Oncolytic Virus Platform

WuXi AppTec, WuXi Biology, Oncology & Immunology Unit

2023.07

OncoWuXi Newsletter

Outline

- **Mechanism of Oncolytic Virus (OV) drug action**
- **Action process of OV drugs and pharmacodynamics concerns**
- **Services of our OV platform**
- **Case studies**
  - Tumor cells selectivity assay on different tumor cells
  - Immune function analysis of OV drugs on monocyte-derived dendritic cells
  - Validation of transgenes biological activity on different T cells
  - Efficacy validation of an OV drug in Hep3B-orthotopic model
  - Efficacy validation of OV drugs in different species derived tumor models and combination therapy
  - Bio-distribution and viral shedding assay
  - Immune profiling assay of OV drug treated MC-38 bearing mouse

Mechanism of OV anti-tumor action

Virus mediated direct killing effect

Oncolysis

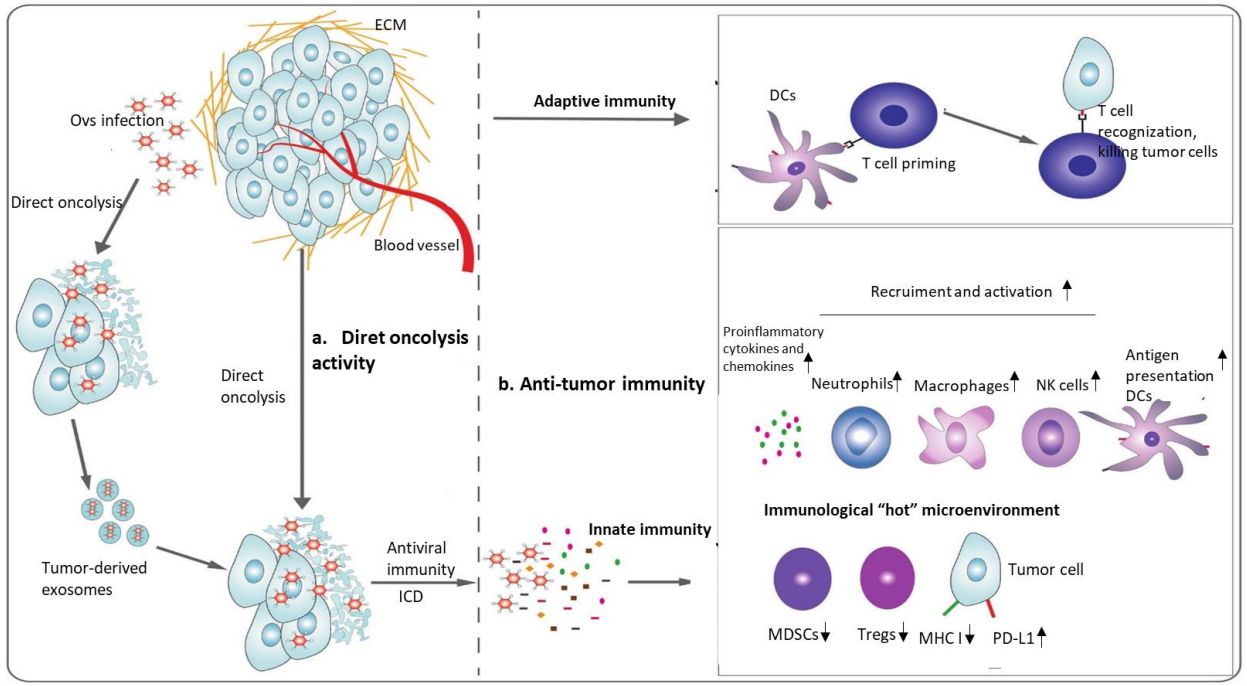
- OVs proliferate rapidly in tumor cells, inhibit tumor cell growth, and eventually lead to cell swelling and death.
- Toxic proteins encoded by OVs (Ad E3 region encoded ADP) can directly mediate tumor cell lysis.

Destroy tumor microvascular system

- OVs selectively infect vascular endothelial cells and induce cell death, eventually lead to the destruction of tumor microvascular system.

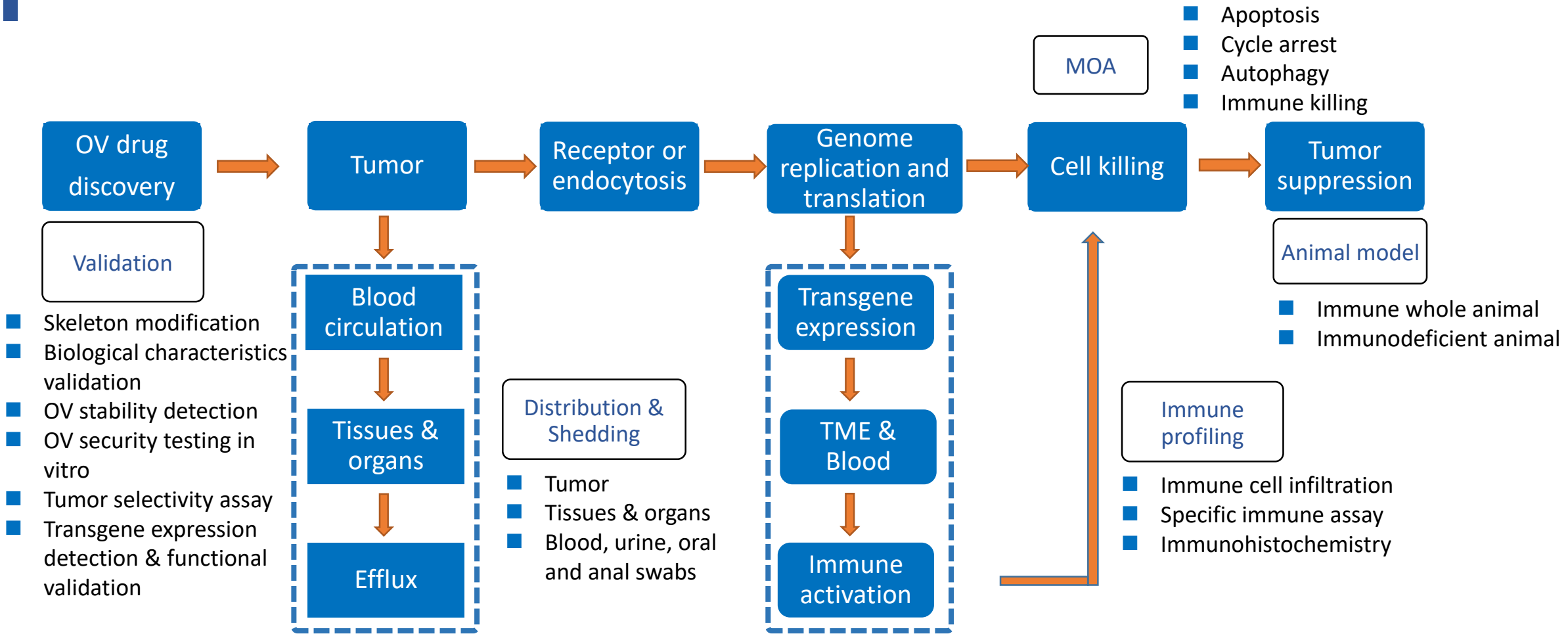
Virus mediated indirect killing effect

- TAA promotes DC maturation, and activates CD4+ and CD8+ T cells, produces distant effects.
- Virus-induced cytokines and DAMPs activate NK cells, macrophages to migrate to tumor sites and exert non-specific killing effects.
- Enhanced host anti-tumor immunity of transgenes.
- Improve the tumor microenvironment, turning “cold” into “hot” tumors.



