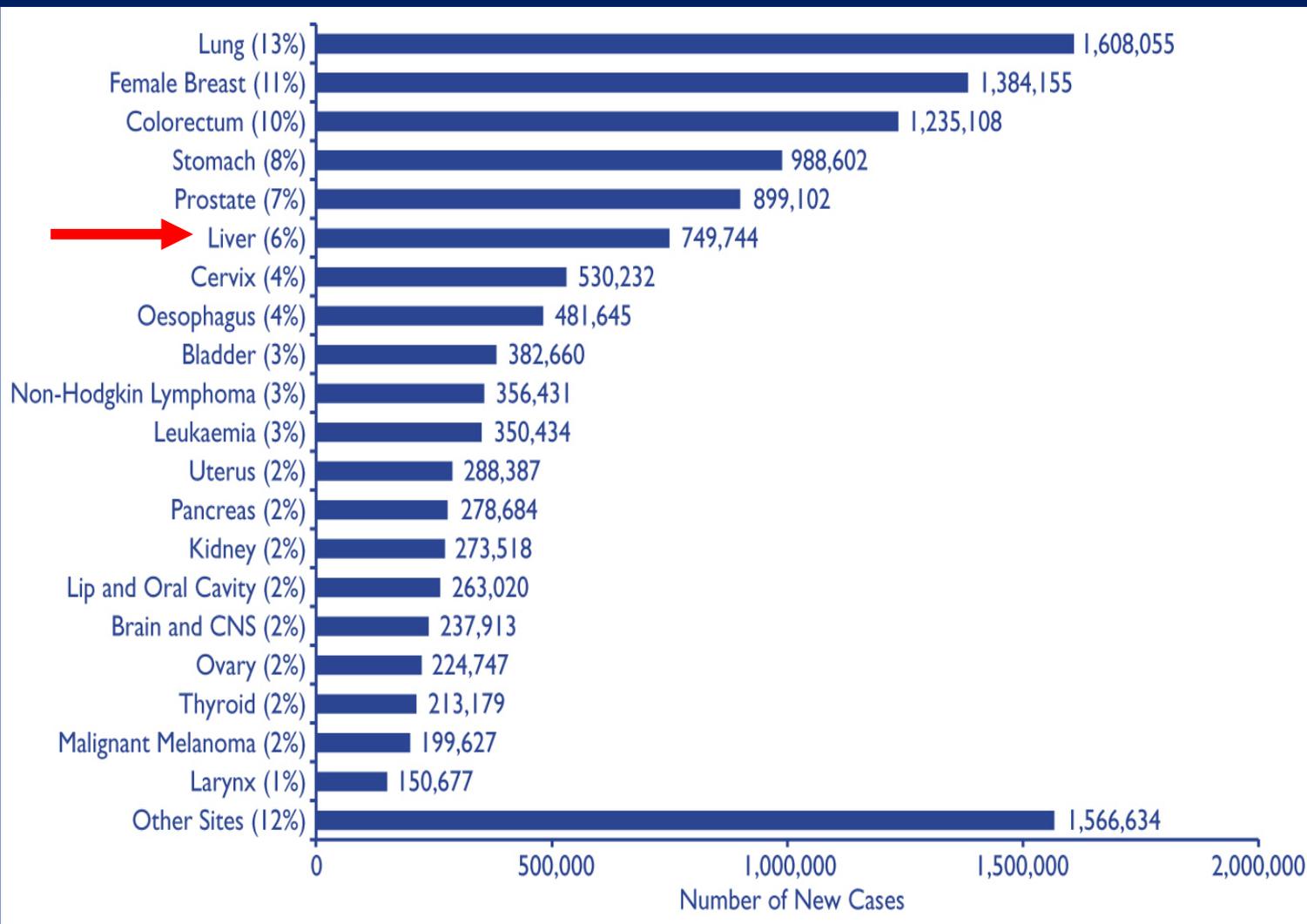


Translating Research into Clinical Practice: Strategies Against Hepatocellular Cancer

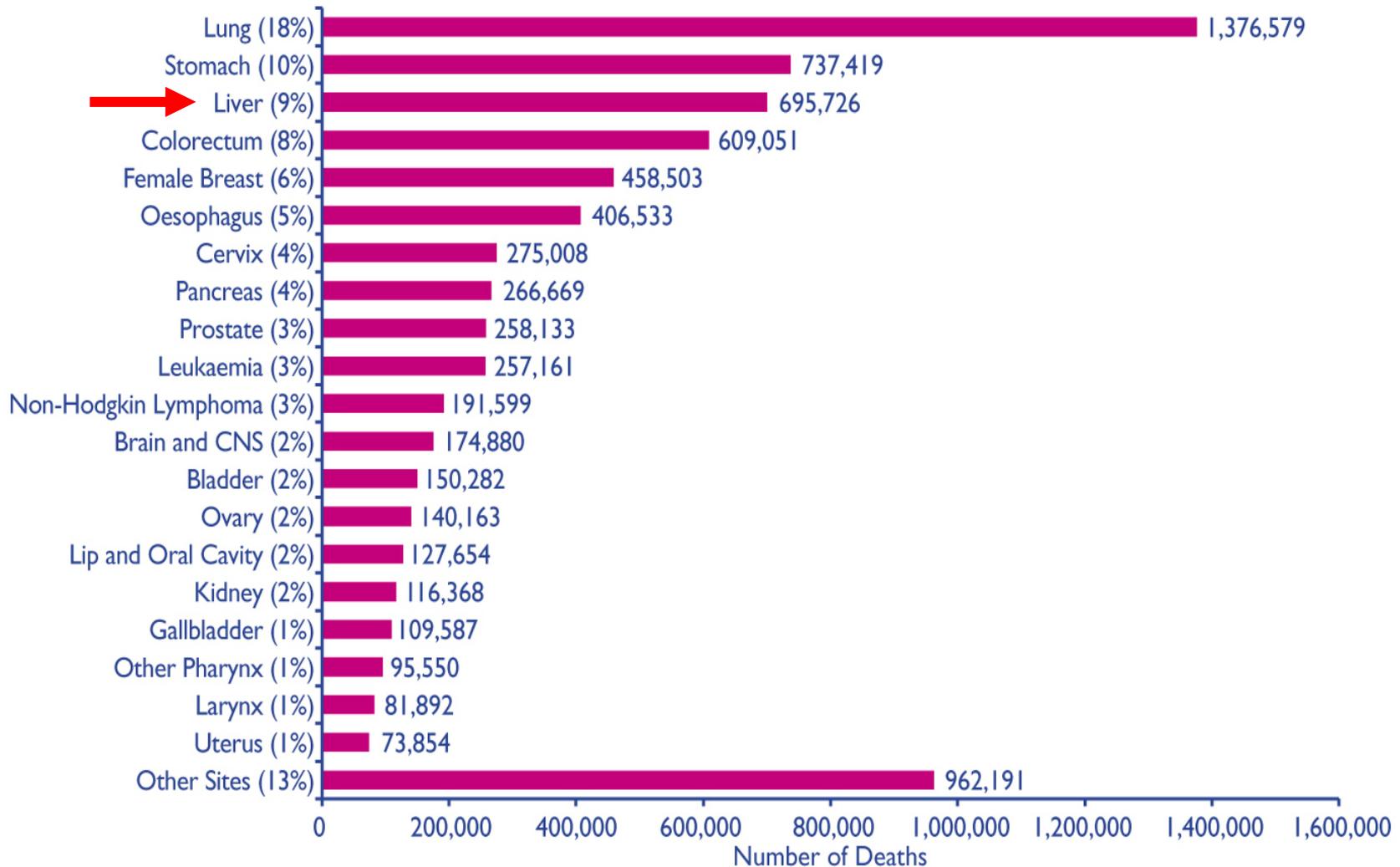


Kevin Staveley-O'Carroll, PhD, MD, FACS
Professor and Chair, Department of Surgery
Director of the Ellis Fischel Cancer Center

The 20 Most Commonly Diagnosed Cancers Worldwide, 2008 Estimates



The 20 Most Common Causes of Death from Cancer Worldwide, 2008 Estimates



Currently-Available Treatment

- 1. Surgical Resection**
- 2. Liver Transplantation**
- 3. Radiofrequency Ablation (RFA)**
- 4. Transarterial Chemoembolization and Radioembolization (TACE)**
- 5. Chemotherapy - sorafenib, FDA approved 2006**

