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Oncolytic Viral Immunotherapy in the Era of Immune Checkpoint Blockade

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Disclosure of Conflicts of Interest

Liang Deng

The following relationships exist related to this presentation:

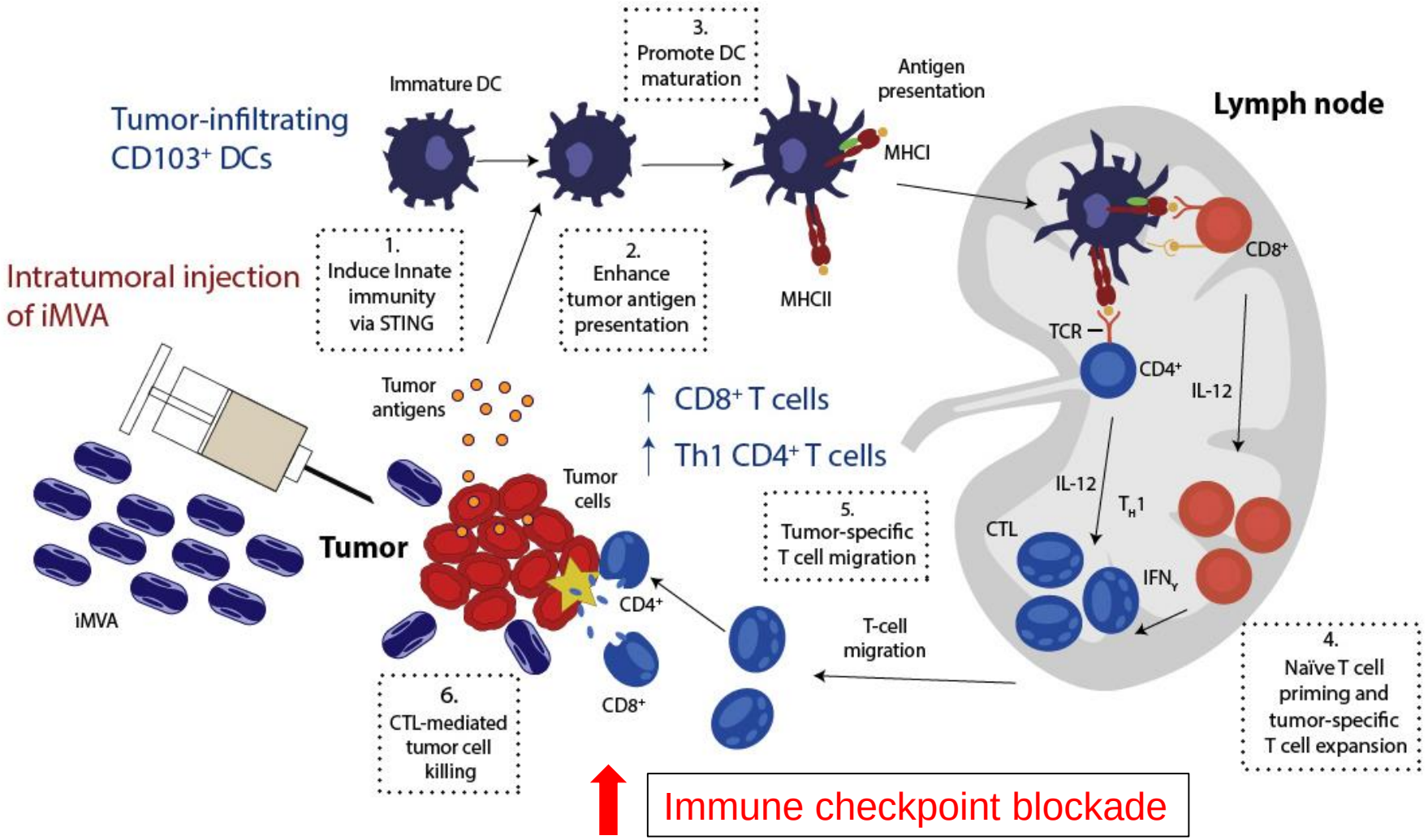
- Inventor of intratumoral delivery of inactivated MVA or recombinant MVA as cancer immunotherapeutics
- Co-founder and stock owner of IMVAQ Therapeutics
- Sponsored Research Agreement from IMVAQ Therapeutics

Rational for combination of viral-based immunotherapy with immune checkpoint blockade

- Immune checkpoint blockade has revolutionized how cancers are treated. However,
  - More than half of the patients do not respond to immune checkpoint inhibition;
  - Resistance and relapse have been observed.
  - Immune–related toxicities
  - Many cancers without pre-existing immune cell infiltrates do not respond to immune checkpoint blockade
  - Virotherapy is an effective way to overcome resistance to immune checkpoint blockade

Zamarin et al., Science Translational Medicine, 2014
Puzanov et al. JCO 2016

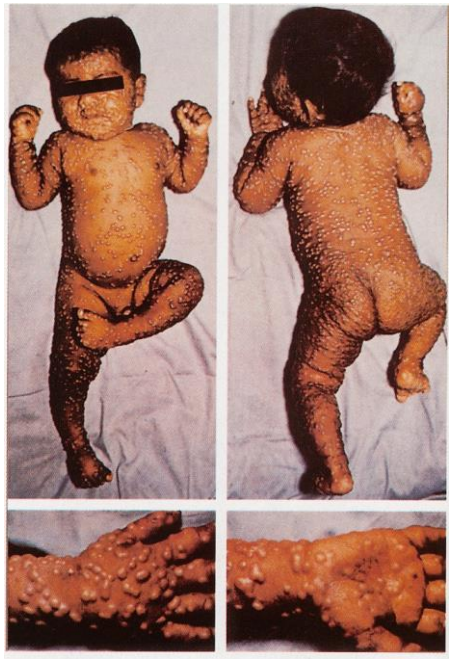
Intratumoral injection of inactivated MVA as "in situ therapeutic vaccine" for cancer