Revised from Yaomei Tian et. al., *Signal Transduct Target Ther.* 2022 Apr 6;7(1):117.

Action process of OV drugs and pharmacodynamics concerns



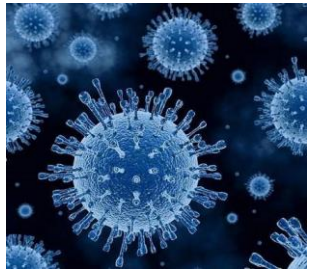
- Selectivity for susceptible and non-susceptible cells
- Selective expression of transgenes

- Parent virus susceptible animal model
- Pharmacological responses of animals to transgenes
- Anticipated clinical dosing schedule
- PK of virus and transgenes in tumor or blood

Service of our OV platform

Virus

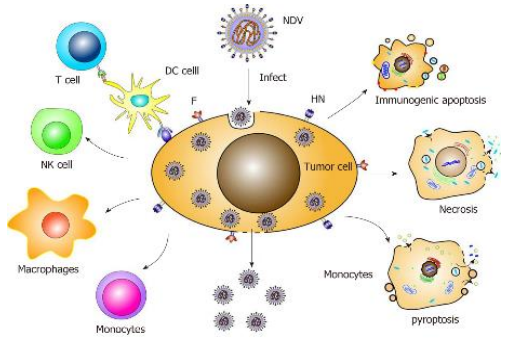
- Adenovirus
- Herpes simplex virus (HSV)
- Vaccinia virus (VACV), Vesicular Stomatitis Virus (VSV)



https://www.sohu.com/a/472815015_100300137

In Vitro

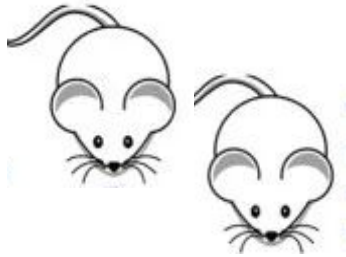
- Stability assay of virus backbone and transgenes
- In vitro safety assay
- Tumor selectivity / lysis assay / MOA
- Immunomodulatory assay on T, NK and MoDC cells



World J Clin Cases. Aug 26, 2019; 7(16): 2143-2154

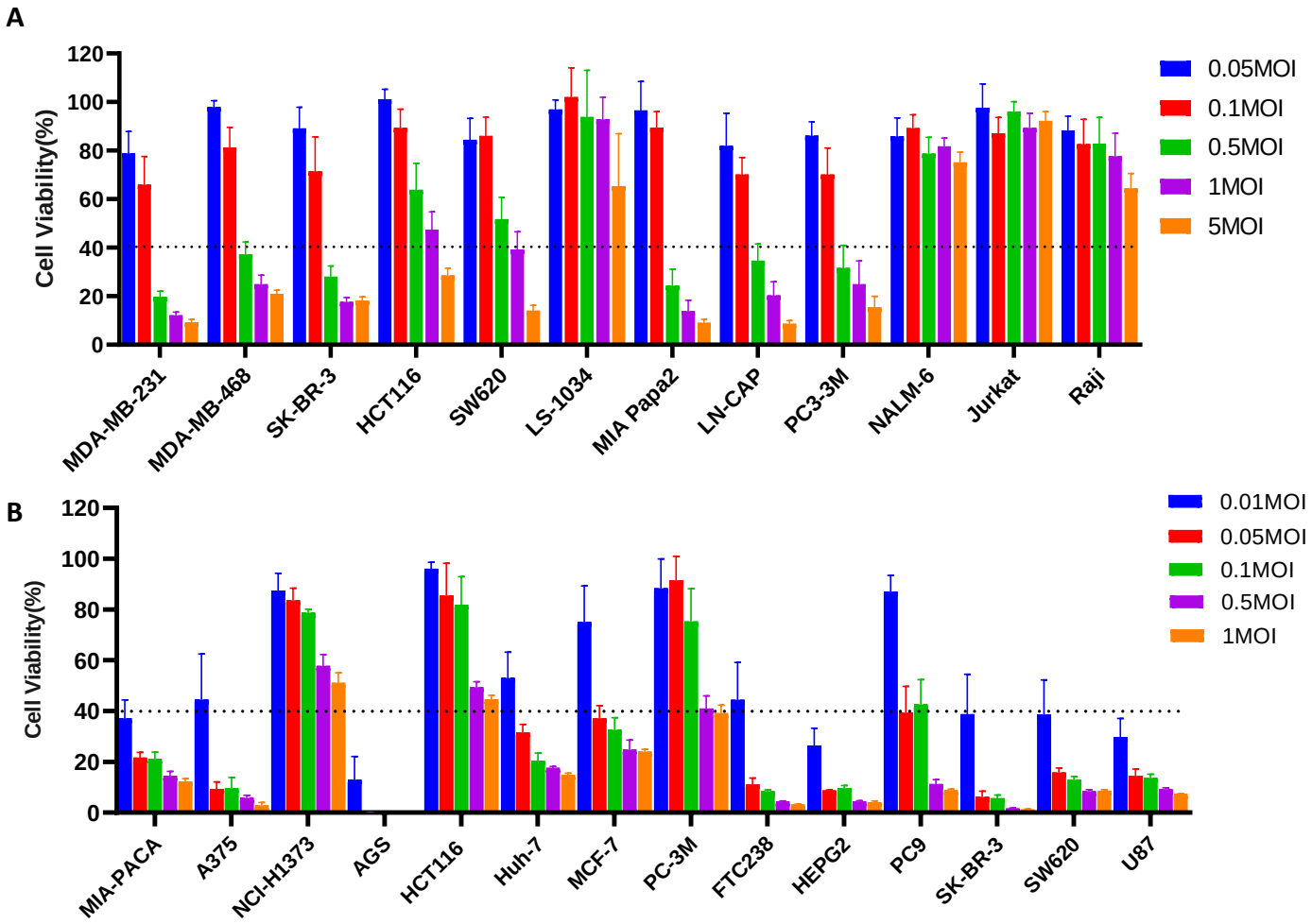
In Vivo

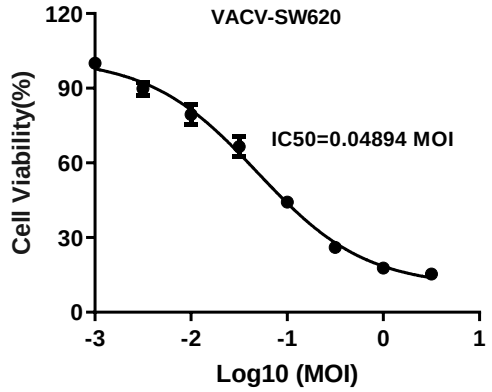
- Efficacy study / POC
- Combination therapy
- Bio-distribution / Shedding / PK
- Nab assay / immune profiling assay
- Non GLP toxicology and safety studies