High mortality rate



High rate of recurrence



Urgent need for new therapeutic approaches



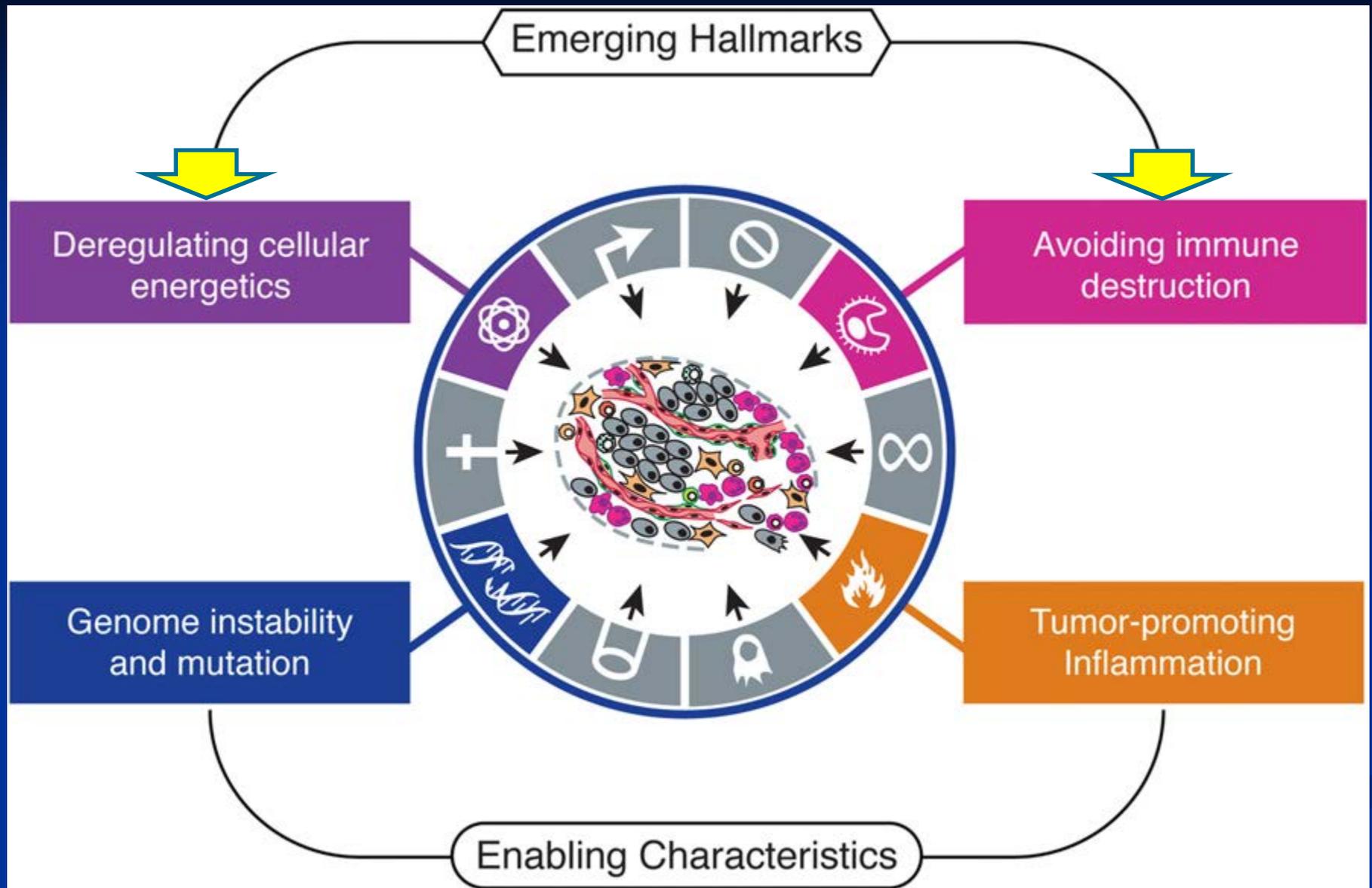
Limited benefit of current therapies

Immunotherapy for HCC

A Promising Strategy

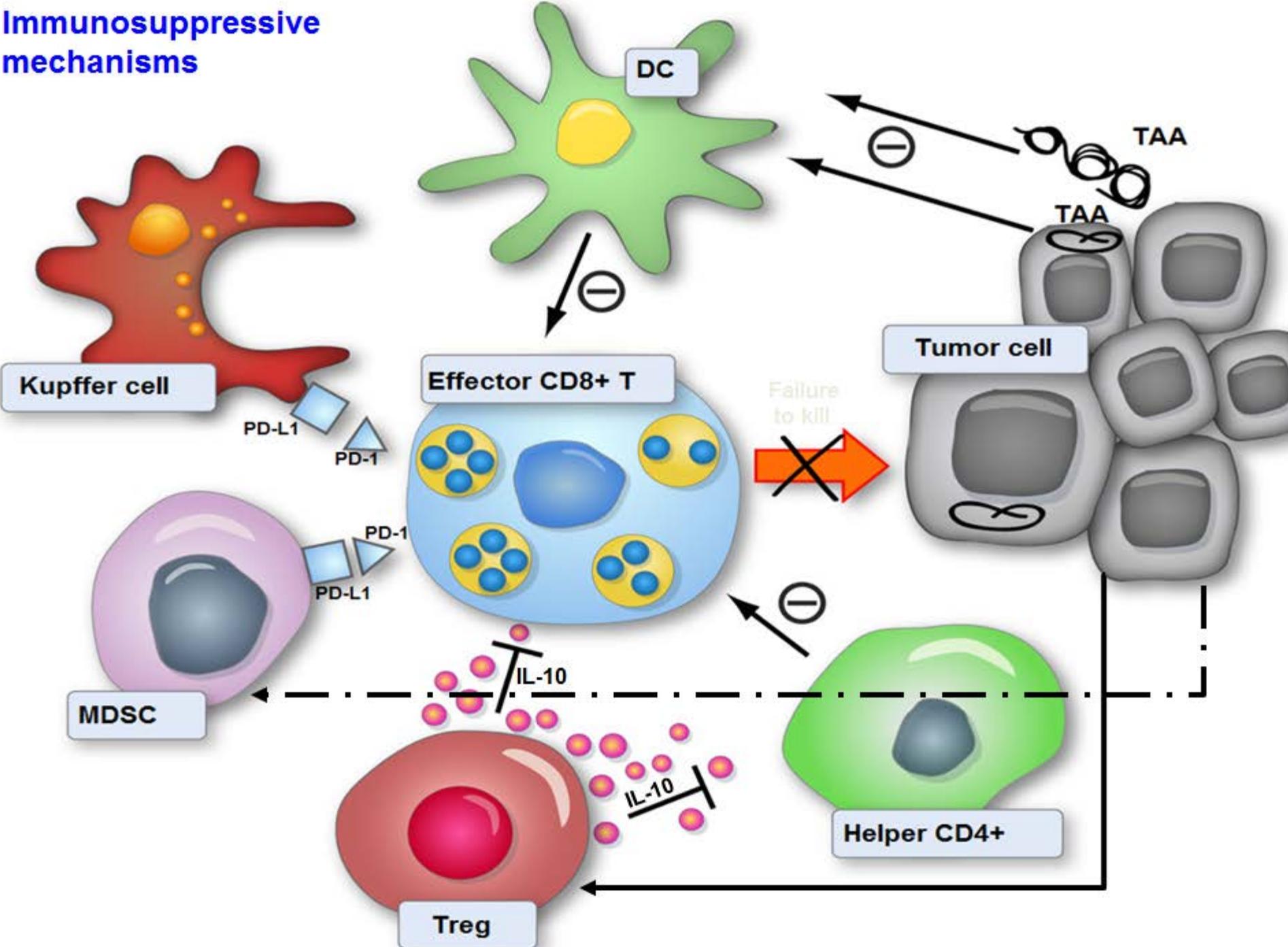
Immune-based Therapy Clinical Trials in Hepatocellular Carcinoma, *J Clin Cell Immunol*, 2015 Dec; 6 (6): 376

Emerging Hallmarks and Enabling Characteristics



Douglas Hanahan, and Robert A. Weinberg. Cell 144, March 4, 2011

Immunosuppressive mechanisms



HCC-Specific Antigens Avoid Immune Destruction

- Hepatocellular cancer (HCC) antigens:
 - AFP (Alpha Fetoprotein), Glypican 3 (GPC3), etc.
- Liver is a tolerogenic organ:
 - maintains immune tolerance to digested antigens
 - induces tolerance in liver transplant recipients

Clinically Relevant Murine model of HCC

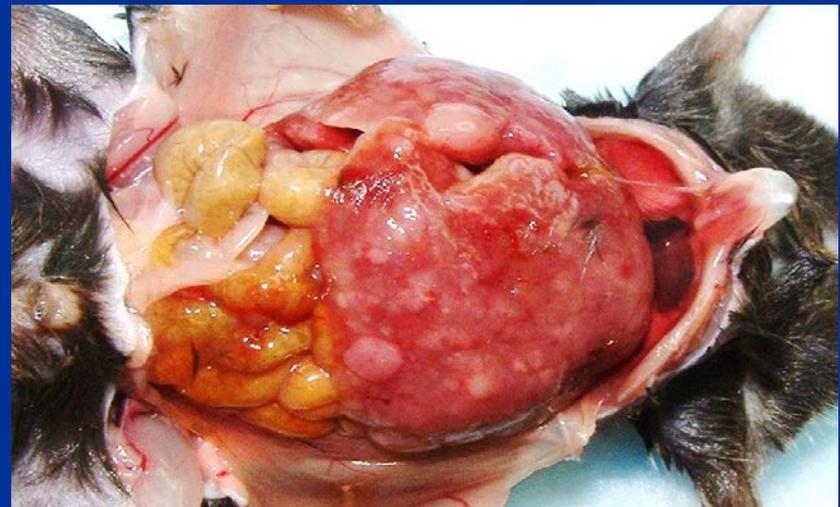
Spontaneous Hepatocellular Cancer Model-MTD2

Strength

- C57BL/6 mice which are transgenic for the SV40 T-antigen
 - Binds and inactivates tumor suppressor proteins p53 and RB
 - Induces spontaneously arising tumors when expressed as a transgene
- Highly immunogenic with well characterized CD8⁺ T-cell response

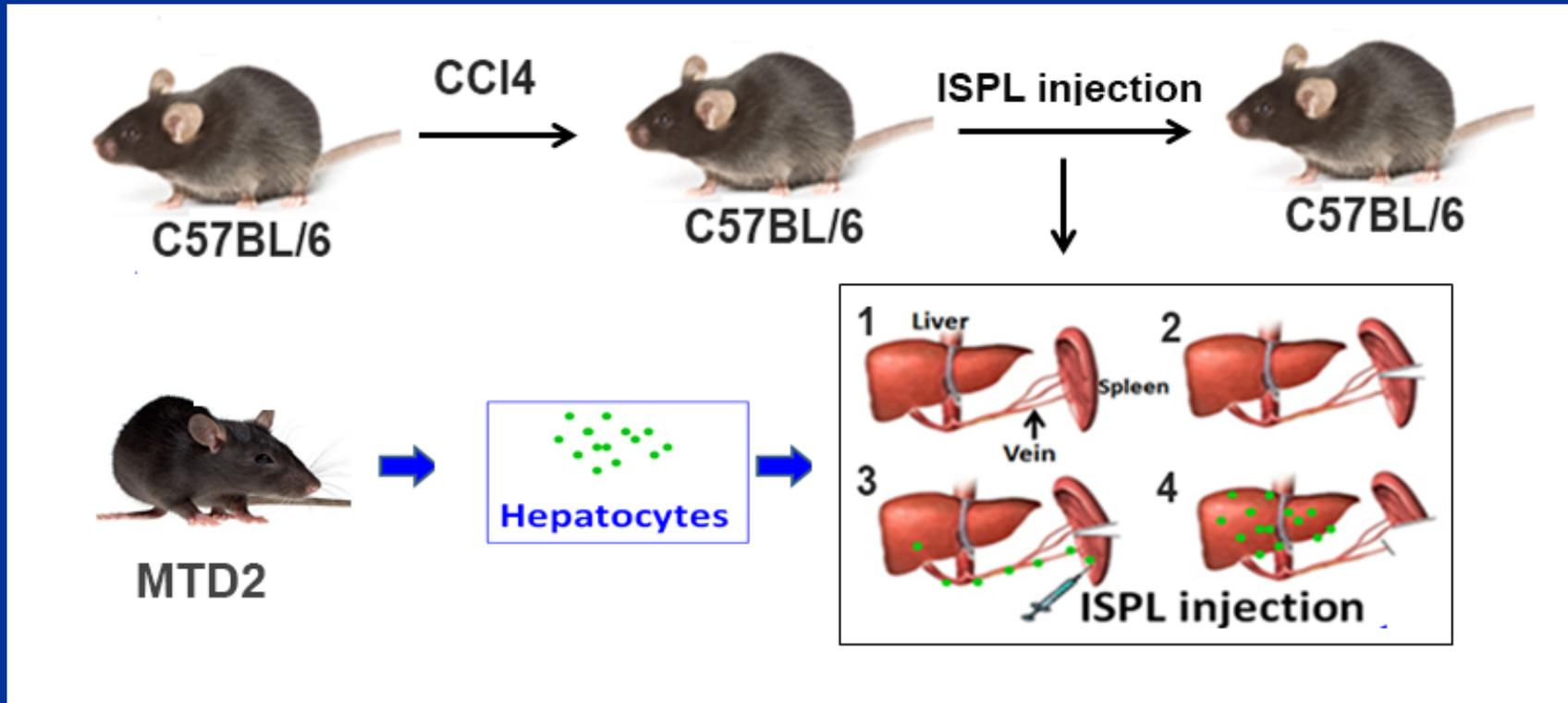
Weakness

- Hepatocytes are all transgenic and potentially tumorigenic
- Rapid tumor progression, early death
- Difficulty monitoring response to therapy
- Central Tolerance

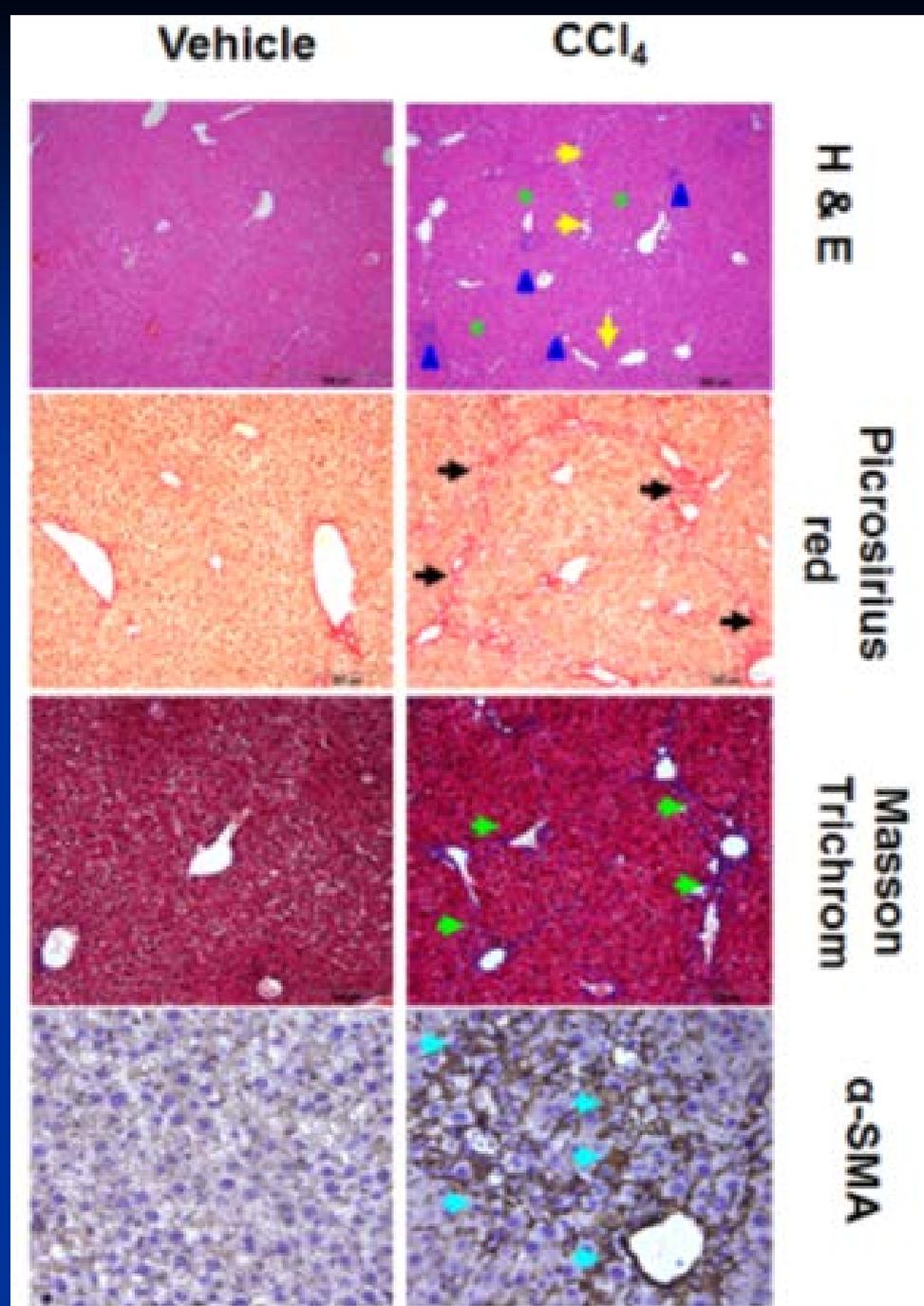


Combinational Strategy to Make Clinically Relevant Murine Model:

