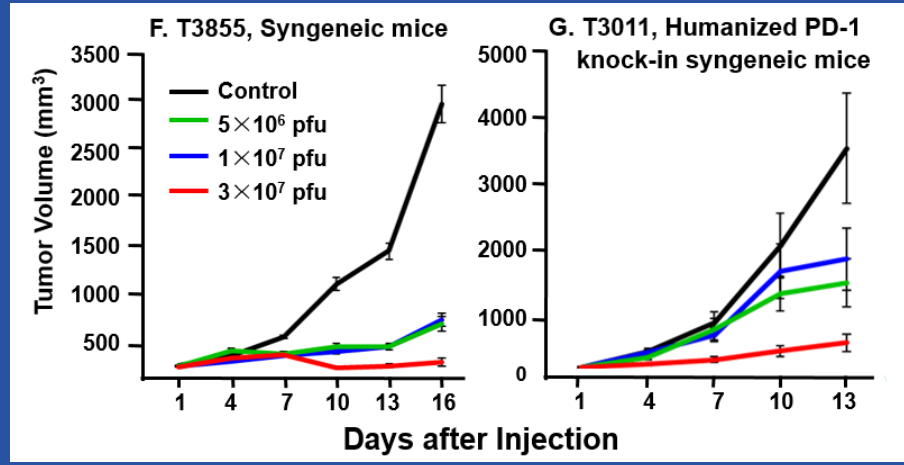
T2850 *vs* T3855



T1012G (oHSV backbone)



T3855 *vs* T3011



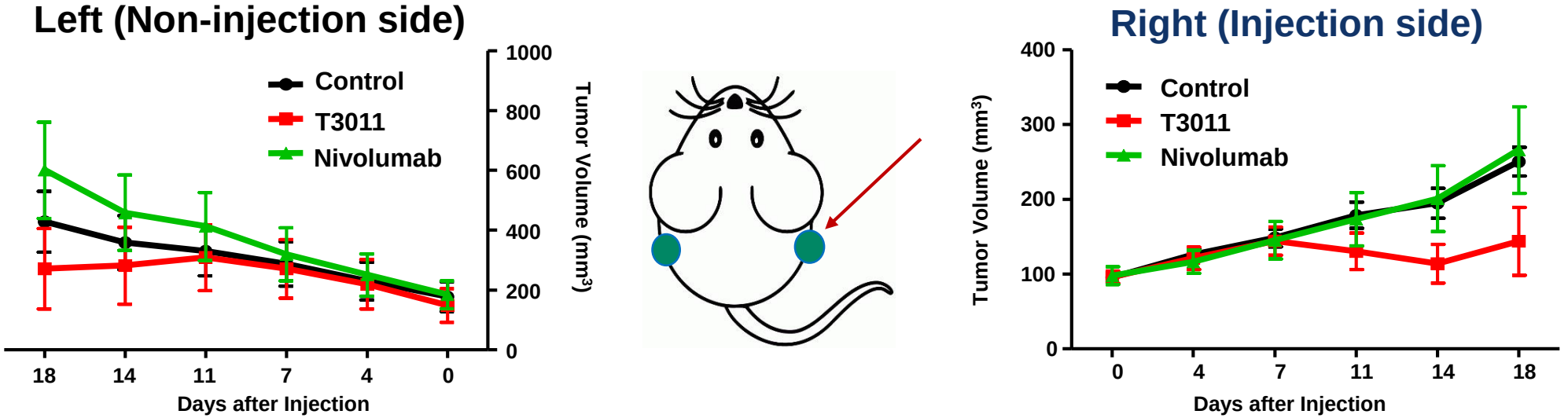
The oncolytic activity of T3011---(2)

Comparison of anti-tumor efficacy of oHSV, PD-1 antibody and IL-12 protein in A20 tumor model

	Group (N=6)		D0	D3	D7	D10	D14
Average tumor volume (mm^3)	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

The oncolytic activity of T3011---(3)

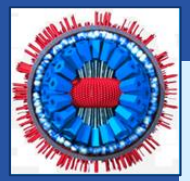
1) T3011 turns “cold” tumor into “hot” tumor
2) Bystander effect of T3011



Humanized PDX model with Gastric Cancer (PD-L1 Negative) N=6

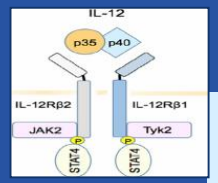
Dosing Scheme：Right flank-T3011 weekly intratumoral injection x 2 (1×10^6 pfu & 5×10^6 pfu); Nivolumab BIW x 3 (3mg/kg) IP injection.