Case study: Efficacy validation of OV drugs *in vitro*

Tumor cells selectivity assay

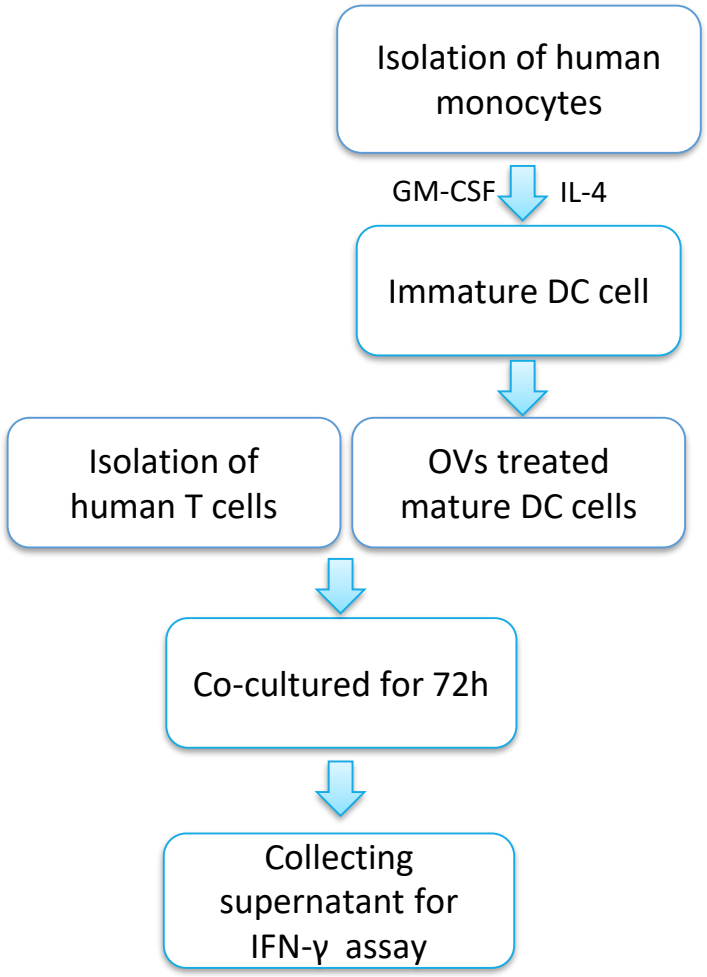


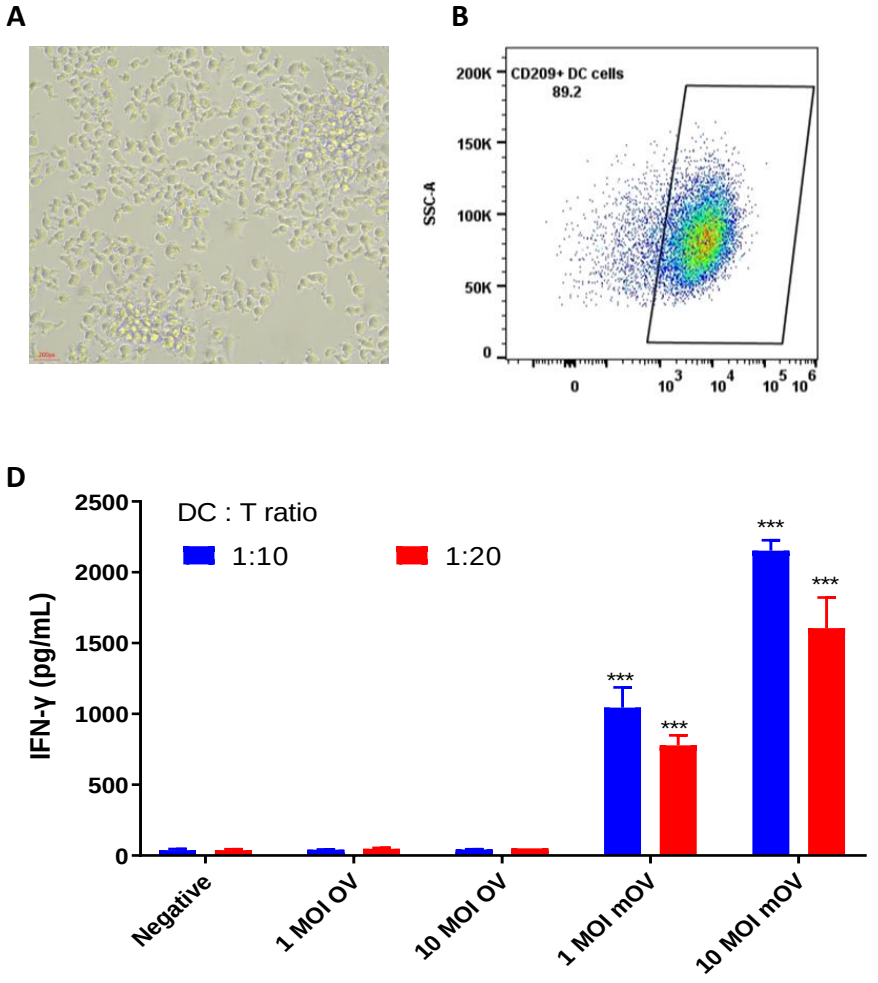


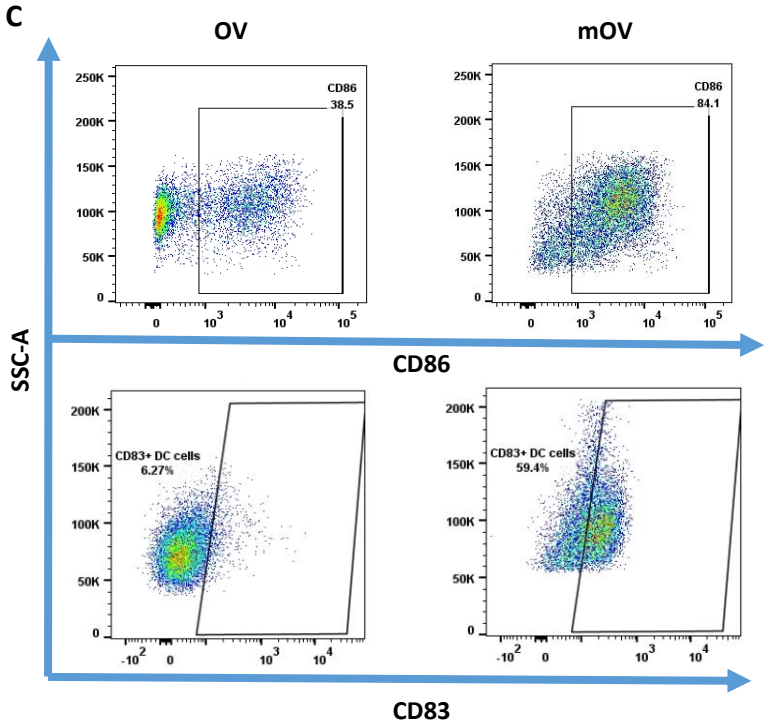
- Oncology cell panel screening of VACV (A) and VSV (B) against different cancer cell lines at various MOI, to screening viral sensitive cell lines.