CCl₄ injection and Intrasplenic Inoculation of Oncogenic Hepatocytes



Liver Fibrosis



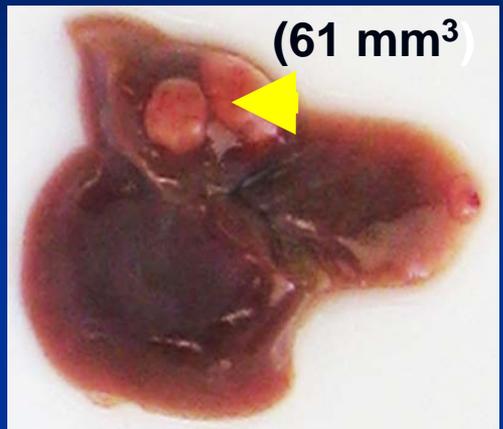
Tumor Initiation and Progression

Normal

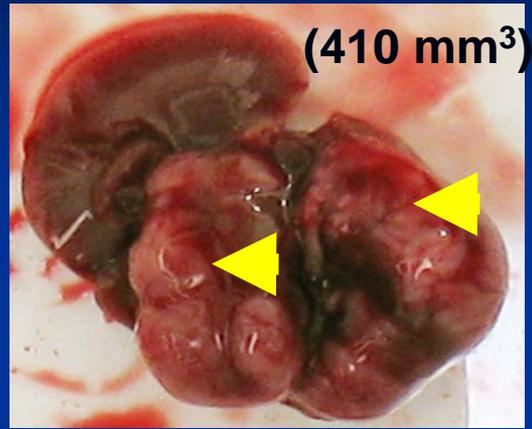


Tumor-bearing mice

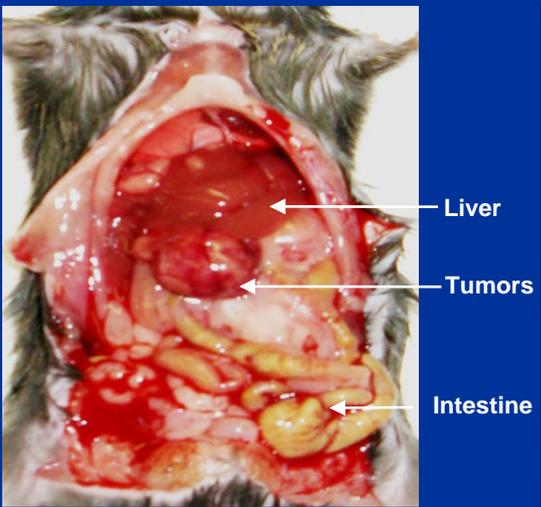
Early (small tumors)



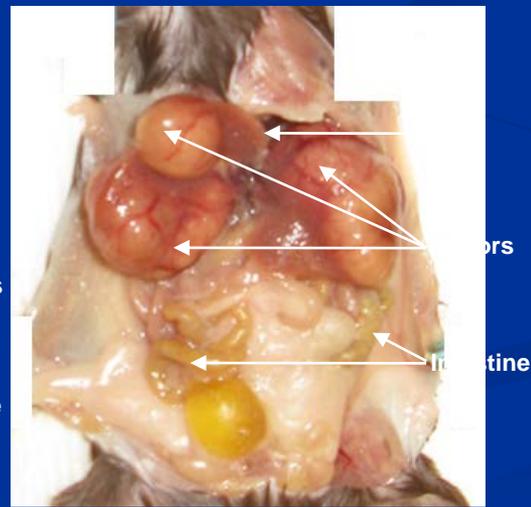
Advanced (large tumors)



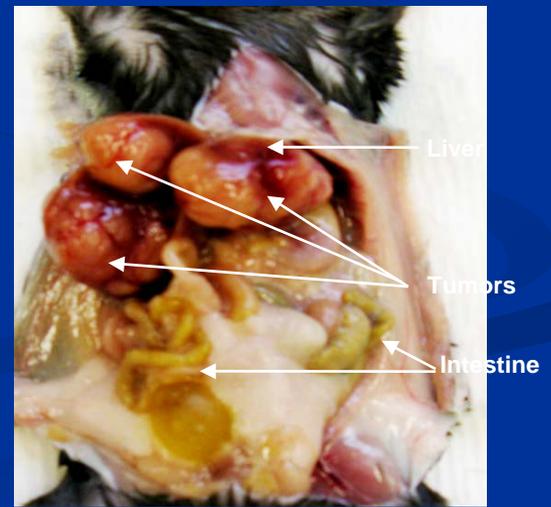
Control



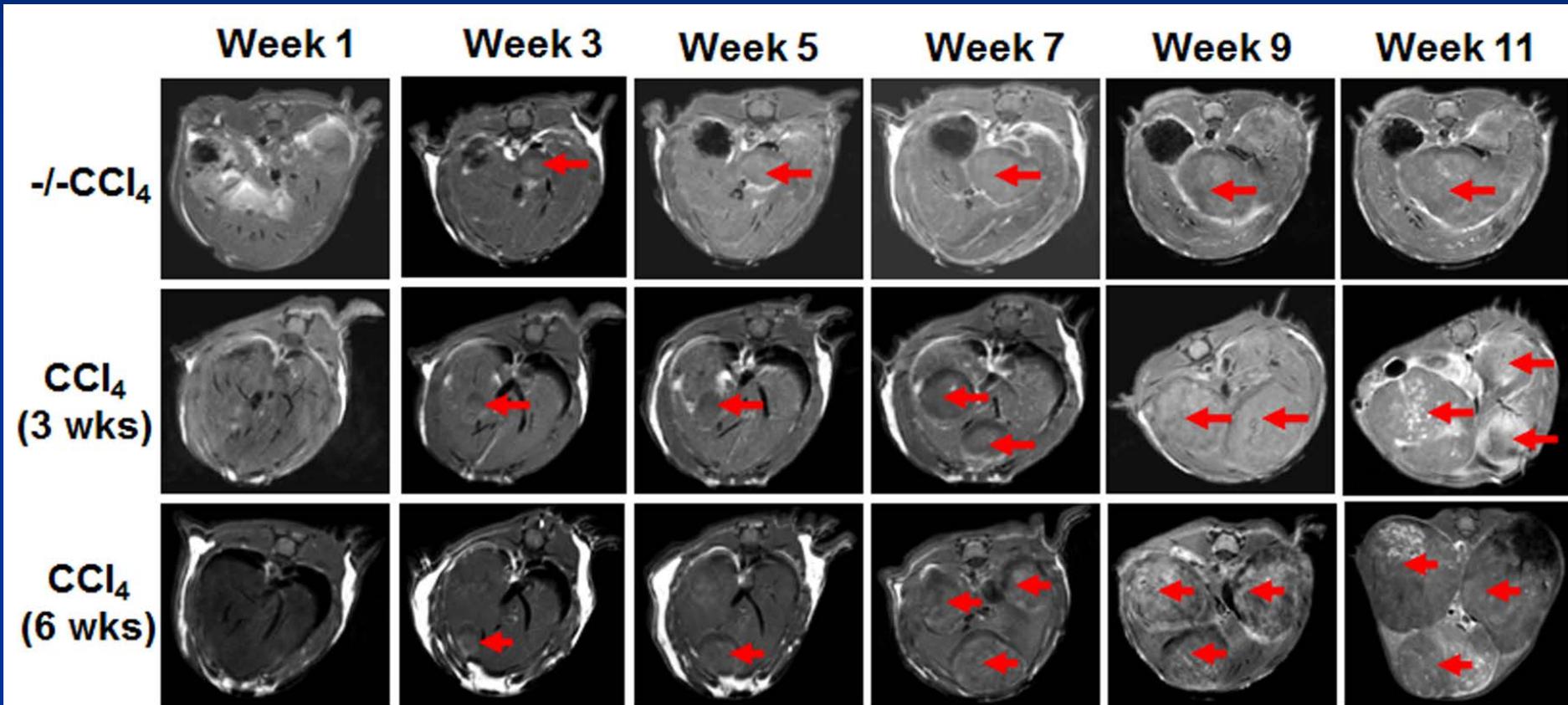
CCl₄ (3 wks)



CCl₄ (6 wks)

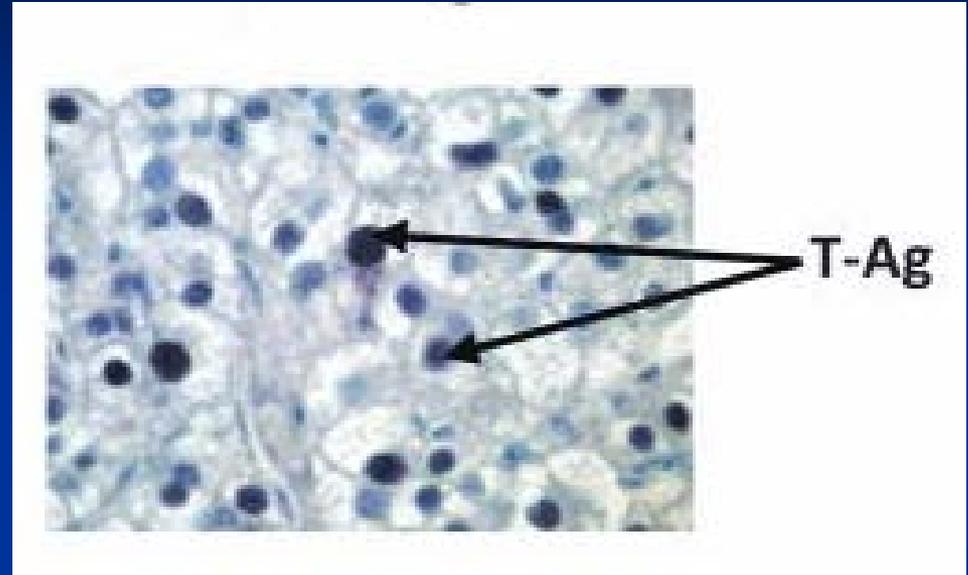


MRI Monitors Tumor Initiation and Progression

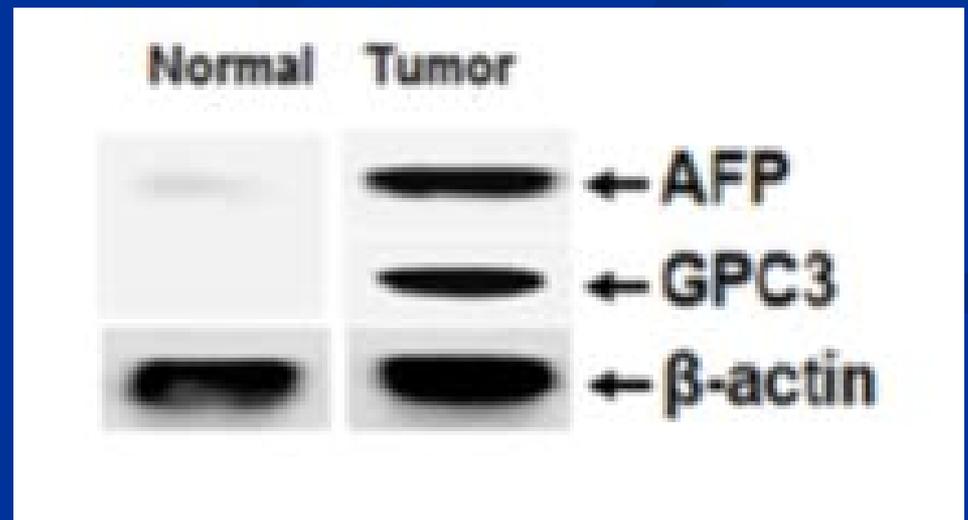


Tumor antigens

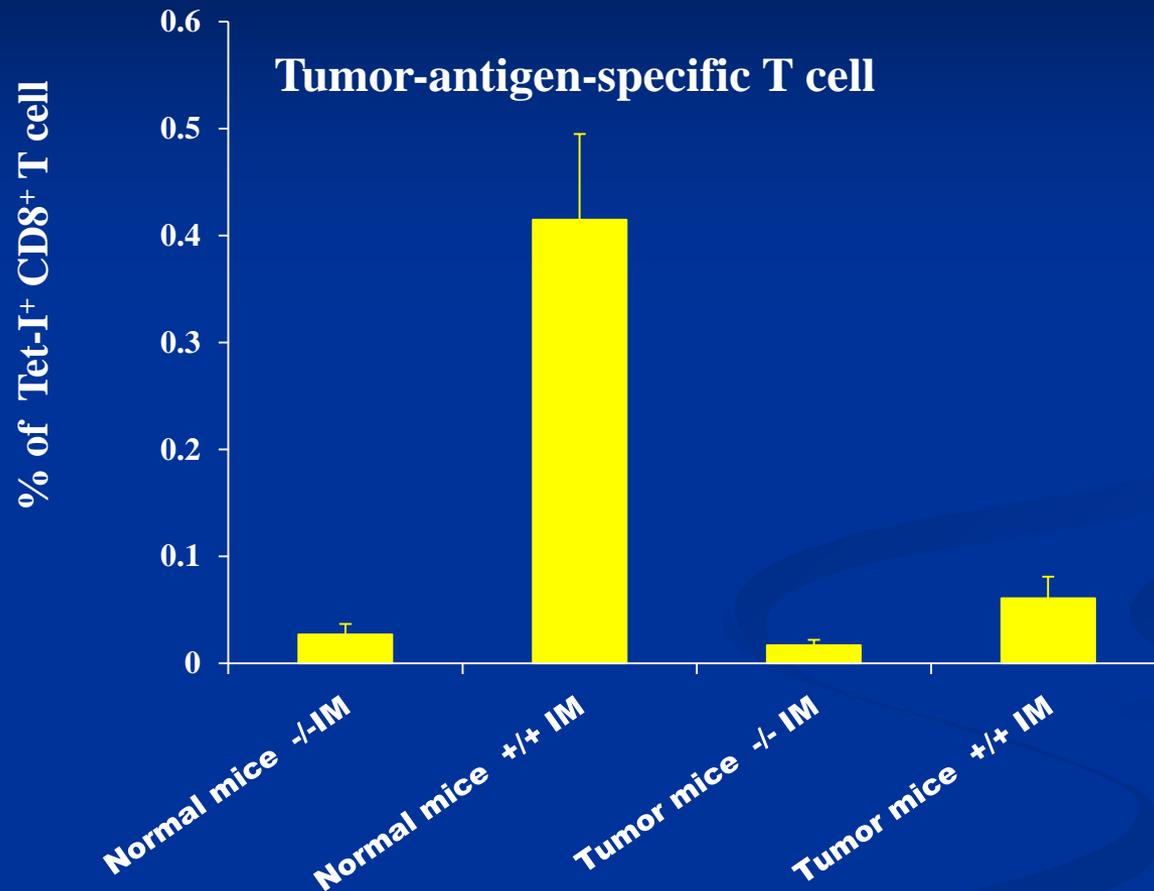
Expression of Tumor-Specific-Antigen (TSA)