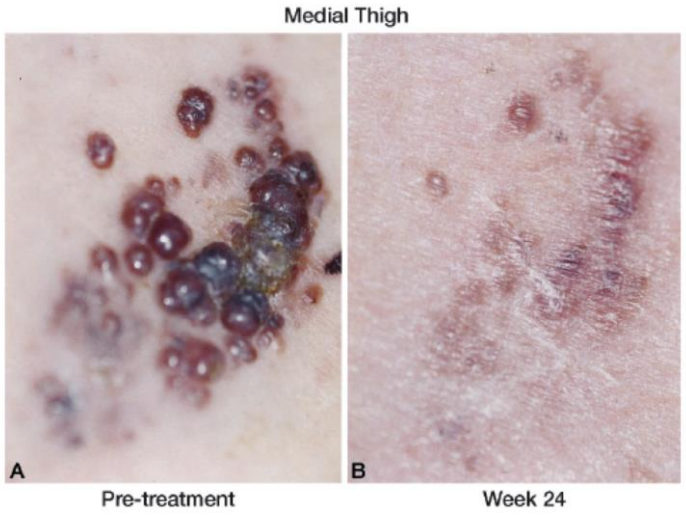
Dai et al., Science Immunology, 2017

From smallpox eradication to the development of viral-based cancer immunotherapeutics

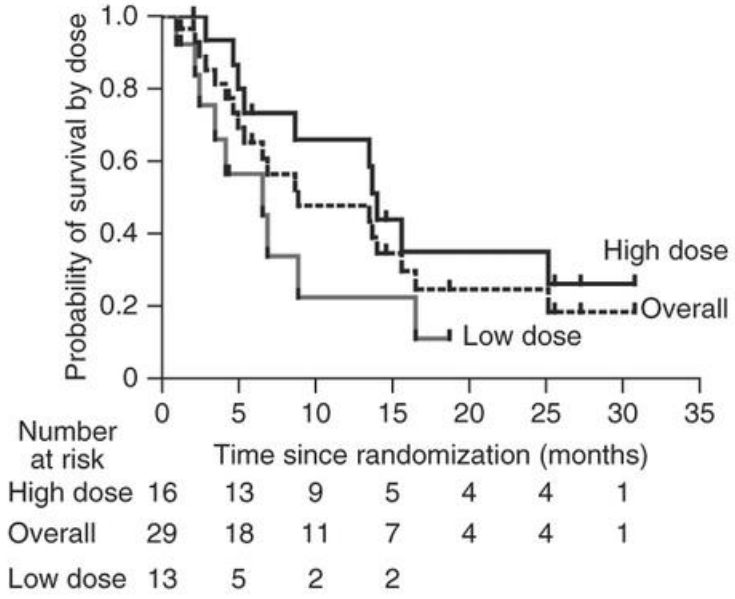
- Poxviruses are large cytoplasmic DNA viruses.
- Vaccinia virus is a prototypic poxvirus that was used successfully for smallpox eradication.
- Modified vaccinia virus Ankara (MVA), an attenuated vaccinia strain, is the new generation of smallpox vaccine and a promising vaccine vector for other infectious diseases and cancers.
- Engineered vaccinia viruses are at the forefront of oncolytic therapy



Smallpox



oncolytic therapy for cutaneous metastatic melanoma with JX-594



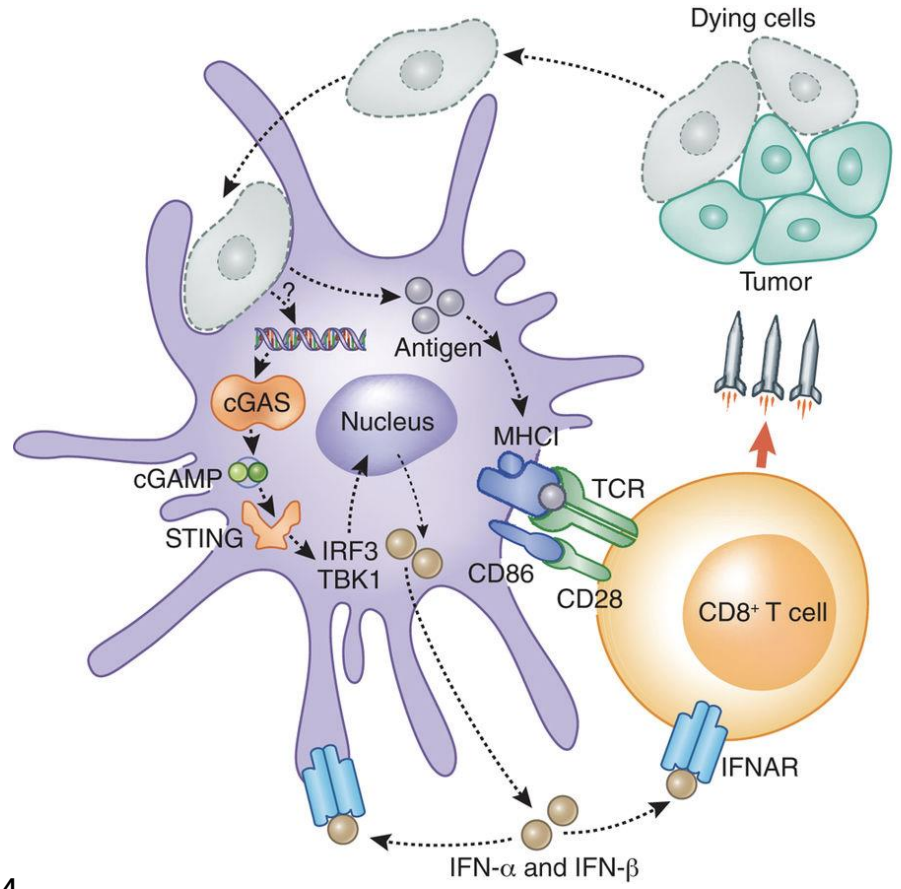
Study Design:
Randomized phase II
dose-finding trial
High dose: 10^9 pfu
Low dose: 10^8 pfu