Case study: Efficacy validation of OV drugs *in vitro*

Immune function analysis of OV on monocyte-derived dendritic cells







Case study: Efficacy validation of OV drugs *in vitro*

Validation of transgenes biological activity on different T cells

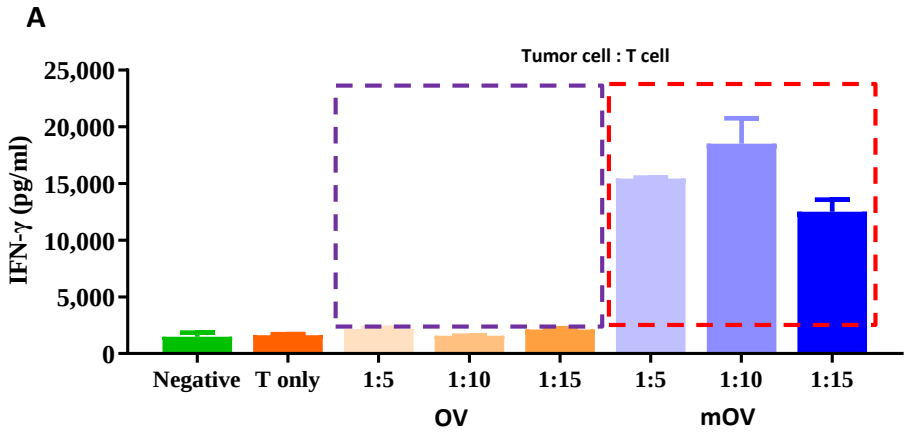
Isolation of human T or mouse spleen lymphocytes