Expression of Tumor-Associated-Antigen (TAA)

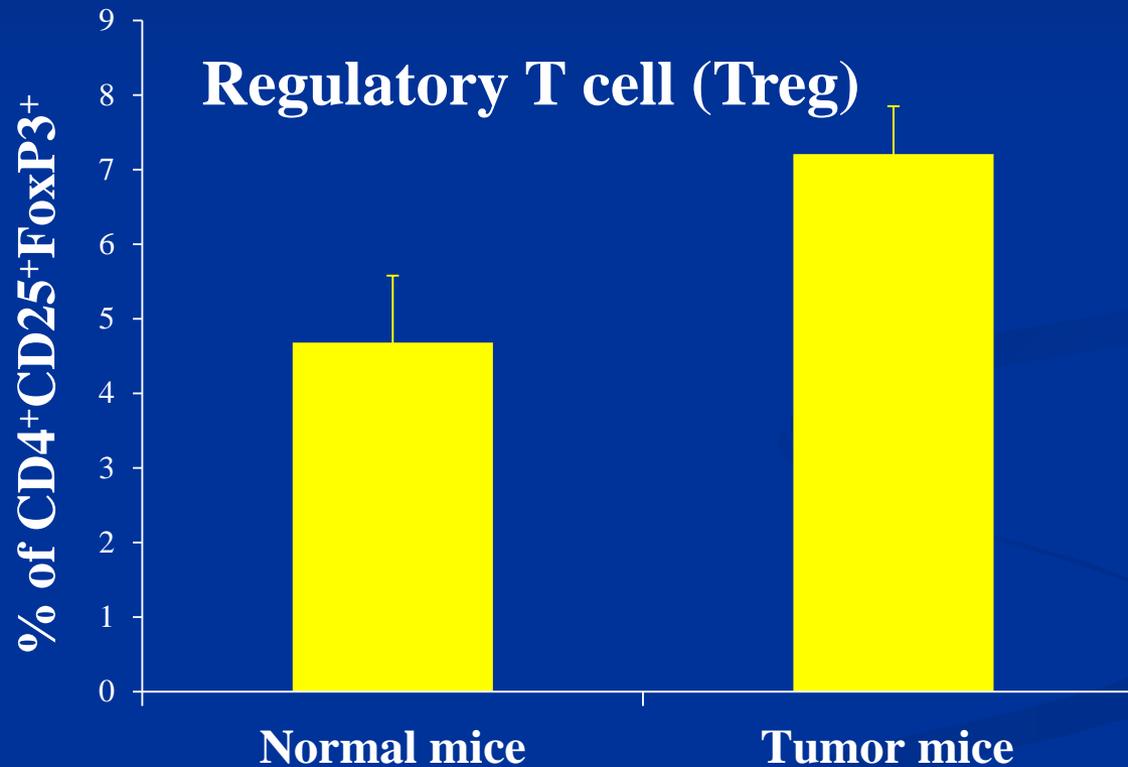


Immune Response in Tumor-bearing Mice

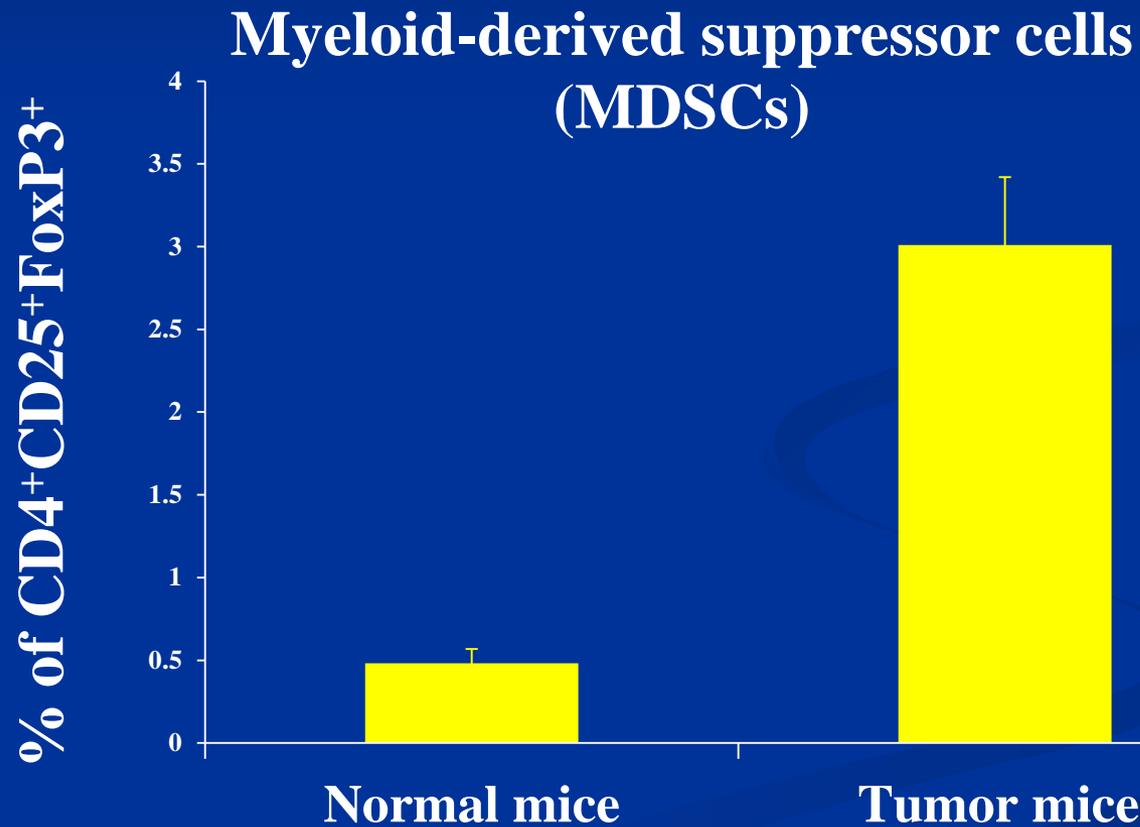


Tumor-specific T cells are turned off as the tumor grows

Tumor growth induces the increase of Tregs



Tumor growth induces the increase of MDSCs



Summary

- *A high-fidelity model of HCC*
- *Mimics human HCC initiation and progression as tumor grows in the setting of liver fibrosis*
- *Reflects typical features of this disease process*
- *Tumors express clinically relevant tumor antigens*
- *Immune response to tumor antigen can be tracked as tumor progresses*

A Synergistic Chemoimmunotherapeutic Approach for HCC

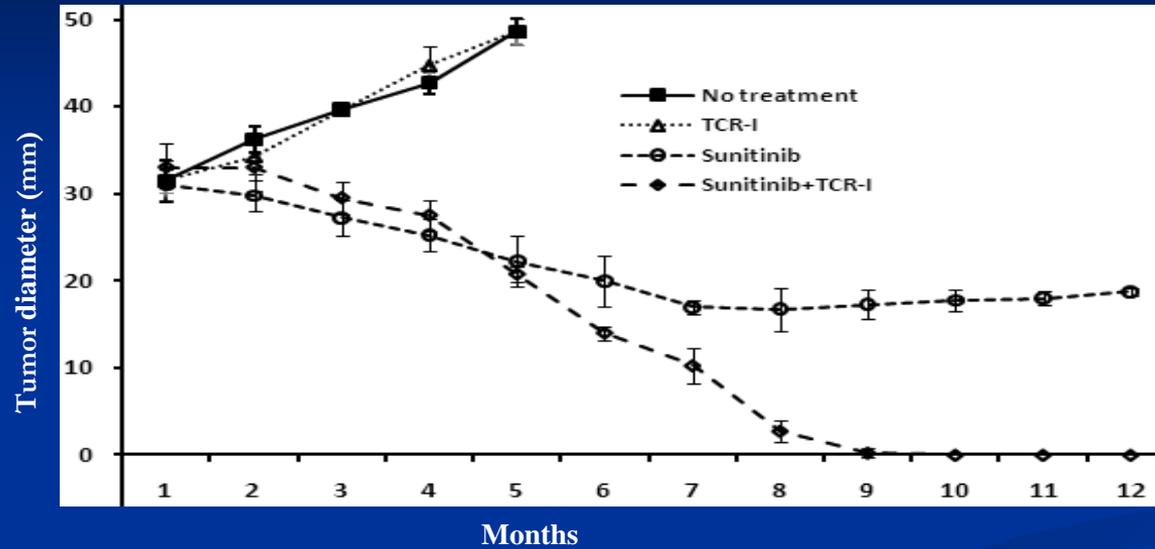
HEPATOLOGY 2012;55:141-152

Sunitinib

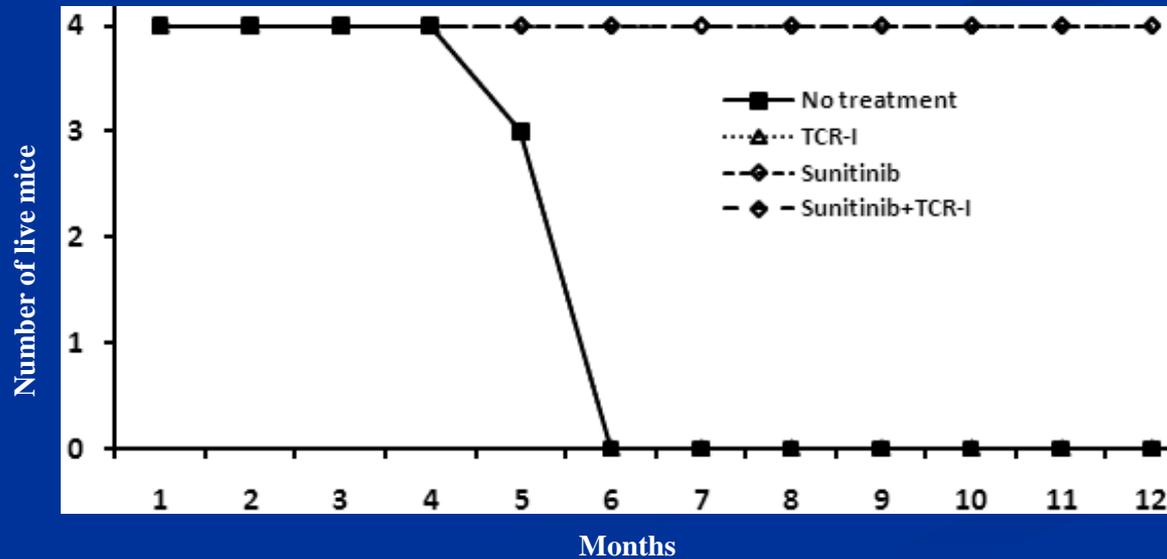
- ❖ A small molecule inhibitor of RTK, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α , PDGFR- β , FLT3, KIT, RET.
- ❖ The drug for treatment of ccRCC and GIST granted by FDA in 2006
- ❖ Being investigated for treatment of breast cancer, colorectal cancer, non-small cell lung cancer, and hepatocellular cancer

The combination of sunitinib treatment with adoptive T cell transfer synergizes to promote HCC regression in tumor-bearing mice