Overall survival:
14.1 vs. 6.7 mo
P = 0.02; n=29

Mastrangelo et al. 1996
Kirn and Thorne, Nat Rev Cancer 2009
Heo et al., Nat Med, 2013

Rationale: harnessing innate immunity for cancer immunotherapy

- Type I IFN plays important roles in host antitumor immunity
- IFNAR1-deficent mice are more susceptible than wild type mice to develop tumors after implantation.
- IFN signaling on Batf3-dependent DCs is important for antitumor T cell spontaneous priming and tumor rejection.
- The cGAS/STING cytosolic DNA-sensing pathway is important in the innate immune sensing of tumor-derived DNA by dendritic cells, which leads to the development of antitumor $CD8^+$ T cell immunity (spontaneous priming model or treatment model)

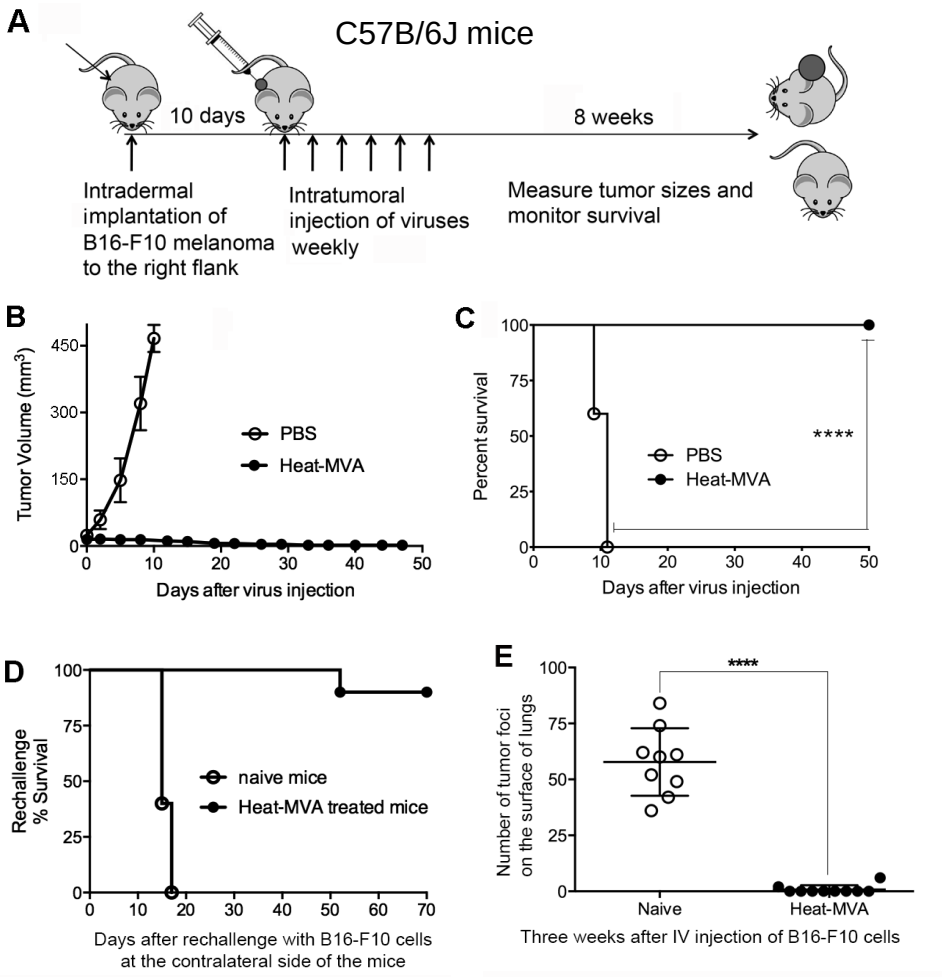


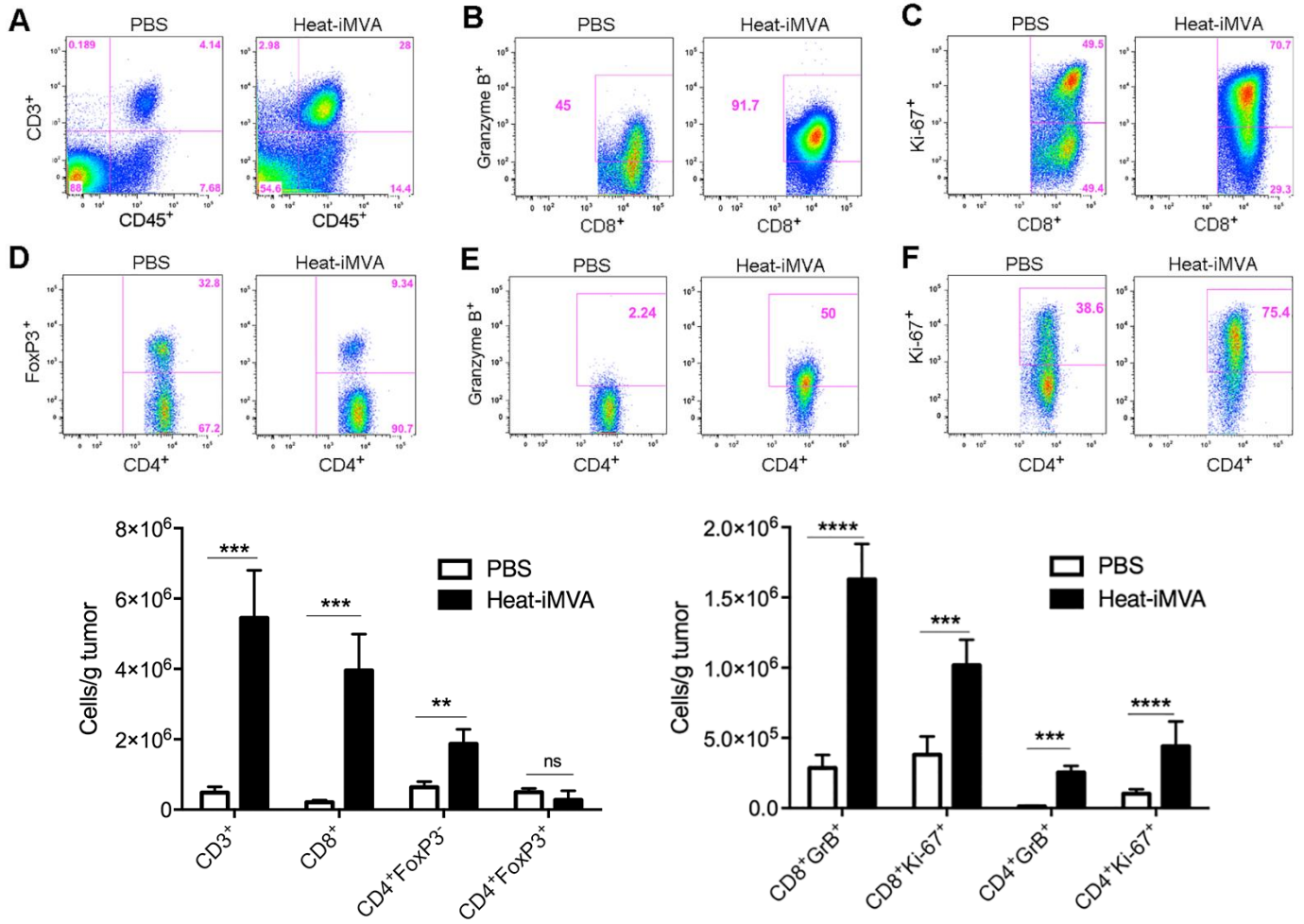
Dunn et al., Nat Immunol. 2005
Diamond *et al.,* JEM, 2011
Fuertes *et al.* JEM, 2011

Woo *et al.* Immunity, 2014
Deng *et al.* Immunity, 2014
Liu *et al.* Nat Med, 2015

Chen *et al.* Nat Immunol, 2016

Intratumoral injection of Heat-iMVA cures melanoma and generates systemic antitumor effects

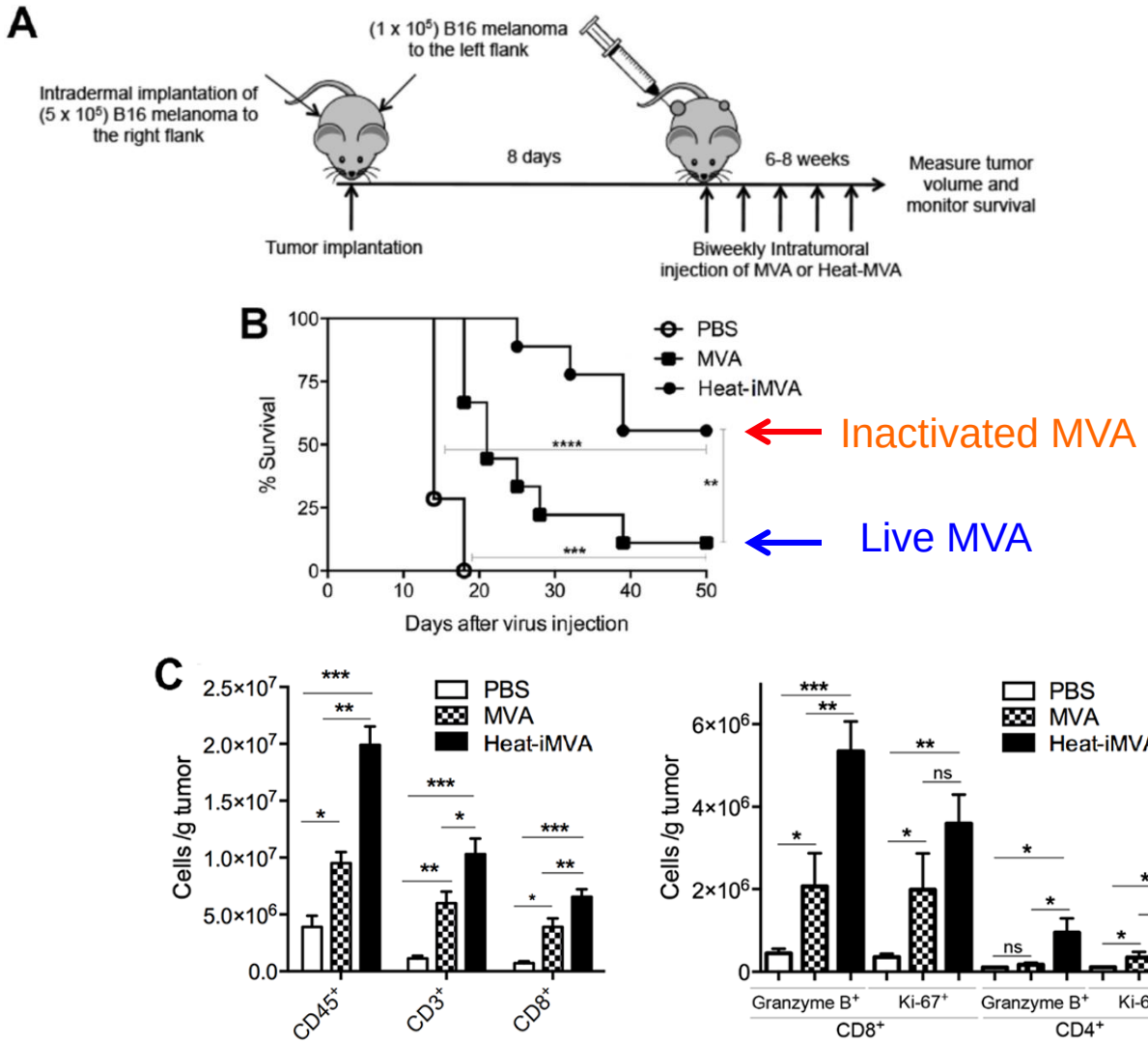




Rechallenge at contralateral side Rechallenge through IV

Dai et al., Science Immunology, 2017

Heat-iMVA induces stronger antitumor effects than live MVA in a bilateral B16-F10 melanoma implantation model