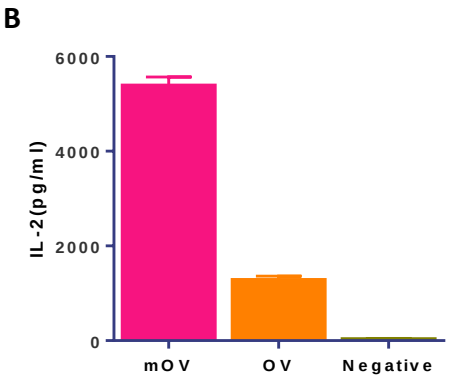
Immune activation for 48h

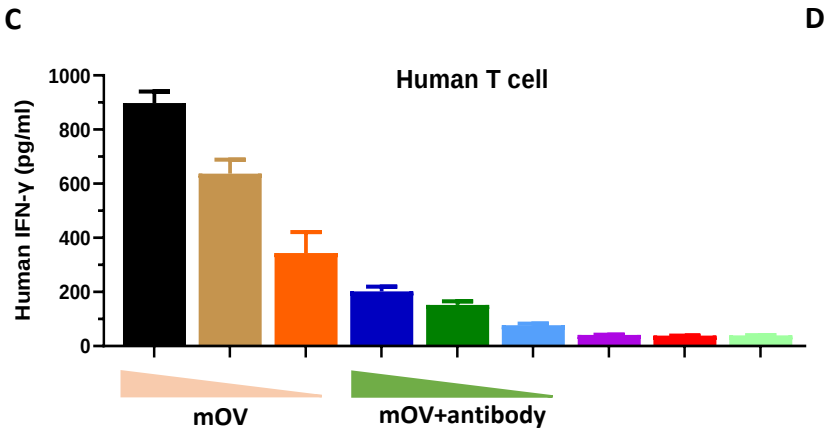
OV infected OV or supernatant

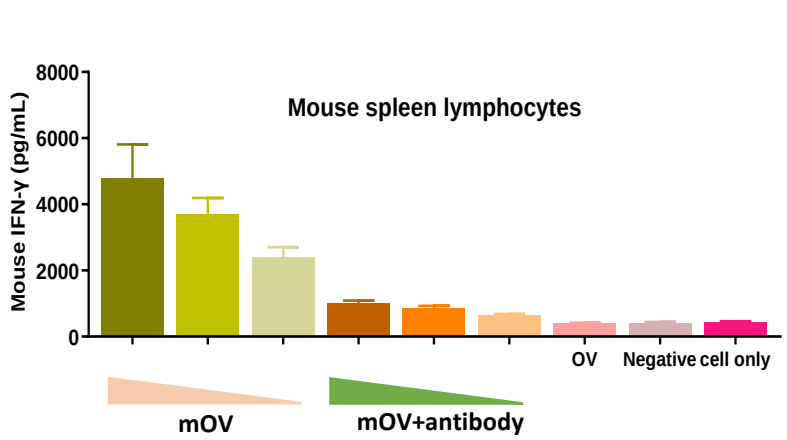
Co-cultured for 72h

Collecting supernatant for IFN-γ /IL2 assay

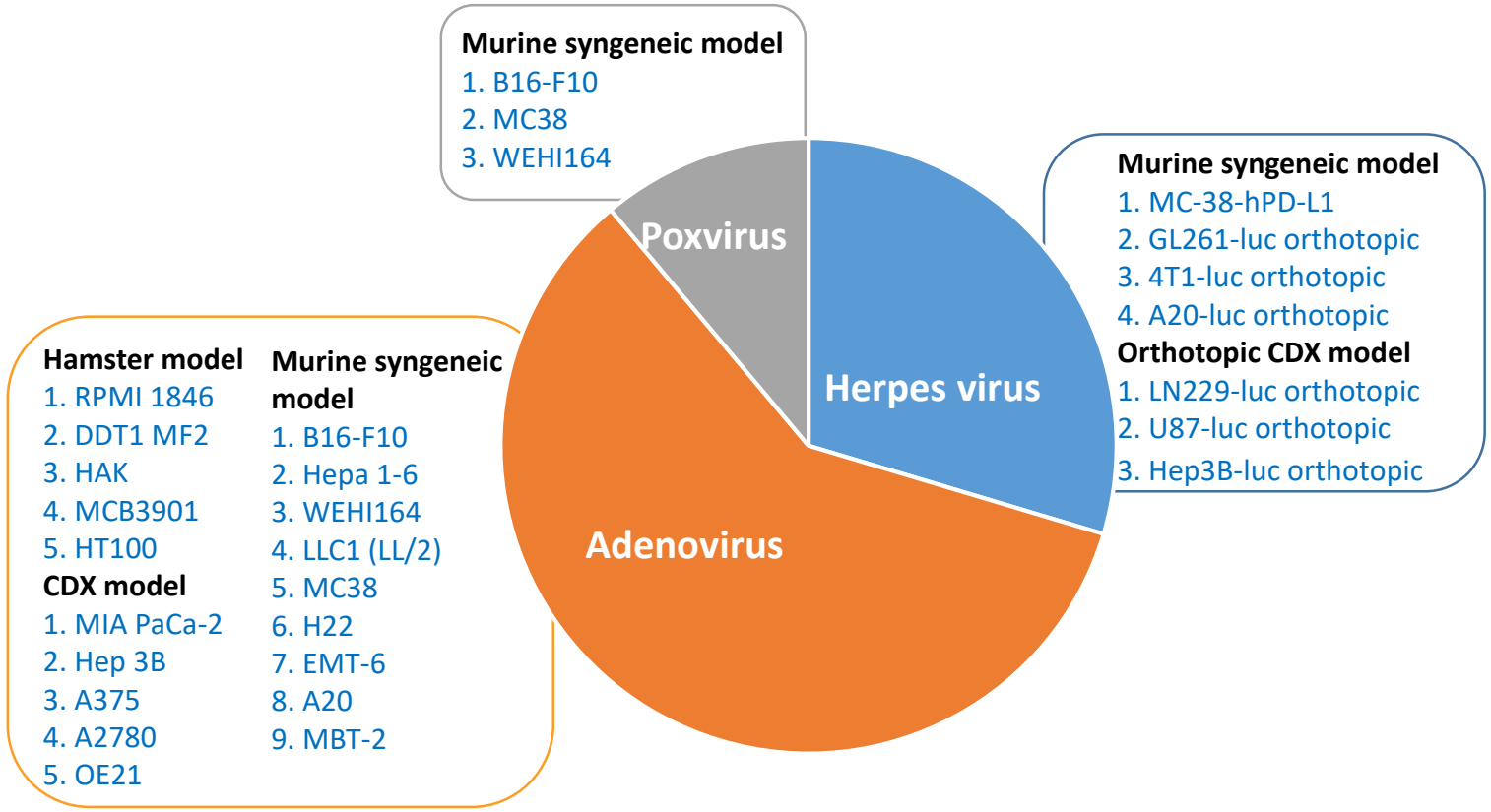


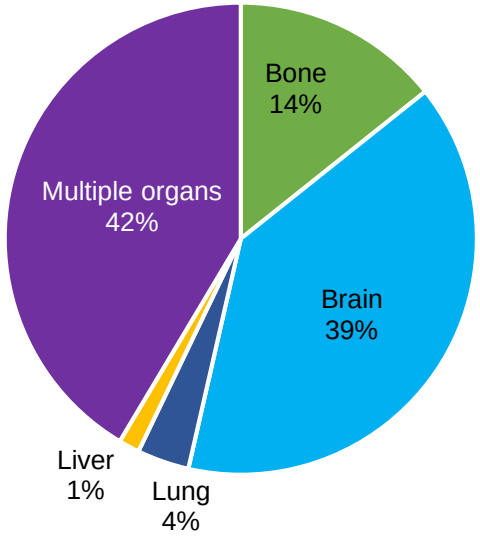






Model summary for *in vivo* evaluation of OV drugs





- **Bilateral and re-challenge tumor model**

1. Adenovirus: A20, EMT-6, LLC1, B16-F10
2. Poxvirus: B16-F10, MC38

- **Combination therapy**

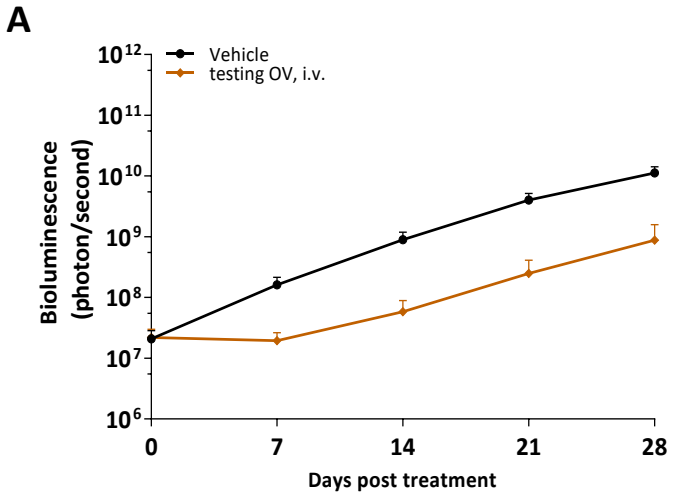
1. Compounds
2. ICIs
3. CAR T

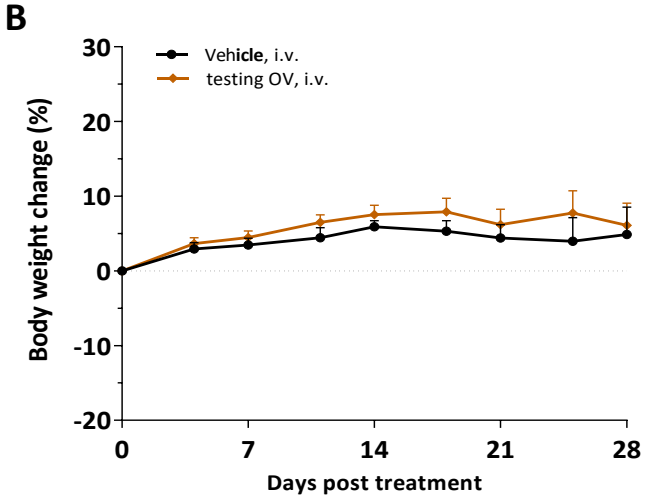
- **Orthotopic and metastasis xenograft model**

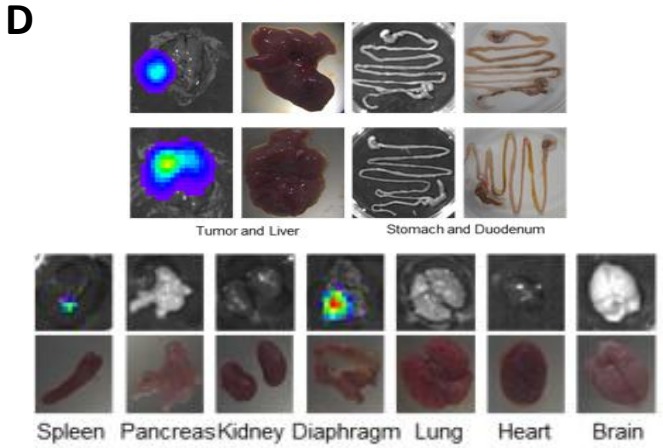
1. Orthotopic model: 40+
2. Metastasis model: 60+
3. Drug resistant model: 30+
4. PDX model： 1400+