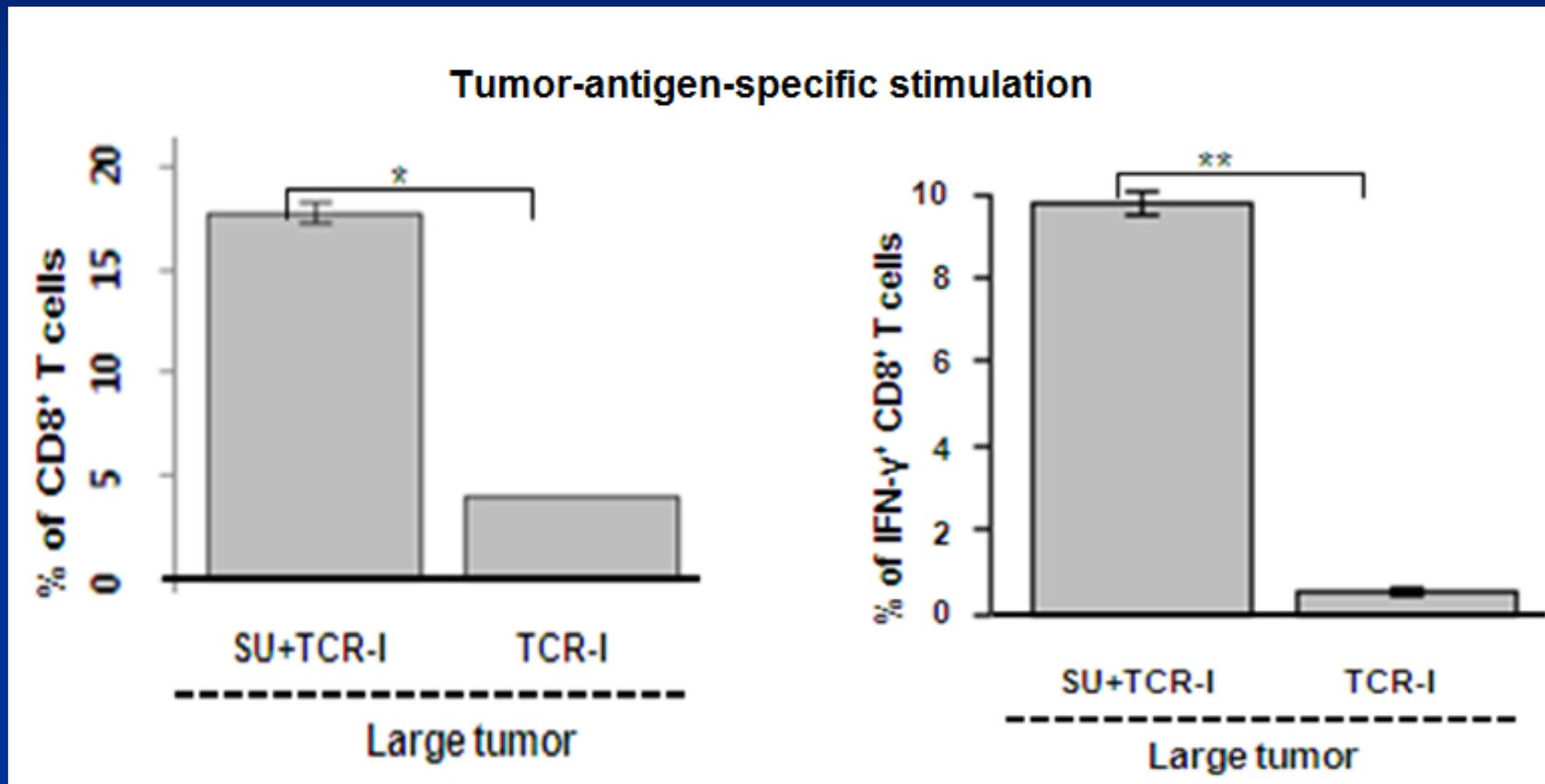
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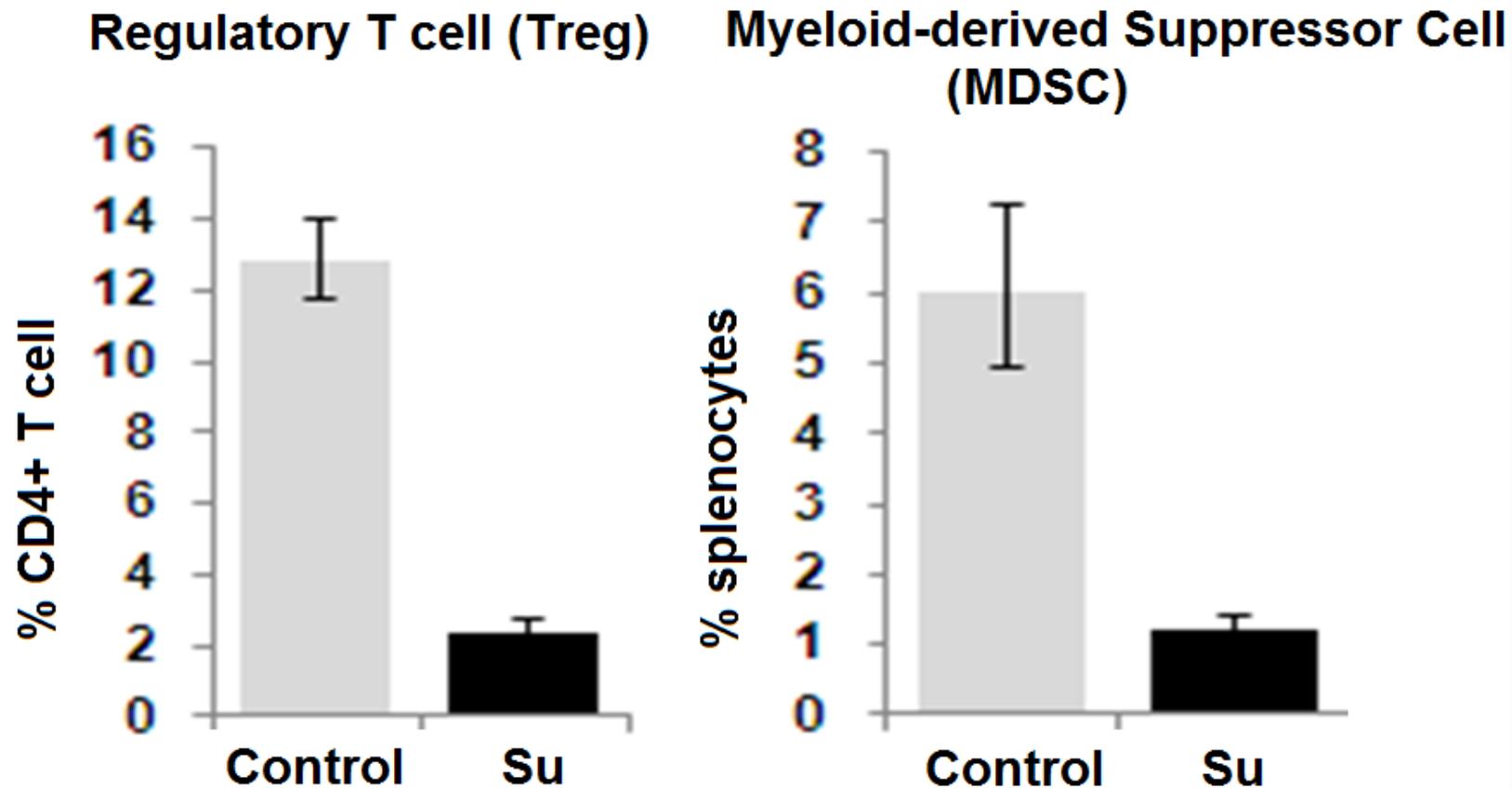
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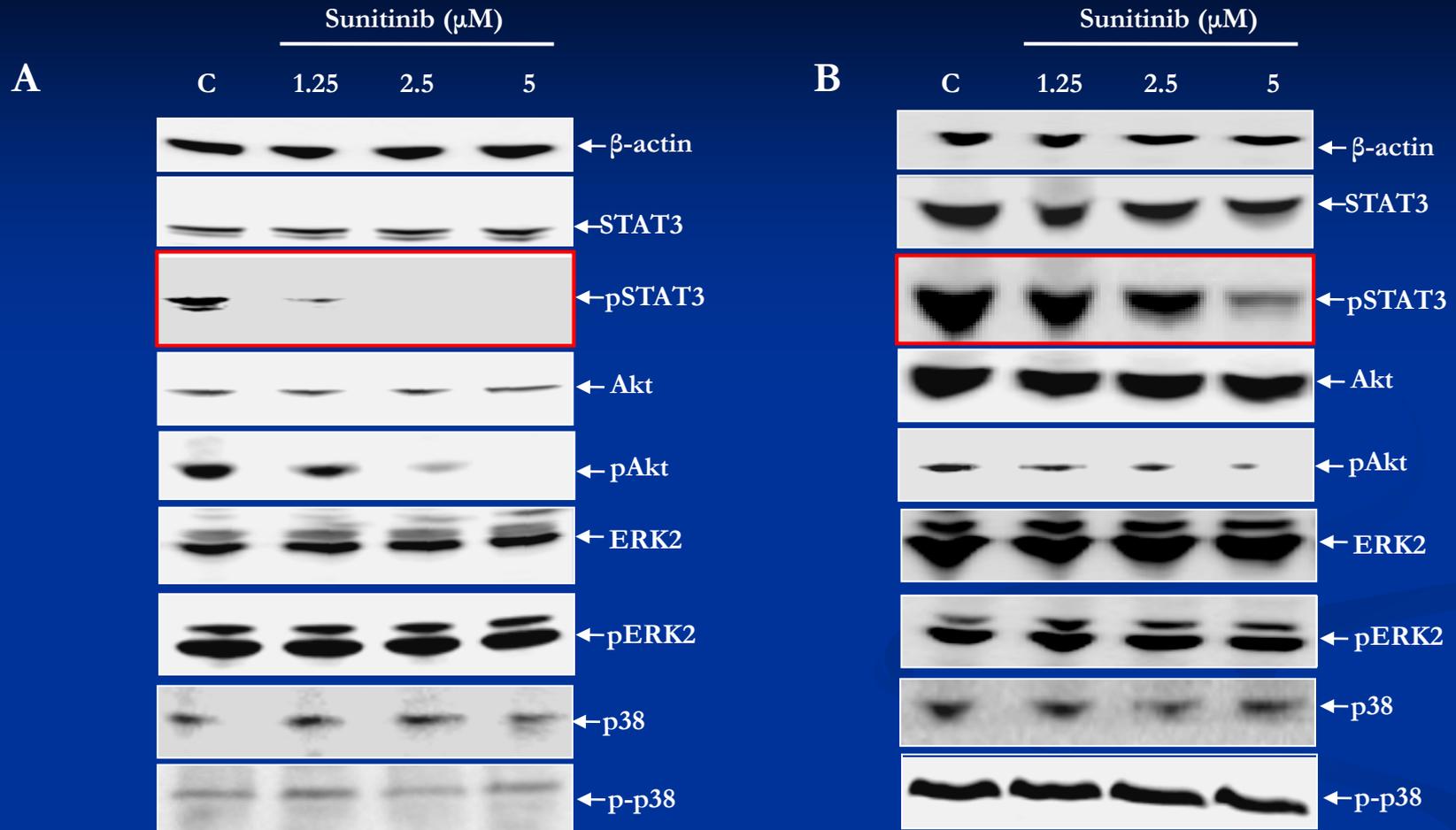
Sunitinib treatment blocks CD8⁺ T-cell tolerance in tumor-bearing mice.



Sunitinib treatment reduces the magnitude of Tregs and MDSCs in tumor-bearing mice.

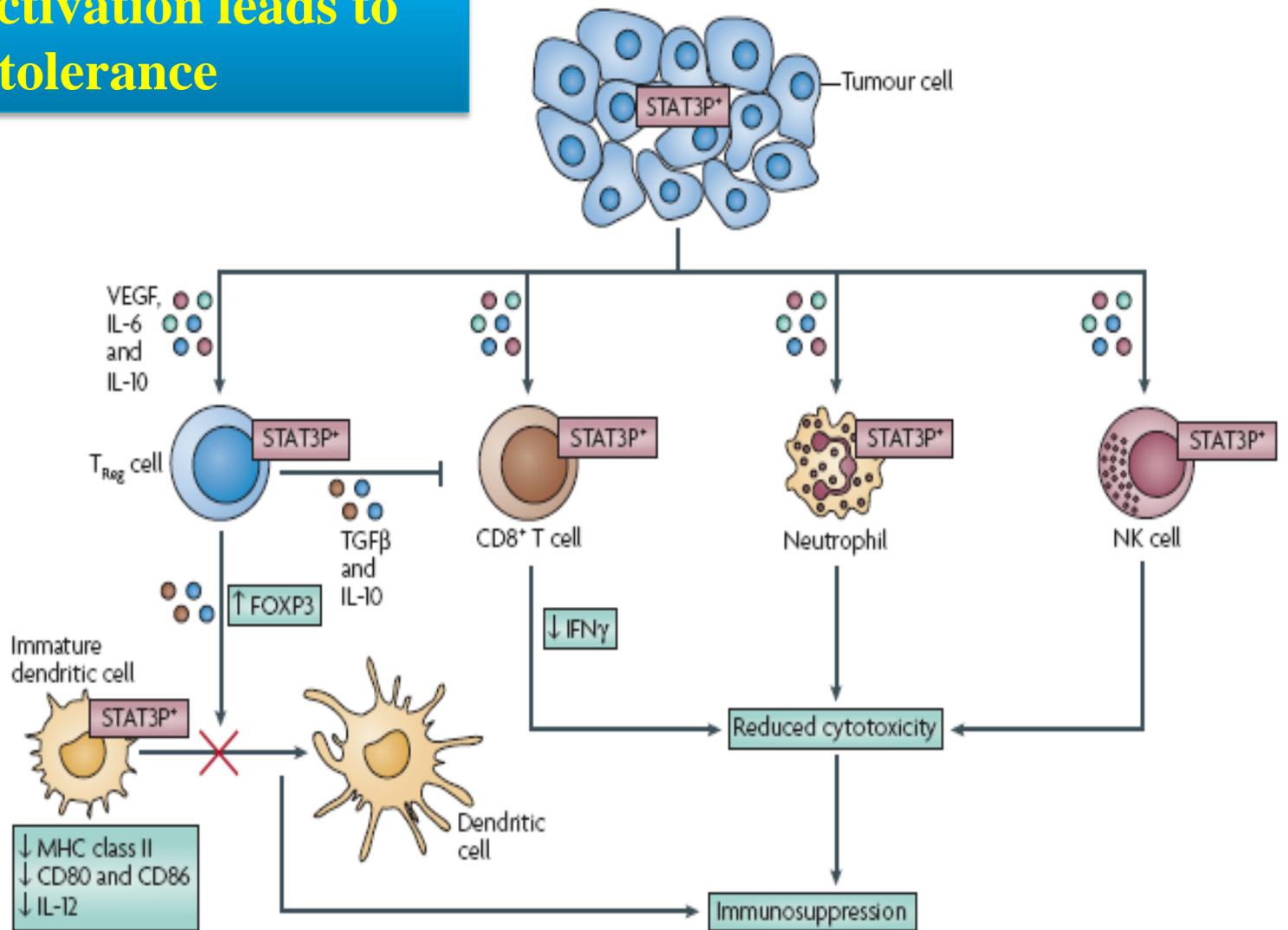


Sunitinib specifically inhibits the activation of STAT3 in HCC cells



Sk Hep1 (A) or HepG2 (B) cells were treated with sunitinib at indicated concentration for 24 h. Western blotting analyses indicated sunitinib dramatically inhibited the activation of STAT3.