The mechanisms of anti-tumor effects of T3011---(1)



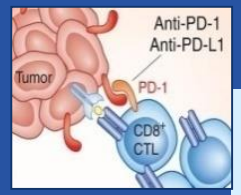
oHSV

- Attach, replicate and lyse tumor cells
- Induce immunogenic cancer cell death to be recognized by immune system
- Provide long-lasting antitumor



IL-12

- Induces secretion of IFN-γ
- Potentiates cytotoxic responses by NK cells and CD8 T cells
- Stimulates antigen presentation and cross-presentation by APCs
- Polarizes T cells into a type 1 helper T (Th1) effector cell phenotype

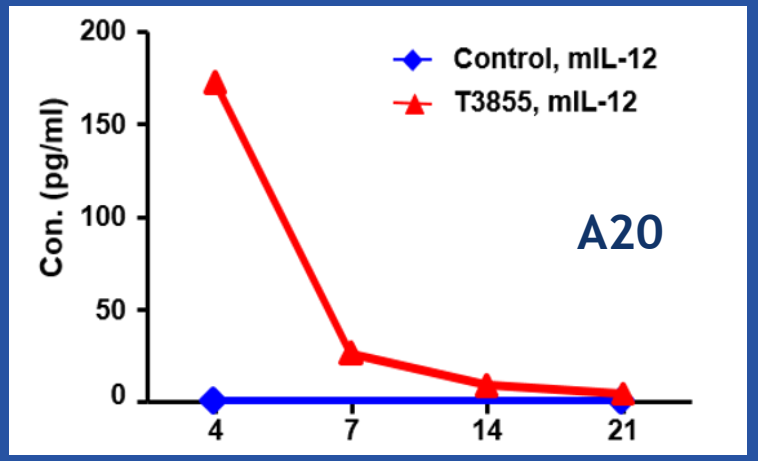


PD-1 Ab

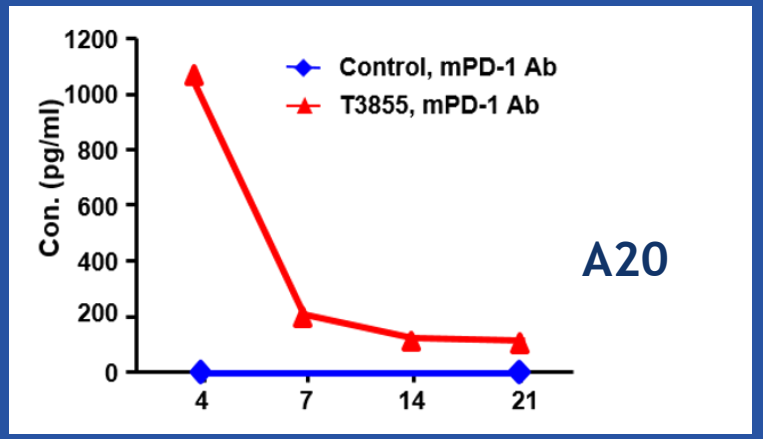
- Check point inhibitor
- Function as a tumor suppressing factor via modulation of immune cell-tumor cell interaction

The mechanisms of anti-tumor effects of T3011---(2)