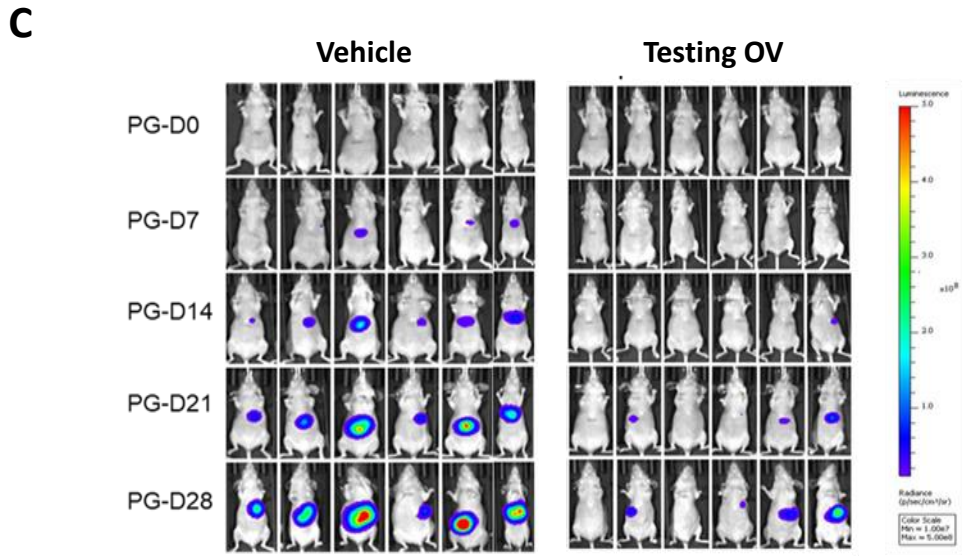
Case study: Efficacy validation of OV drugs *in vivo*

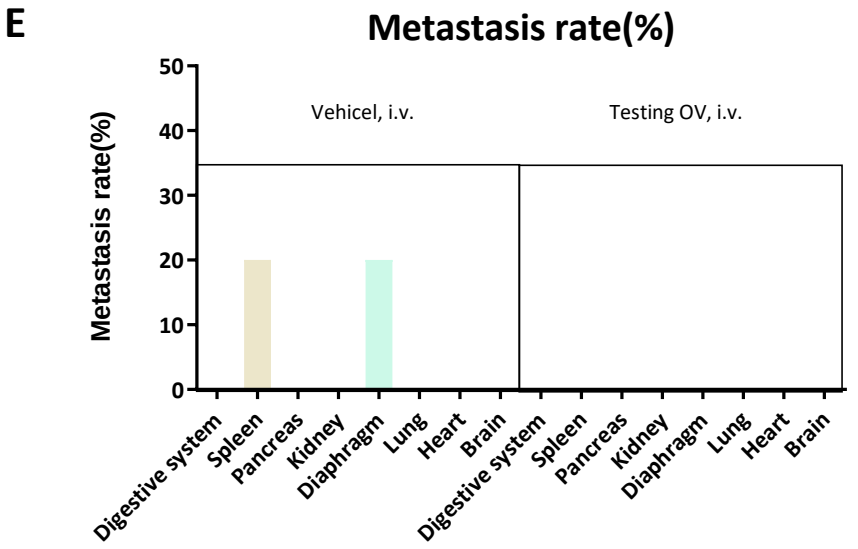
Efficacy validation of an OV drug in Hep3B-orthotopic CDX model







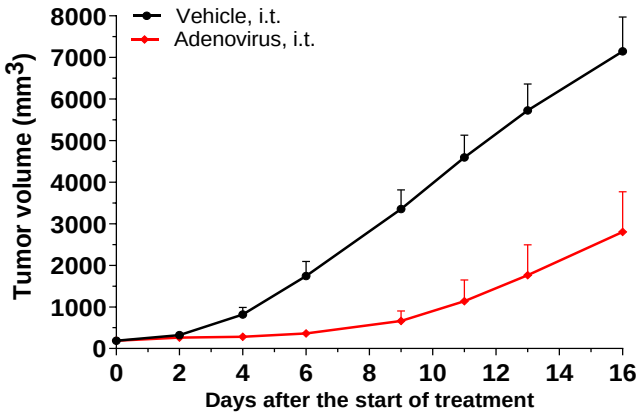




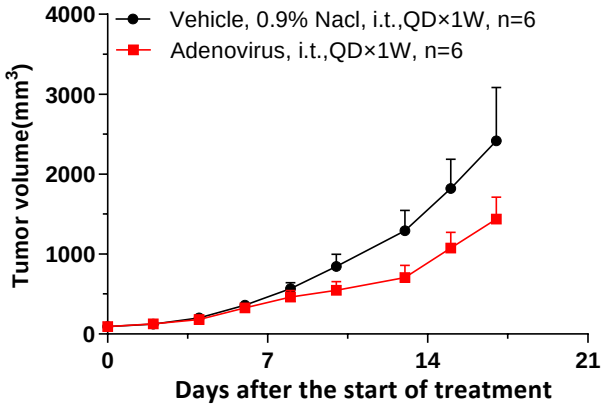
Case study: Efficacy validation of OV drugs *in vivo*

Efficacy validation of OV drugs in different species derived tumor models and combination therapy

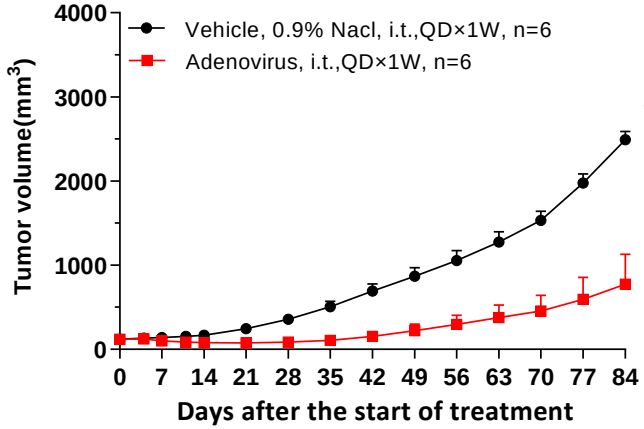
RPMI 1846 (Male)