STAT3 activation leads to immune tolerance



Summary:

Sunitinib inhibits HCC tumor growth directly through the STAT3 pathway and prevents tumor antigen-specific CD8 T-cell tolerance, thus defining a synergistic chemoimmunotherapeutic approach for HCC.

Supported by NIH/NCI Grants

1. **1 R01 CA164335-01A1**

2. **CA 100094-01A1**

RFA in Combination with Immunotherapy in the Treatment of HCC

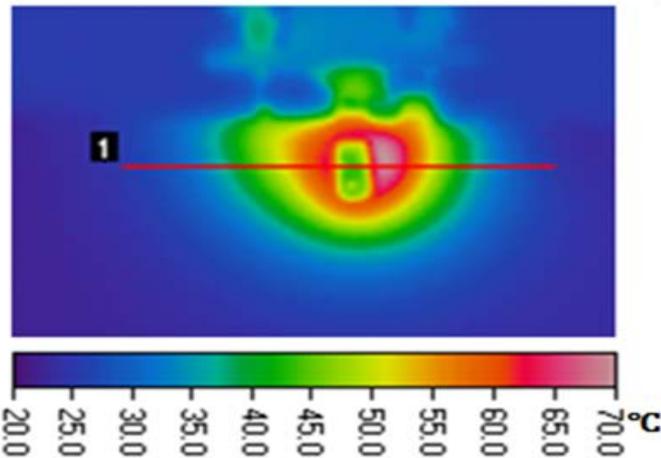
Potential of Radiofrequency Ablation in Combination with Immunotherapy in the Treatment of Hepatocellular Carcinoma. *J Clin Trials* 6:257. doi:10.4172/2167-0870.1000257

A tissue-mimicking media for optimizing RFA conditions

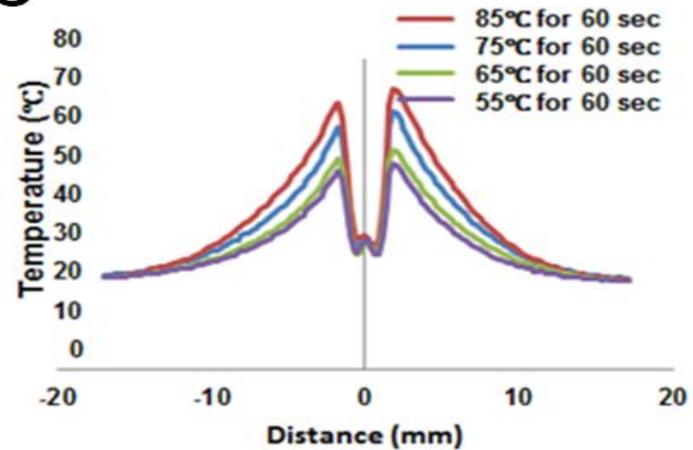
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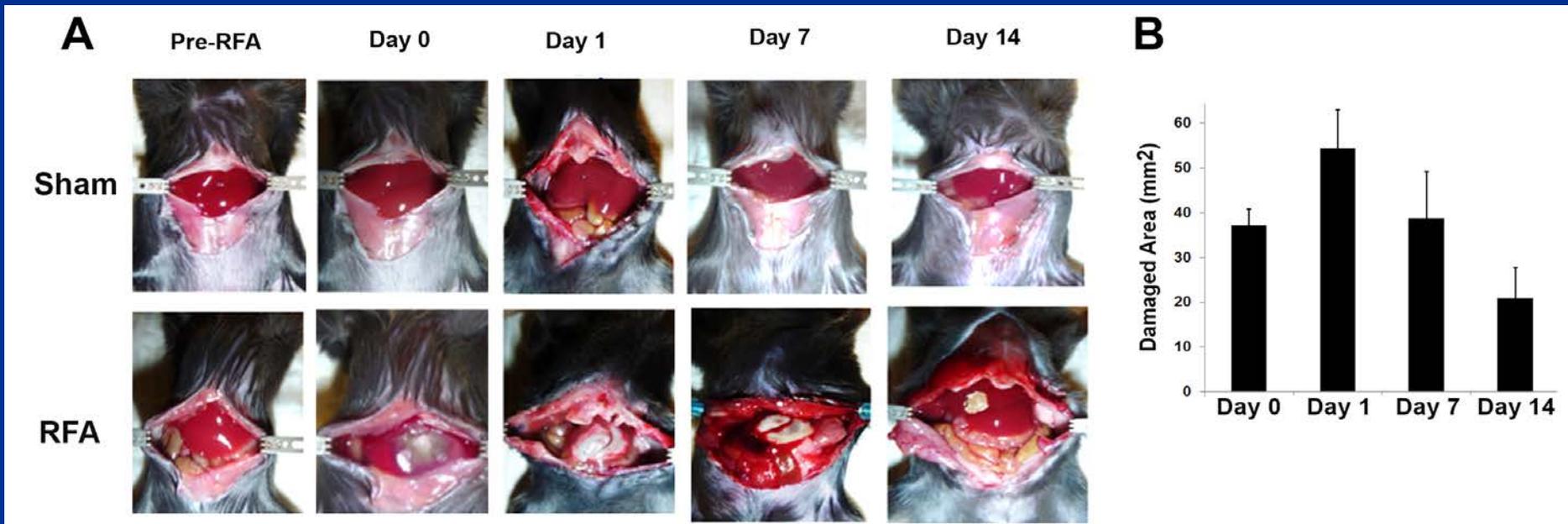
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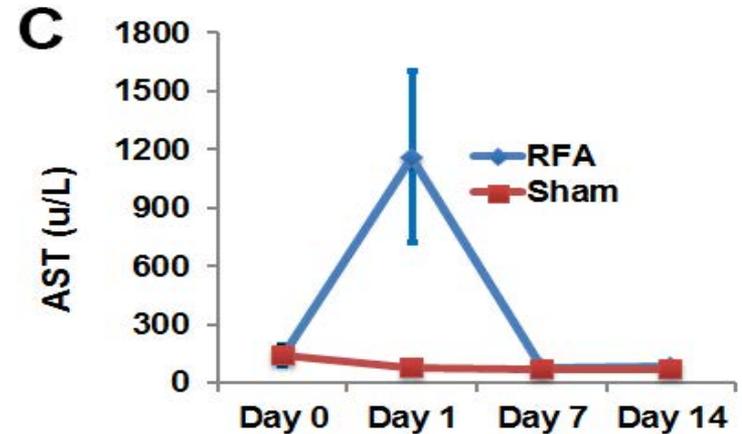
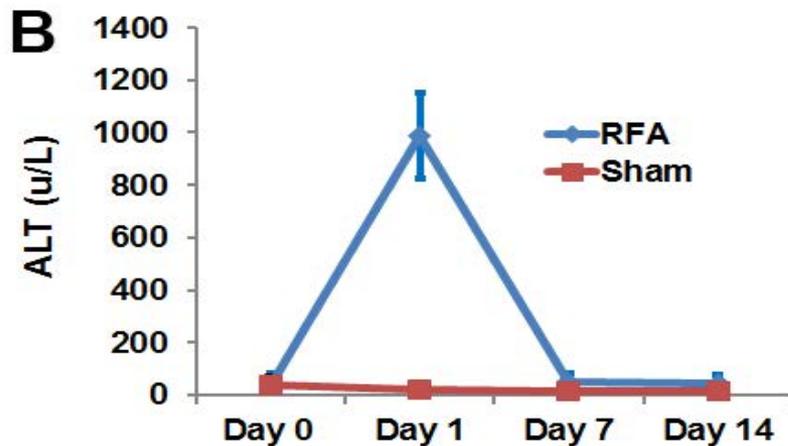
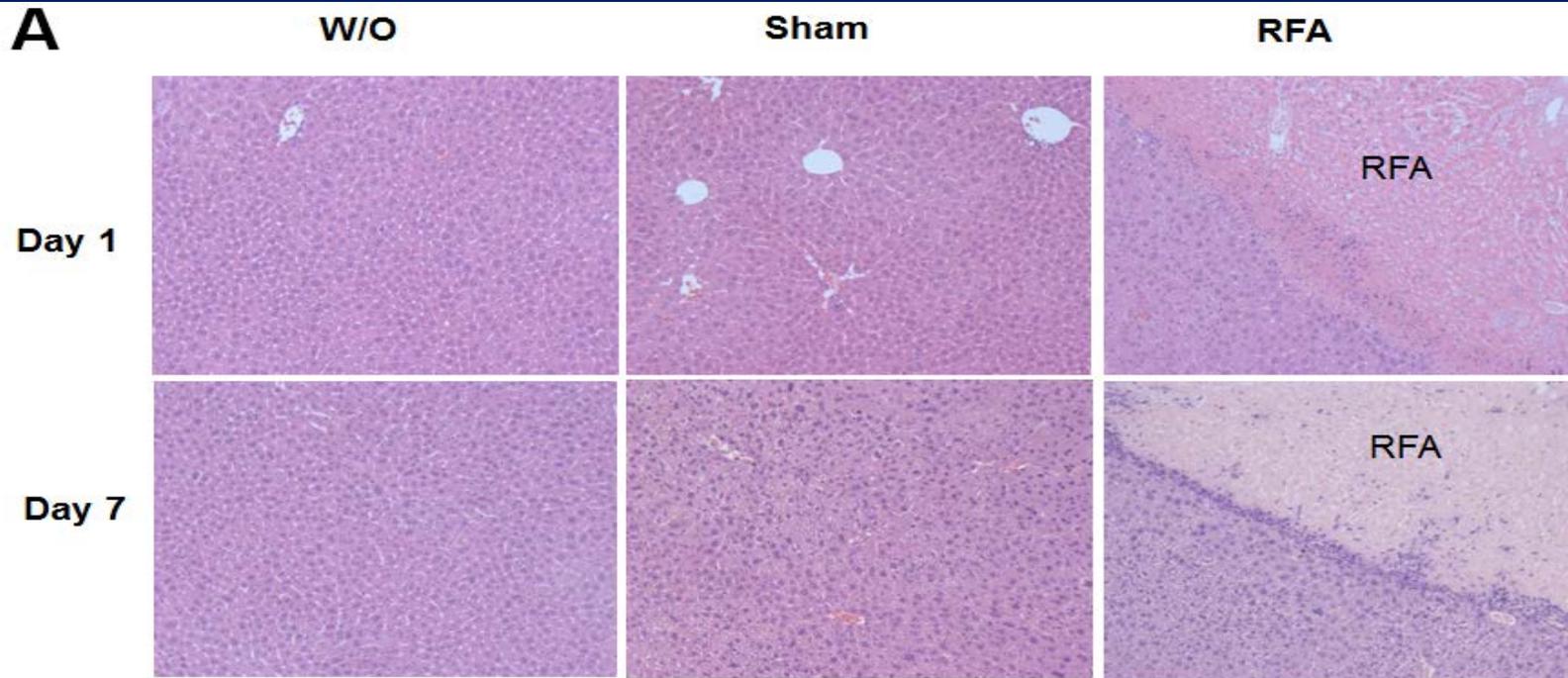
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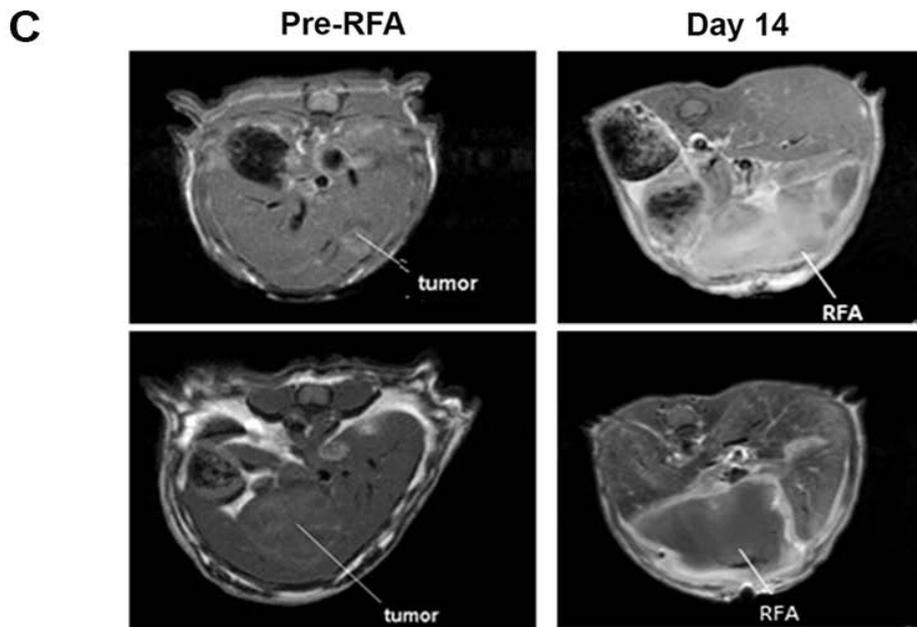
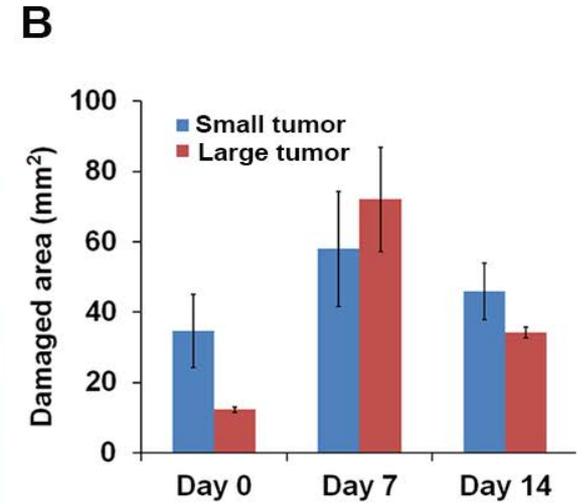
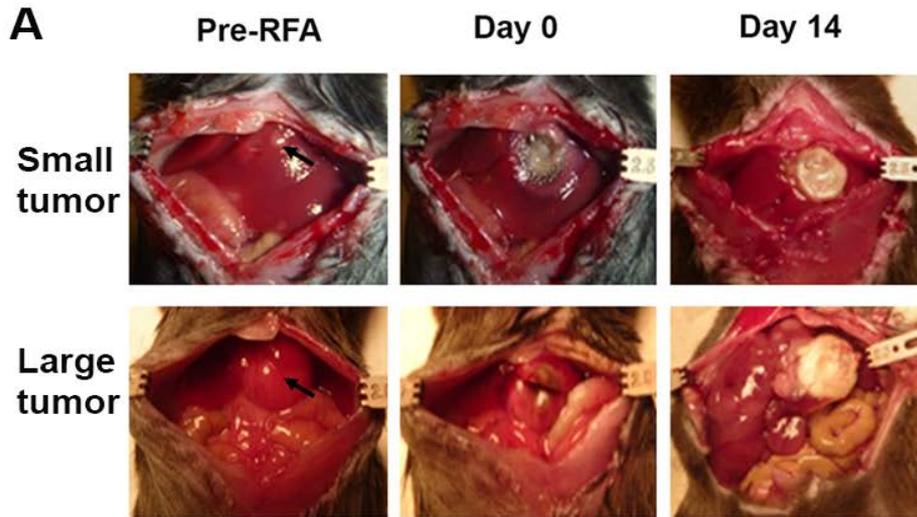
Liver ablation of normal mice with RFA