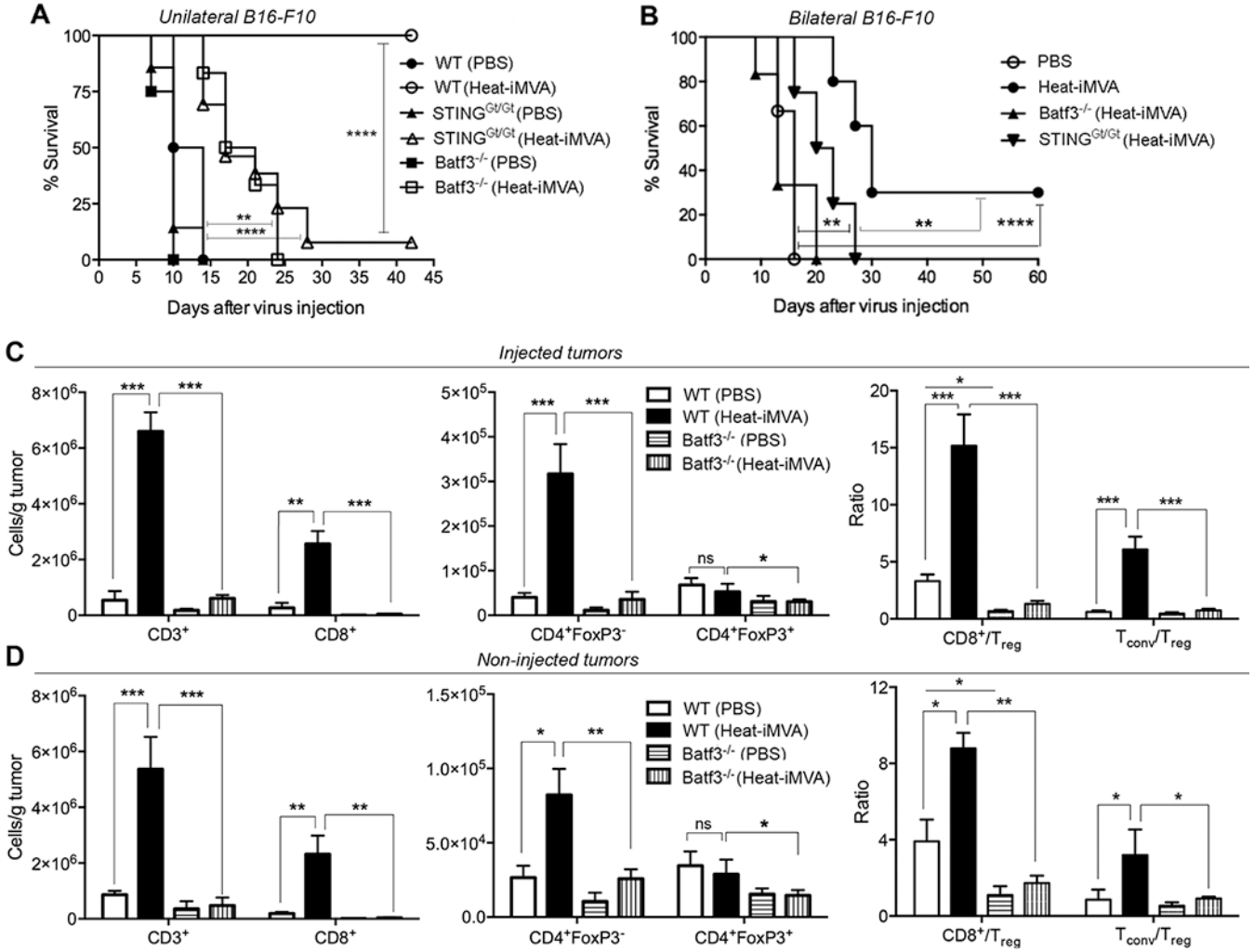


- MVA infection of conventional DCs induces type I IFN via the cytosolic DNA-sensing pathway mediated by cGAS/STING.
- Heat-iMVA induces higher levels of type I IFN, proinflammatory cytokines and chemokines in conventional DCs than MVA.
- Heat-iMVA induces higher levels of type I IFN, proinflammatory cytokines and chemokines in human and murine melanoma cells than MVA.