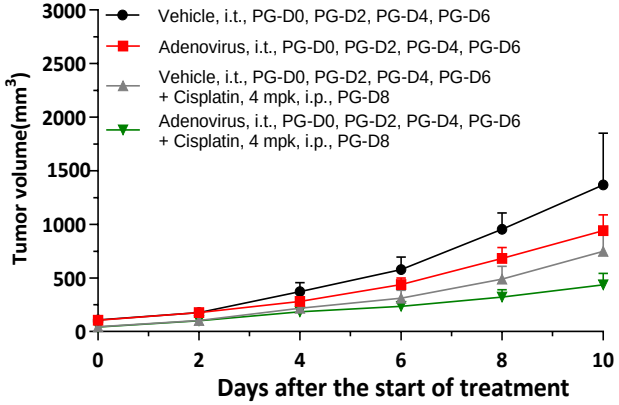
MC38



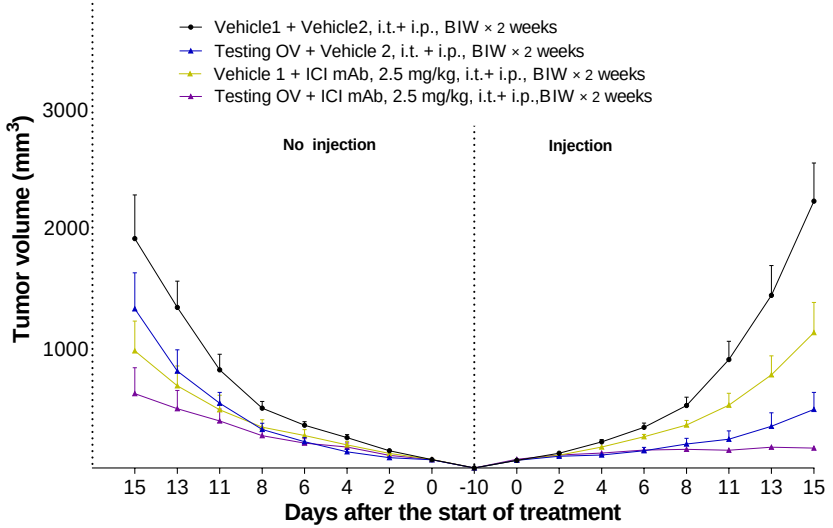
MIA PaCa-2



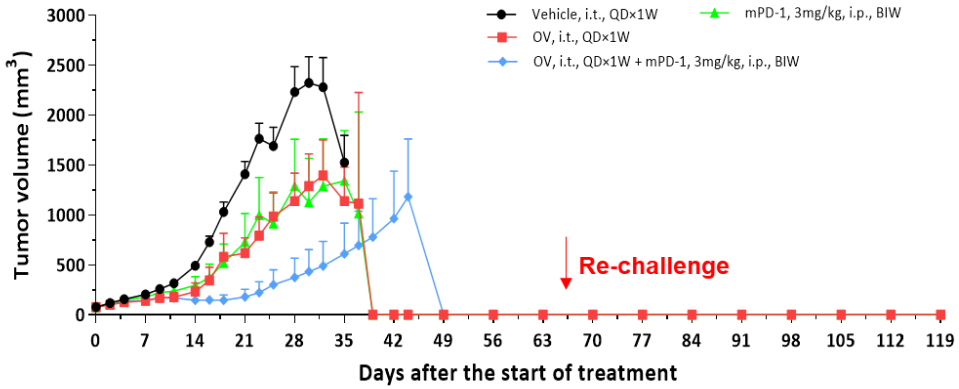
MBT-2



OV efficacy study in bilateral tumor model (B16F10)

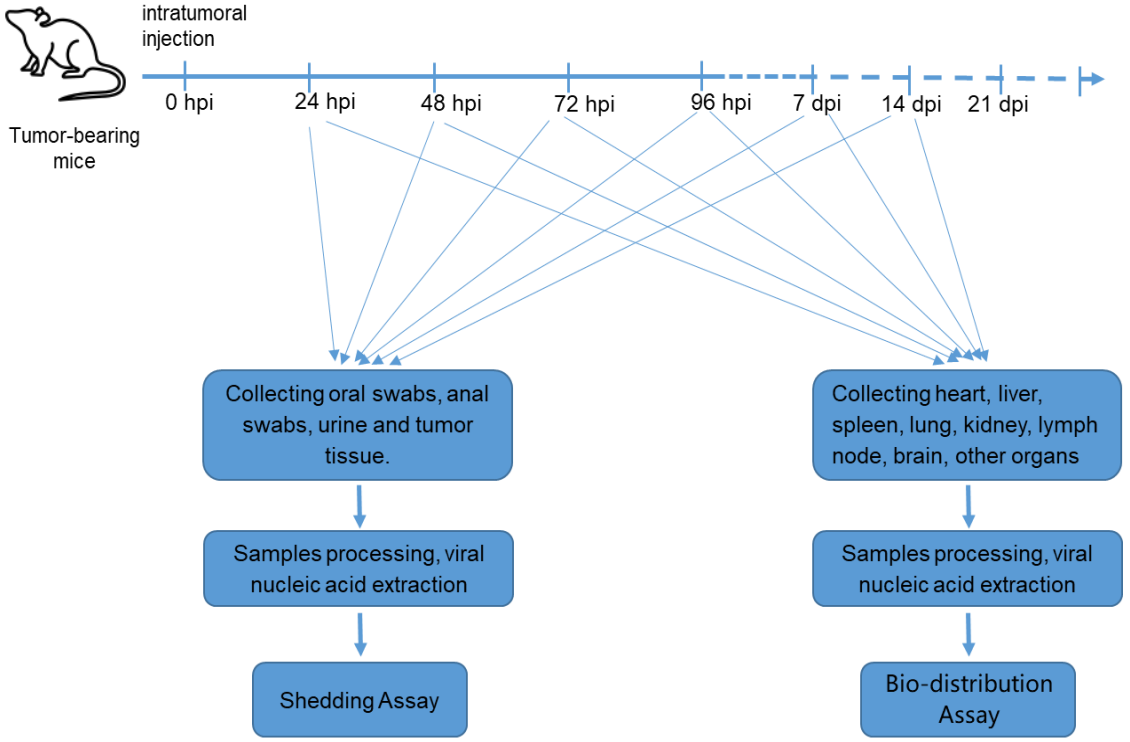


OV and ICI combination therapy efficacy study on EMT-6

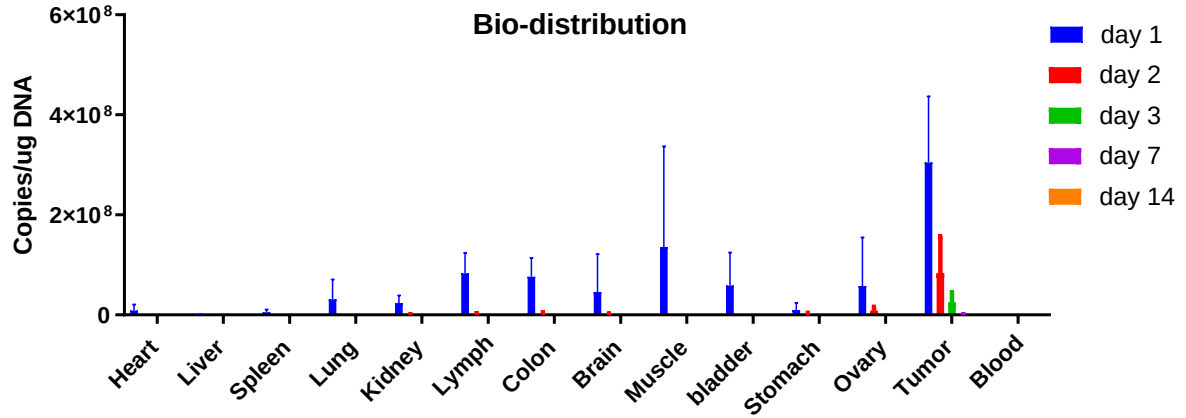


Case study: Efficacy validation of OV drugs *in vivo* & *ex vivo*

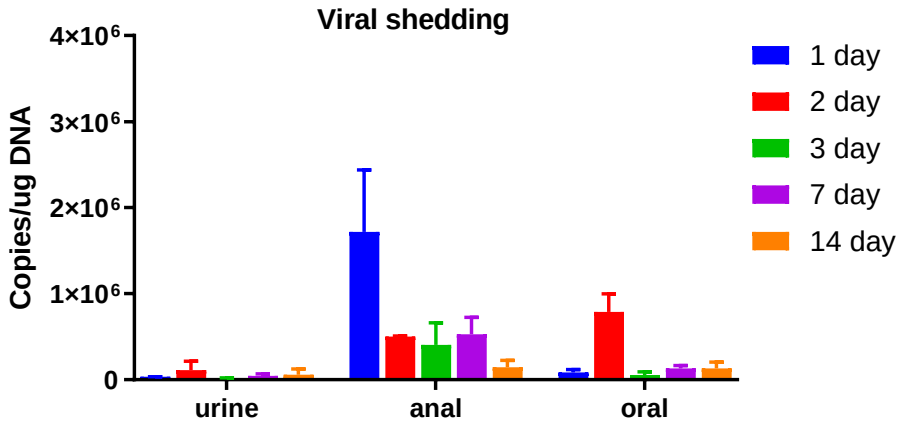
Bio-distribution and viral shedding assay