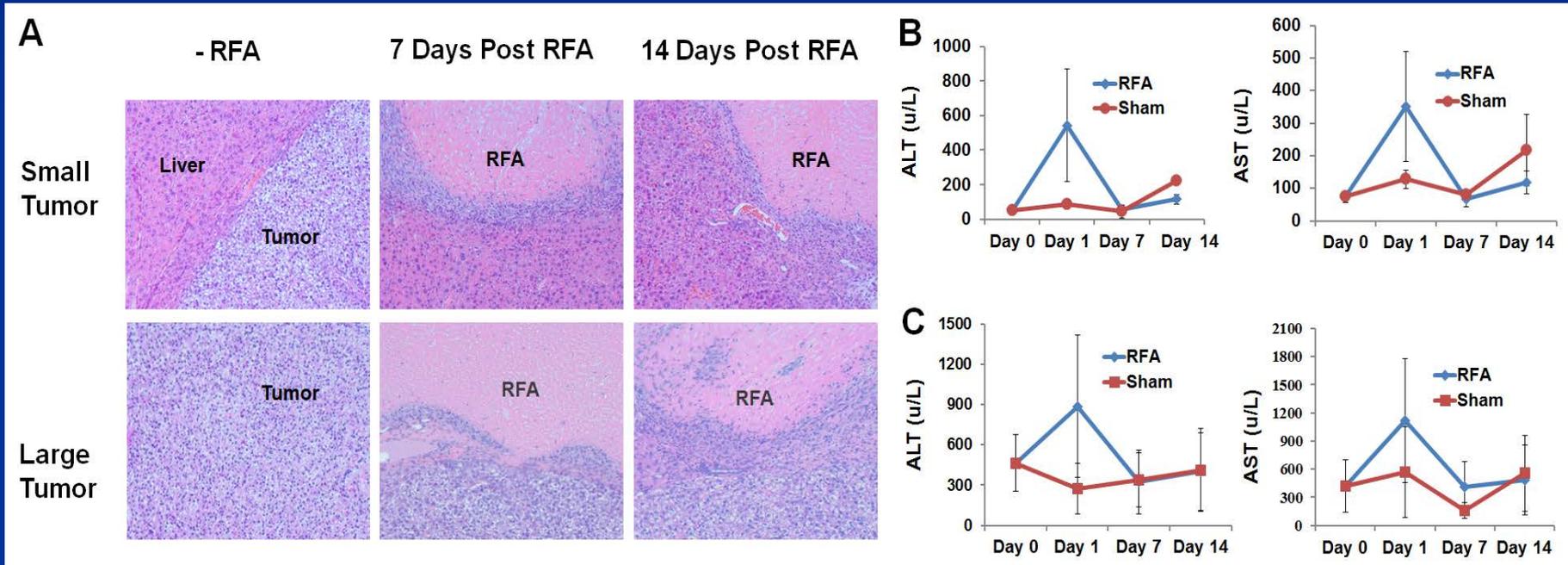
H & E staining of liver tissue and the levels of ALT and AST in the blood of RFA-treated mice



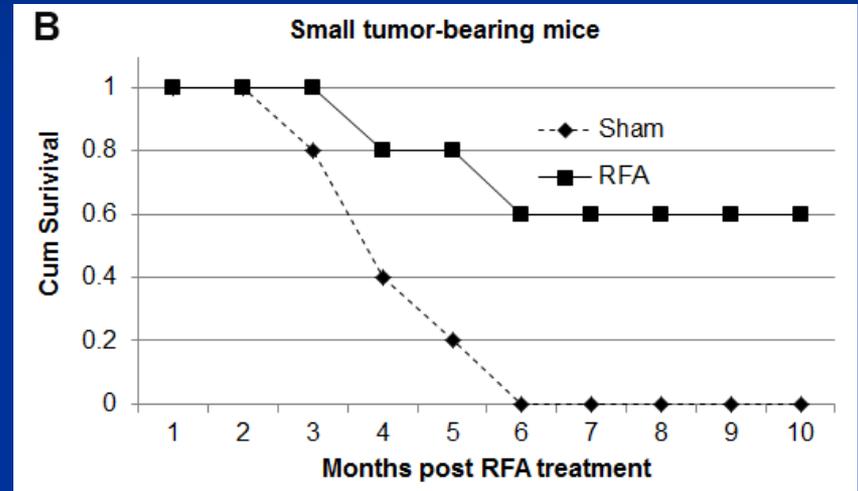
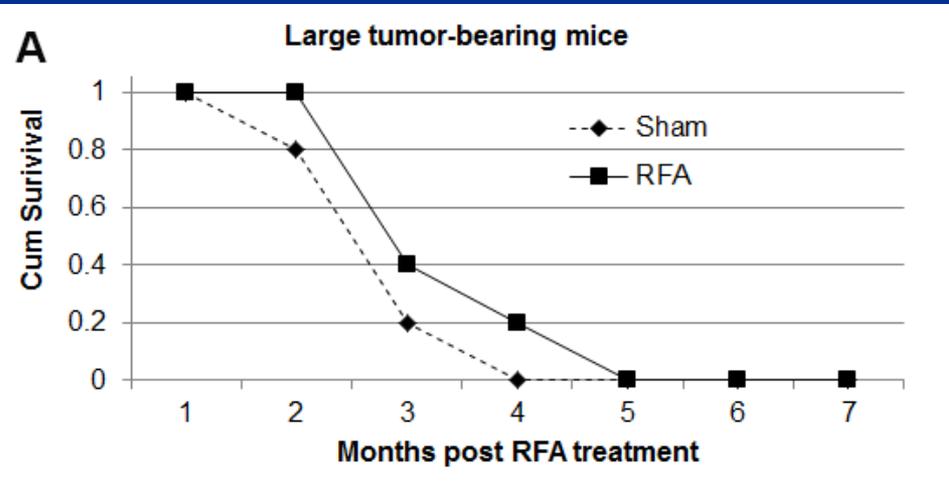
RFA Destroys Small and Large Tumor



Characteristics of RFA-induced Tumor Damage



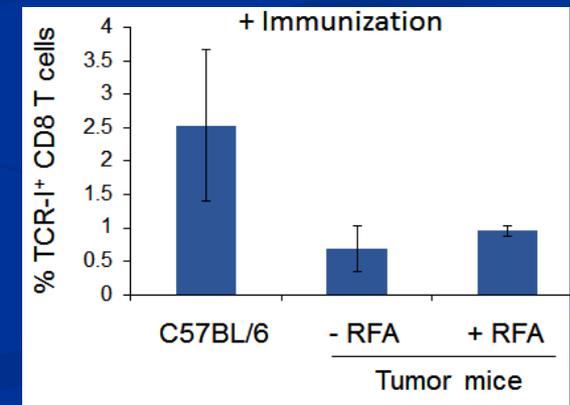
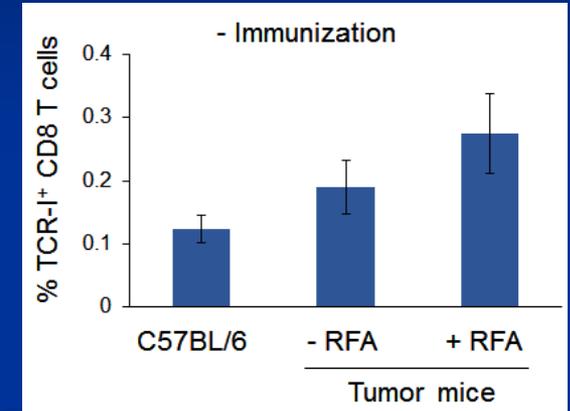
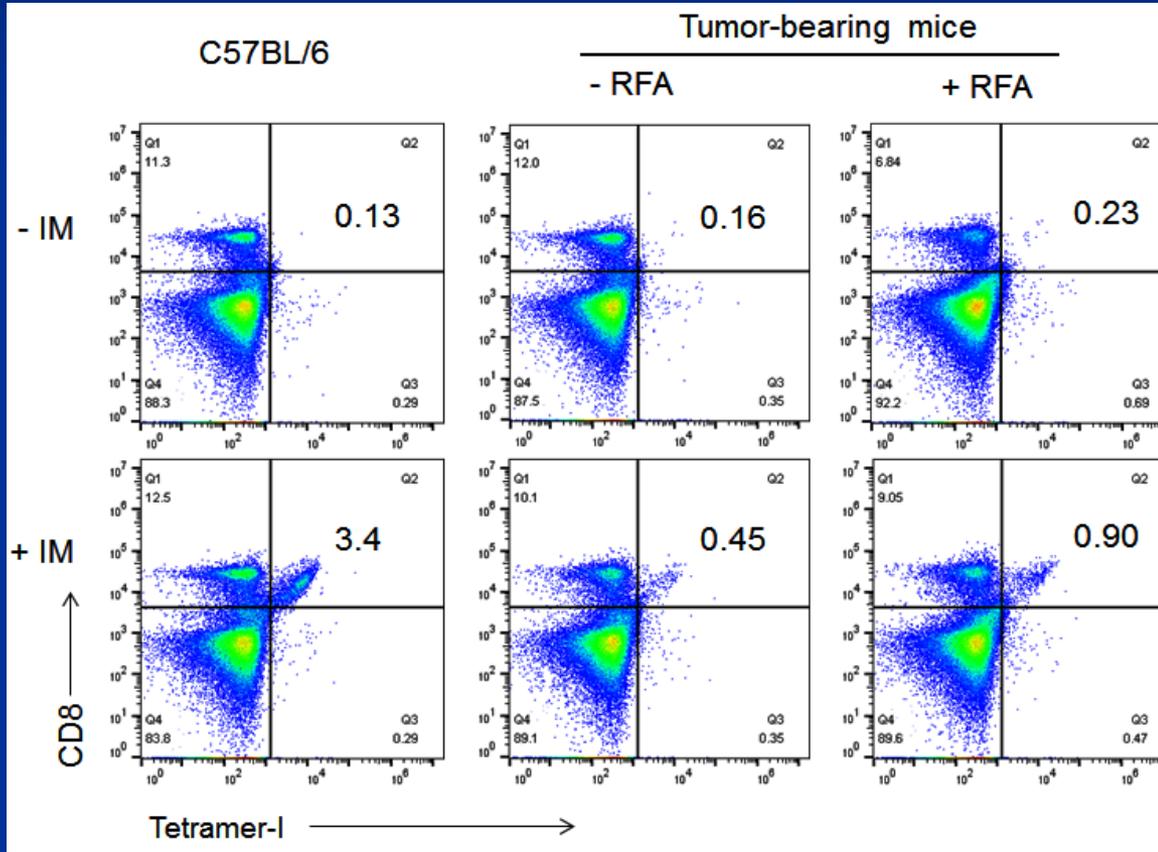
Monotherapeutic efficacy of RFA on small and large tumor-bearing mice