Dai et al., PLoS Pathogens 2014

Dai et al., Science Immunology, 2017

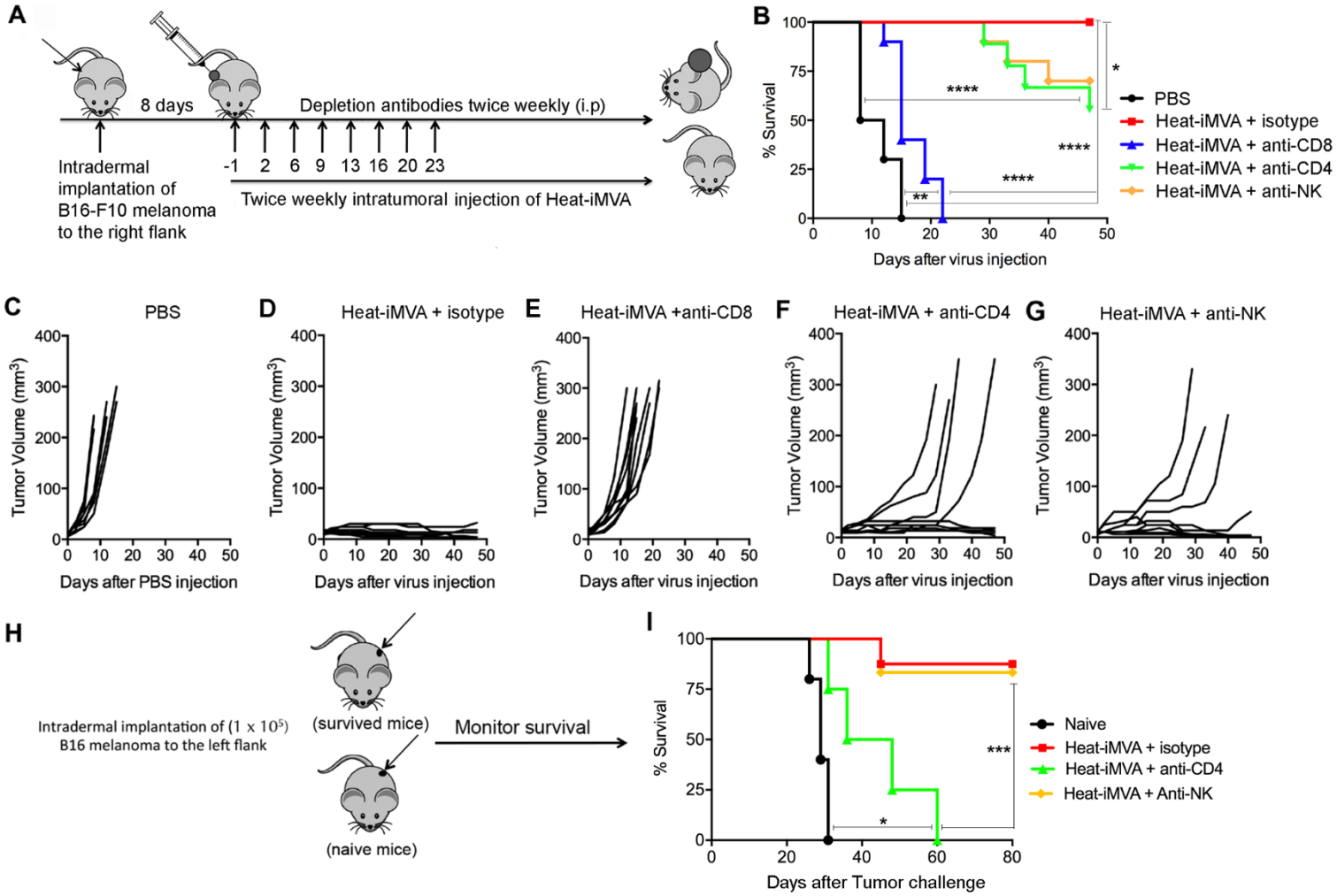
Heat-iMVA-mediated antitumor effects requires STING and Batf3-dependent DCs



- Heat-iMVA infection of conventional DCs induces type I IFN and DC maturation in via the cytosolic DNA-sensing pathway mediated by cGAS/STING.
- Batf3 is a transcription factor important for the development of CD103$^+$/CD8α^+ DCs.