A

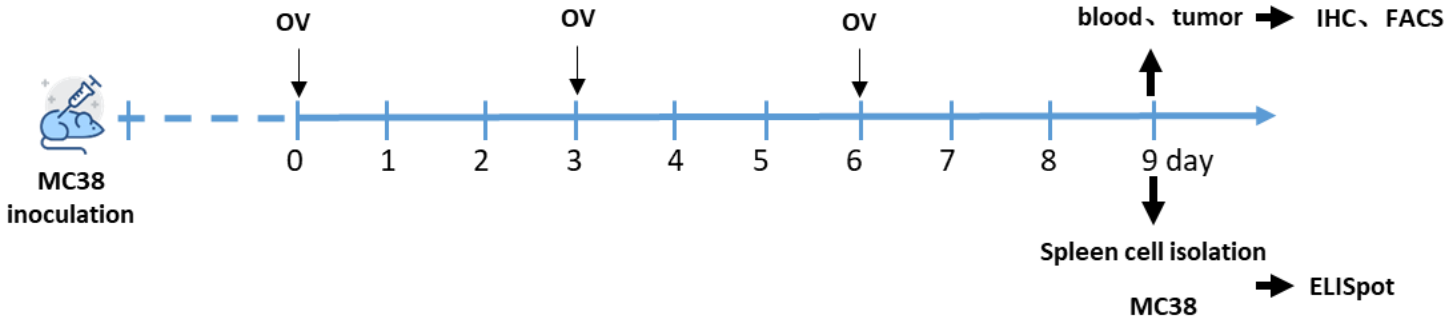


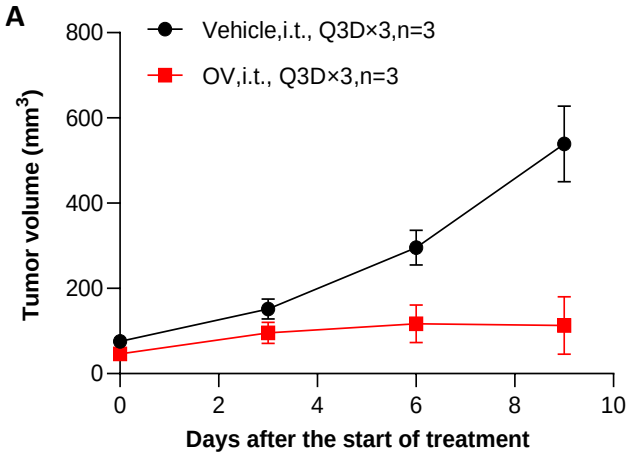
B

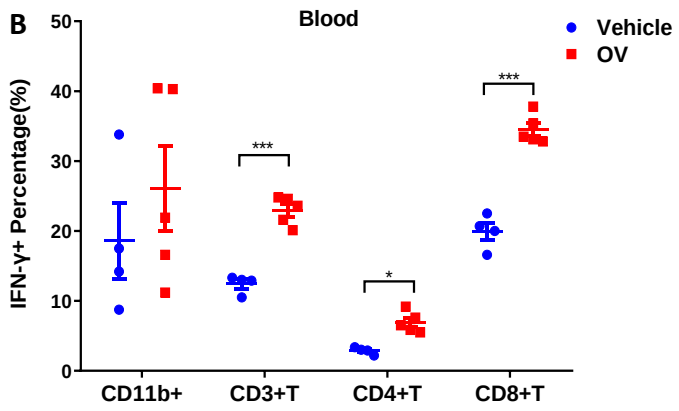


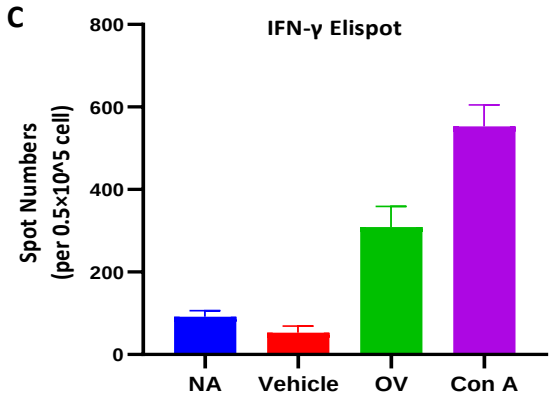
Case study: Efficacy validation of OV drugs *in vivo* & *ex vivo*

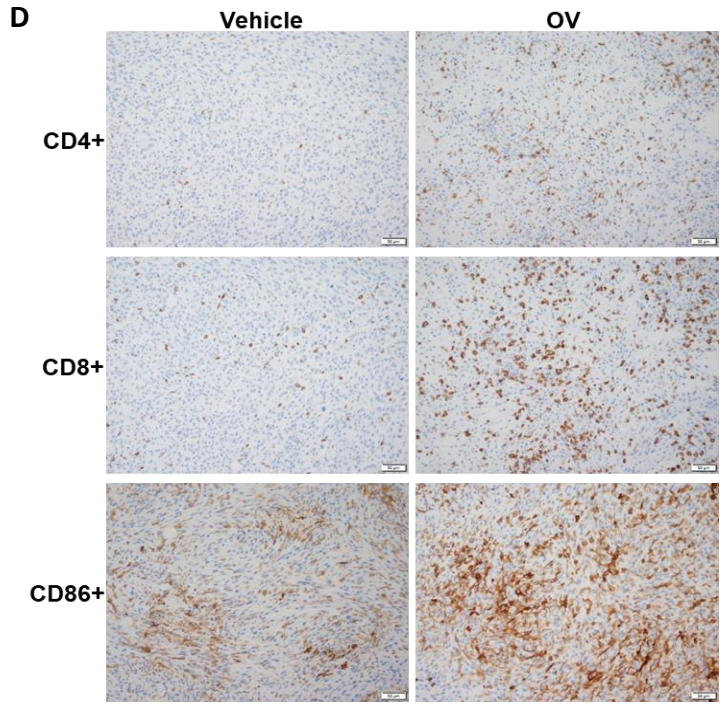
Immune profiling assay of OV drug treated MC-38 bearing mouse











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