Accumulation of IL-12 and PD-1 Ab



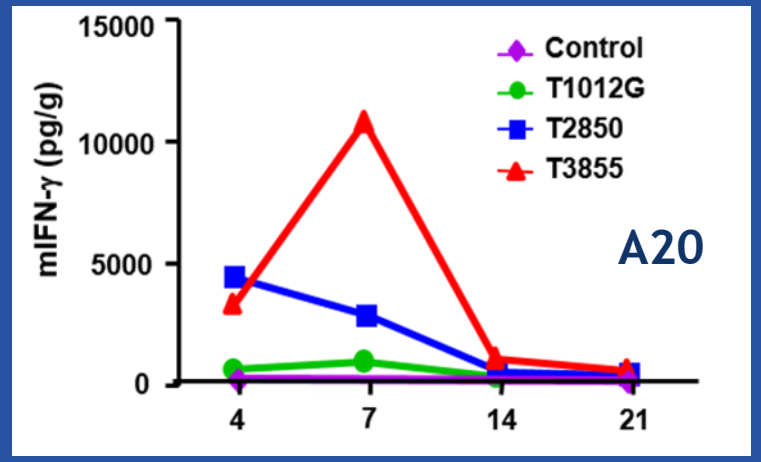
IL-12



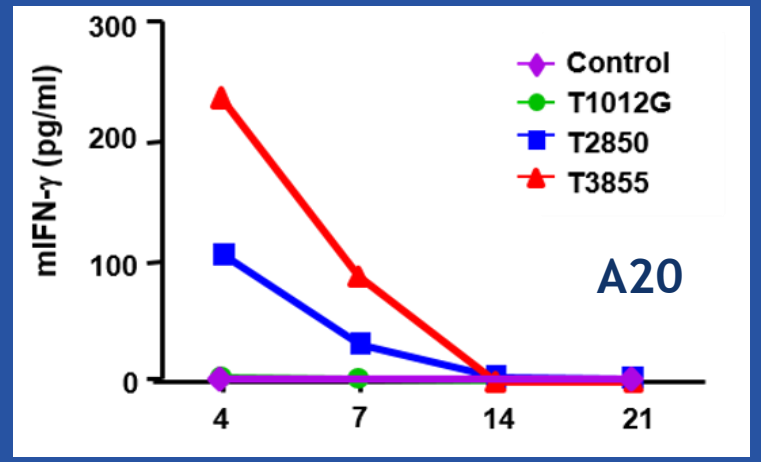
PD-1 Ab

Days of Injection

Induction of IFN-γ



Tumor bed

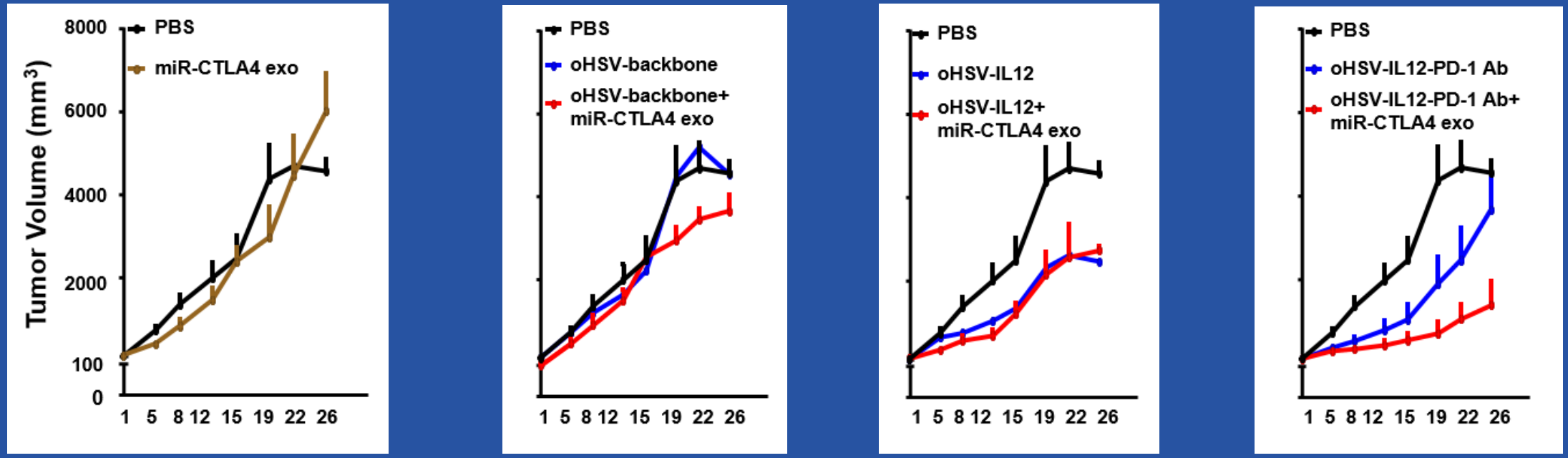


Serum

Days of Injection

Combination of T3011 with exosome carries miRNA against CTLA-4

T3011 + exosome carries miR-CTLA-4



Days after injections of MFC tumor-burden syngeneic mice.

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Xiaoqing Chen, Xusha Zhou, Bernard Roizman, Grace Zhou. (PCT/CN2019/094645)

Take-Away messages

- Insertion of the gene encoding PD-1 Ab (T3011) significantly augmented the oncolytic activity of oHSV backbone or expressing IL-12 alone.
- T3011 induced IL-12, PD-1 Ab were restricted to the tumor bed whereas the induced IFN-γ accumulated to high levels both in tumor bed and blood.
- T3011 was superior to systemic administration of IL-12 and antibody to PD-1.
- The oncolytic activity of T3011 was further enhanced by concurrent intratumoral administration of exosomes carrying miRNA targeting CTLA-4.