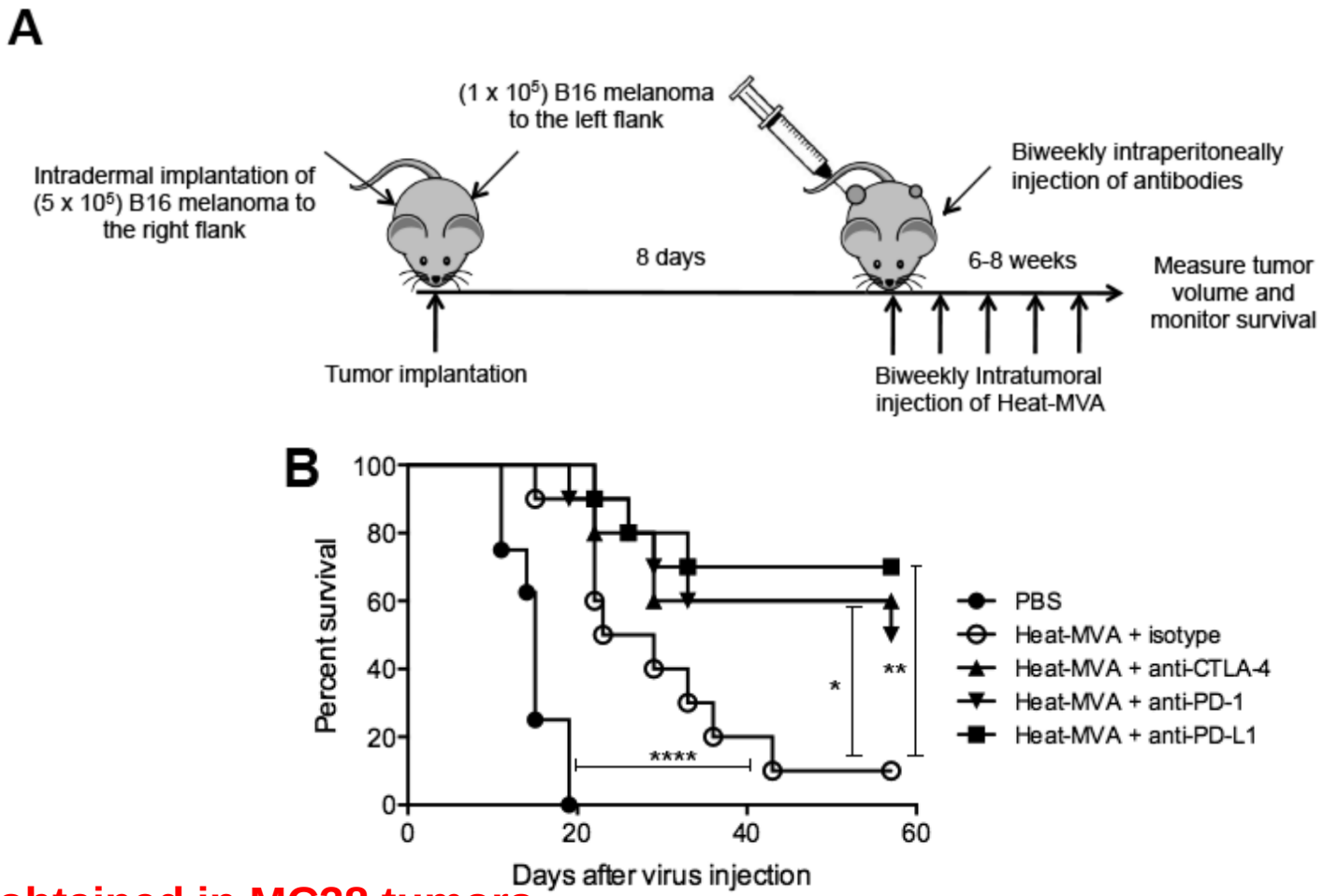
Dai et al., Science Immunology, 2017

Heat-iMVA-mediated antitumor effects requires CD8⁺ T cells and Heat-iMVA-induced long-term antitumor memory responses requires CD4⁺ T cells



Dai et al., Science Immunology, 2017

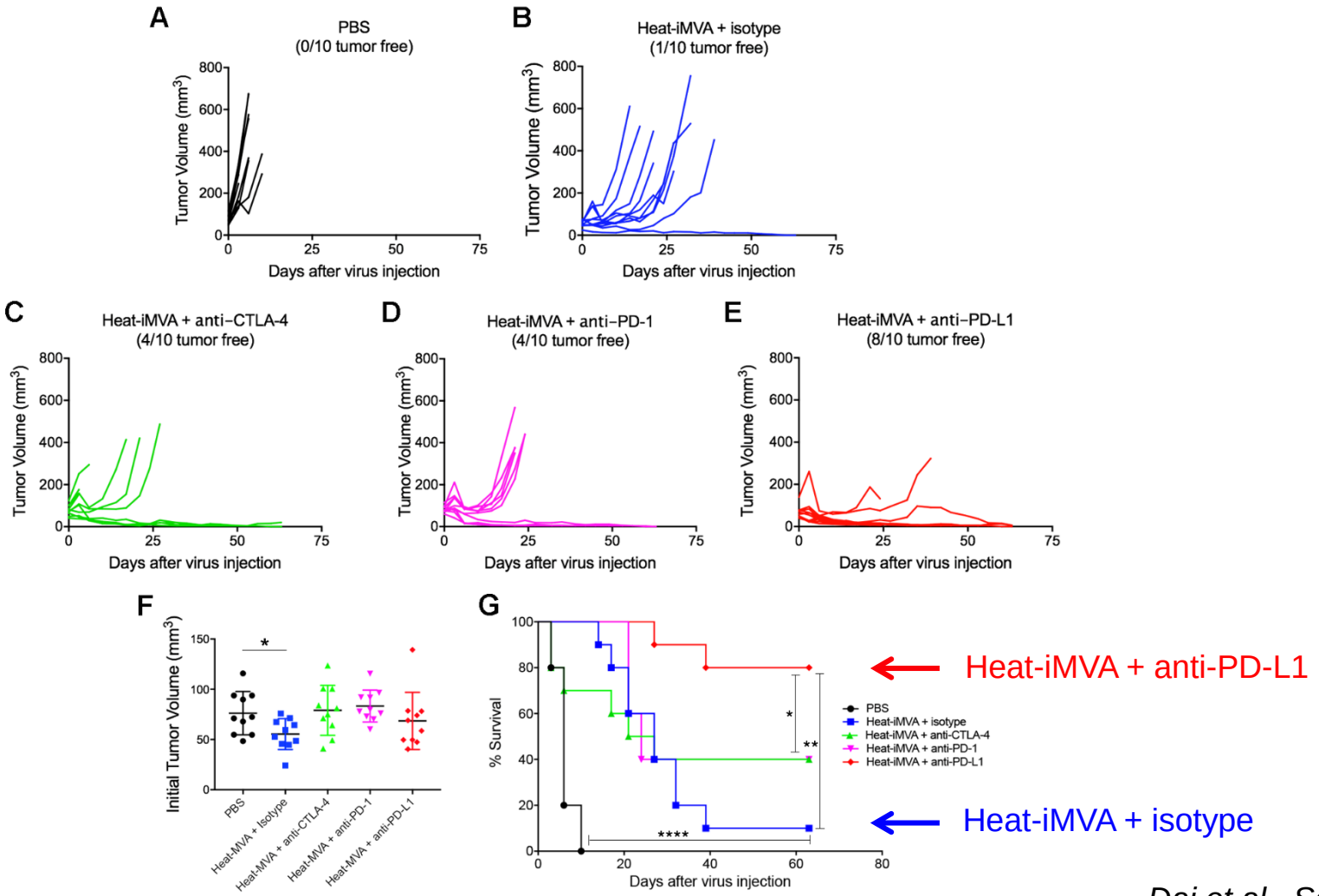
The combination of intratumoral injection of Heat-inactivated MVA with immune checkpoint blockade has synergistic antitumor effects



Similar results were obtained in MC38 tumors

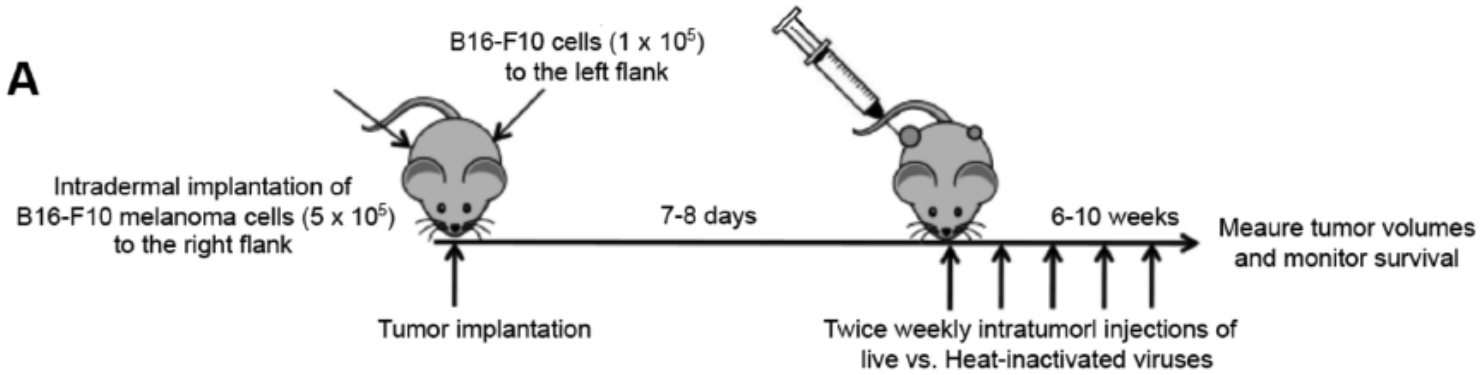
Dai et al., Science Immunology, 2017

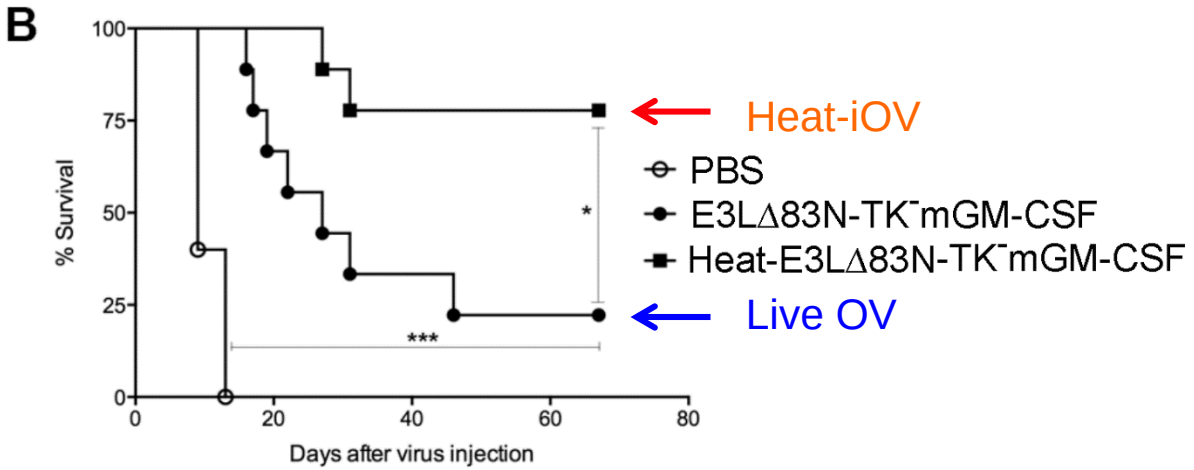
The combination of intratumoral injection of Heat-iMVA and systemic delivery of immune checkpoint blockade leads to cure of large established B16-F10 melanoma



Dai et al., Science Immunology, 2017

IT Heat-iOV (oncolytic virus) is superior to live OV in antitumor effects in a bilateral tumor implantation model





Wang et al., SITC 2017

Lessons and Take Home Messages

- Intratumoral delivery of Heat-iMVA can turn “cold tumors” into “hot tumors”, which become responsive to immune checkpoint blockade.
- Heat-iMVA-induced systemic antitumor effects require host STING, Batf3-dependent $CD103^+/CD8\alpha^+$ DCs, and $CD8^+$ T cells.
- IT Heat-iMVA generates systemic long-lasting antitumor immunity in spleens, and distant non-lymphoid organs (such as the lung) .
- The combination of Heat-iMVA and immune checkpoint blockade is powerful to eradicate non-injected distant tumors and large established tumors.

Combinatory immunotherapy is the key
and virotherapy can be a versatile and effective component!

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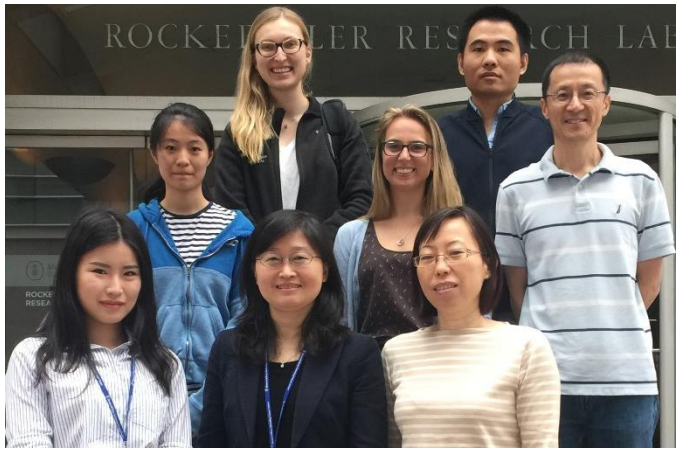

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