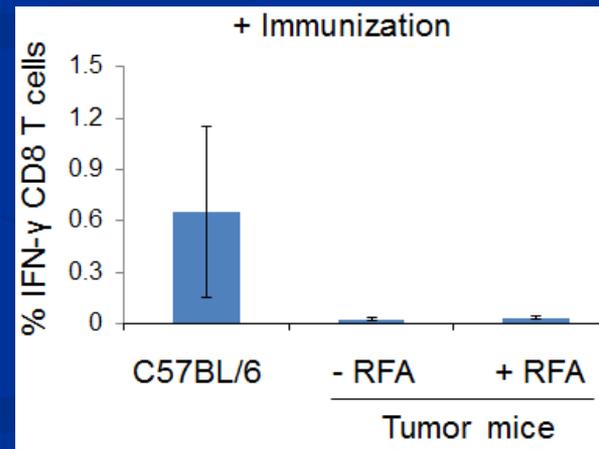
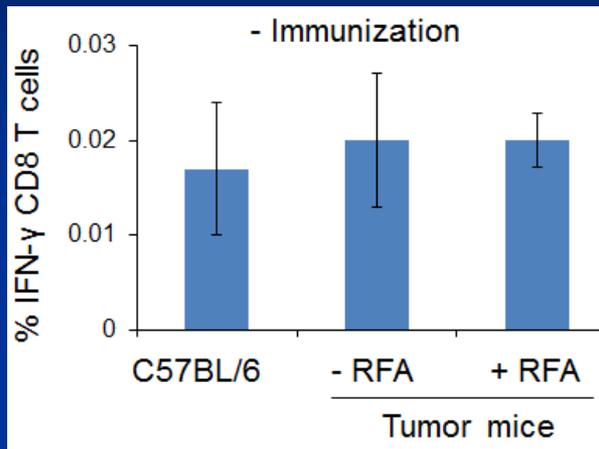
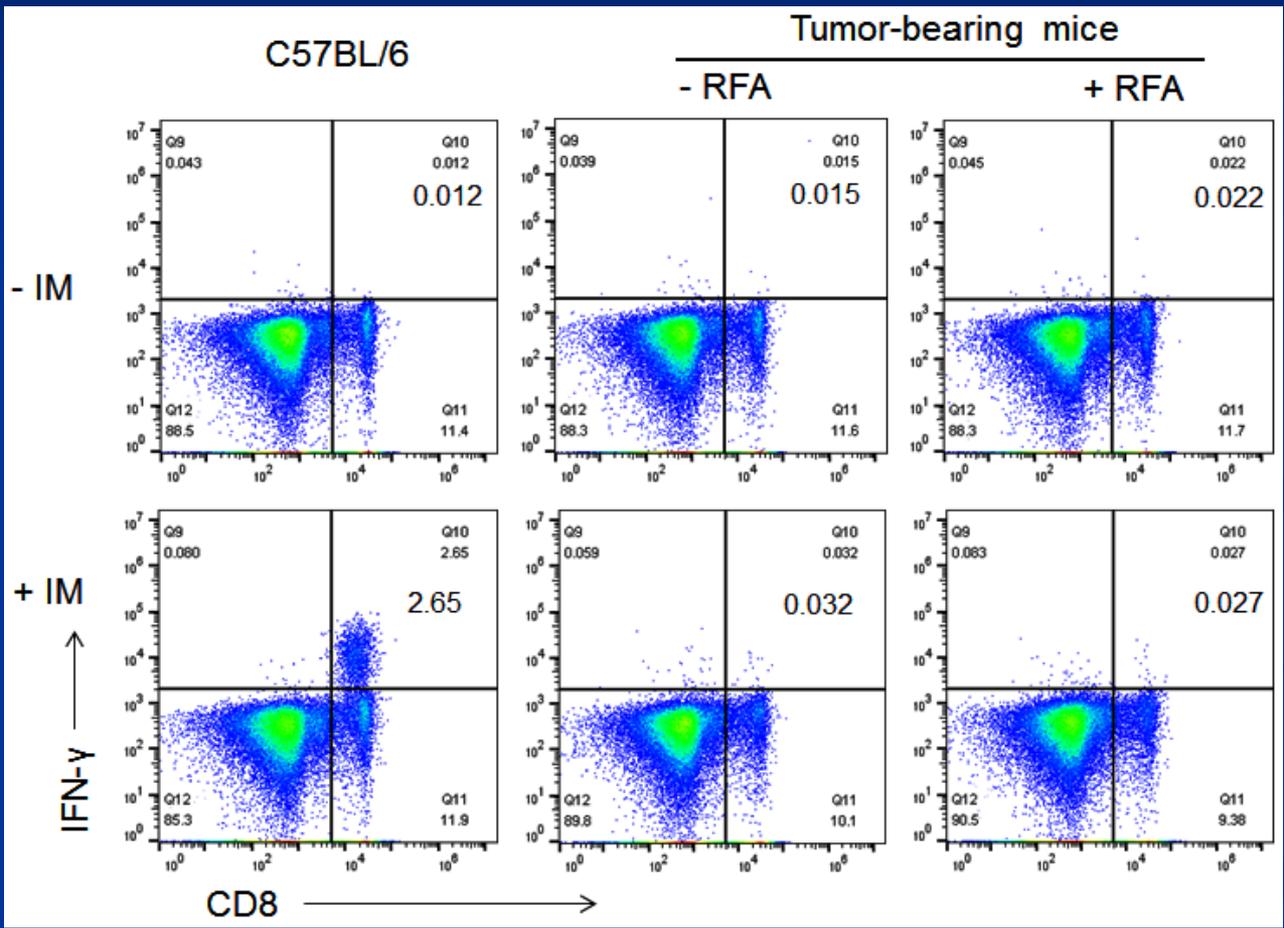
Cancer Biol Ther. 2015;16(12):1812-9. doi: 10.1080/15384047.2015.1095412.

Impact of RFA on Immune Response in Large Tumor- bearing Mice

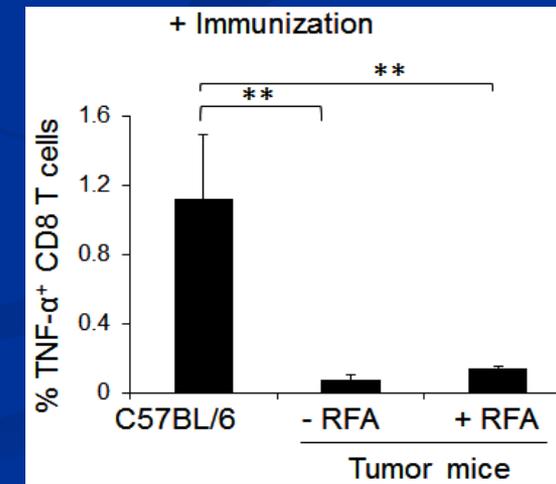
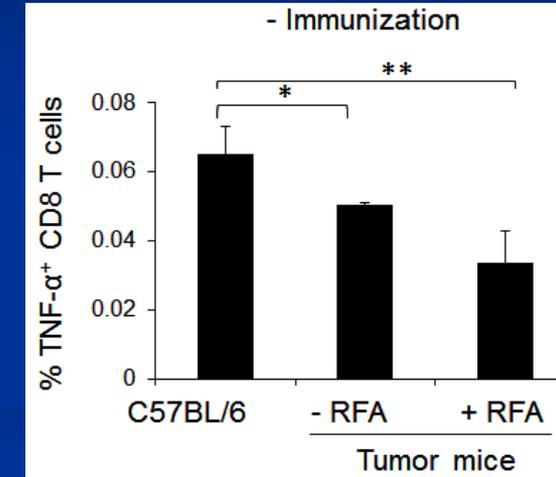
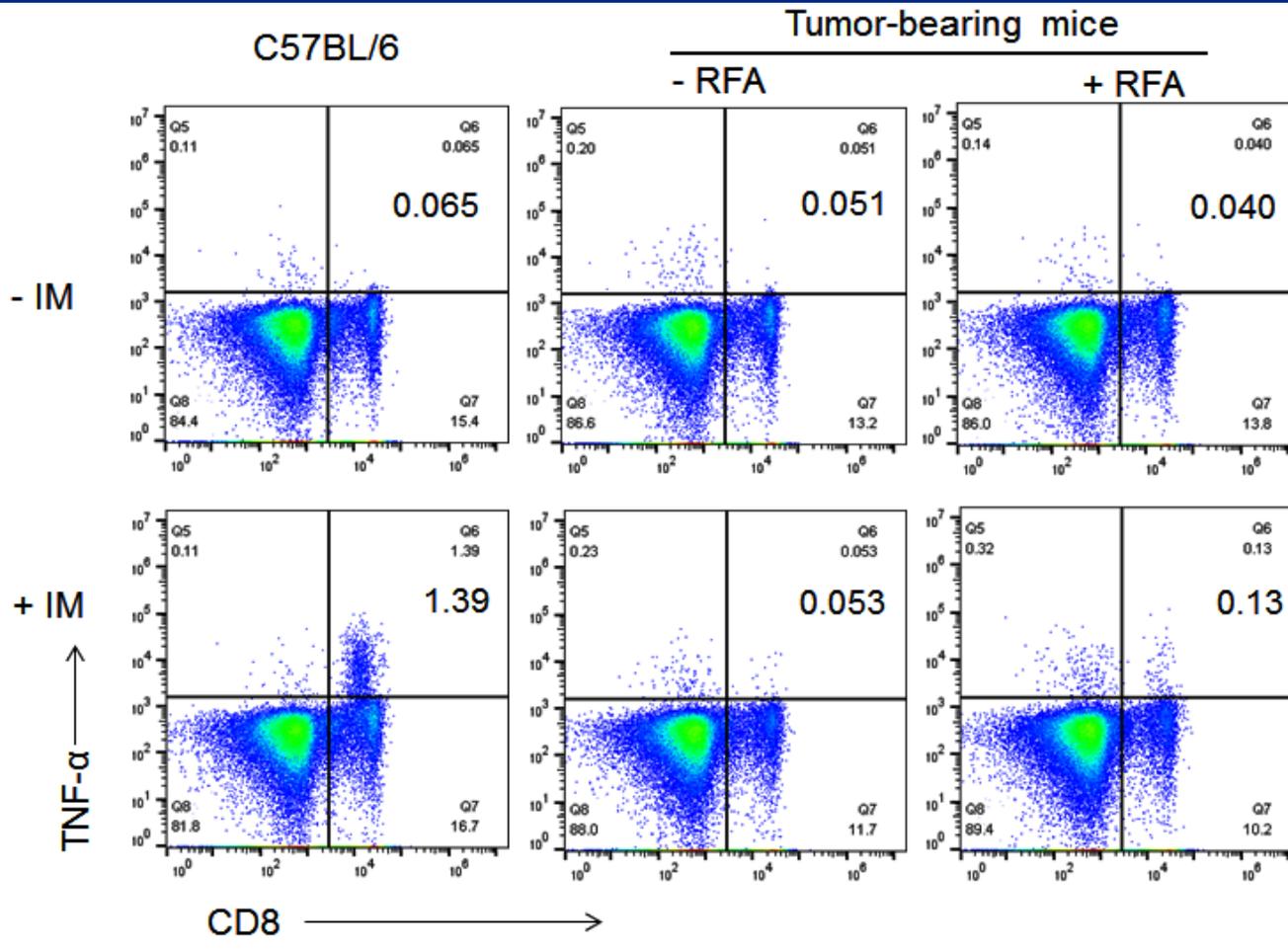
RFA does not significantly increase the frequency of TSA-CD8⁺ T cells



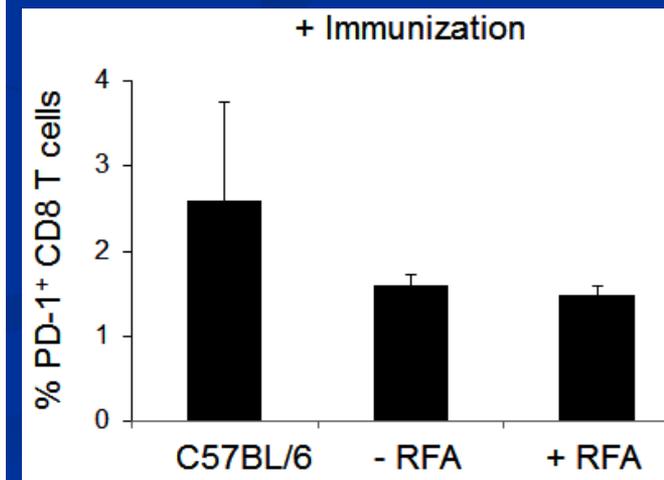
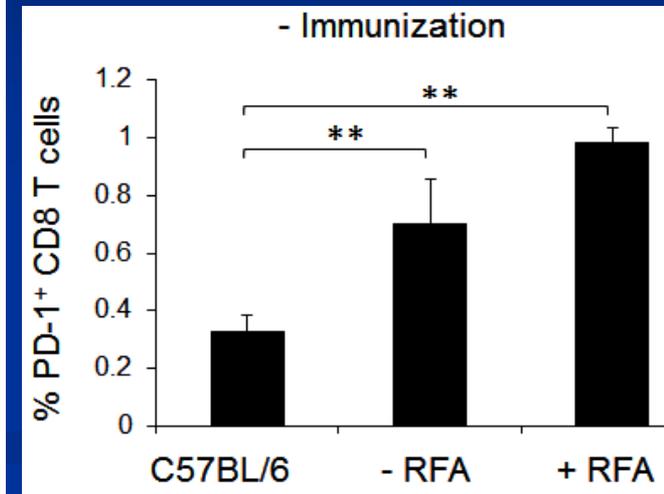
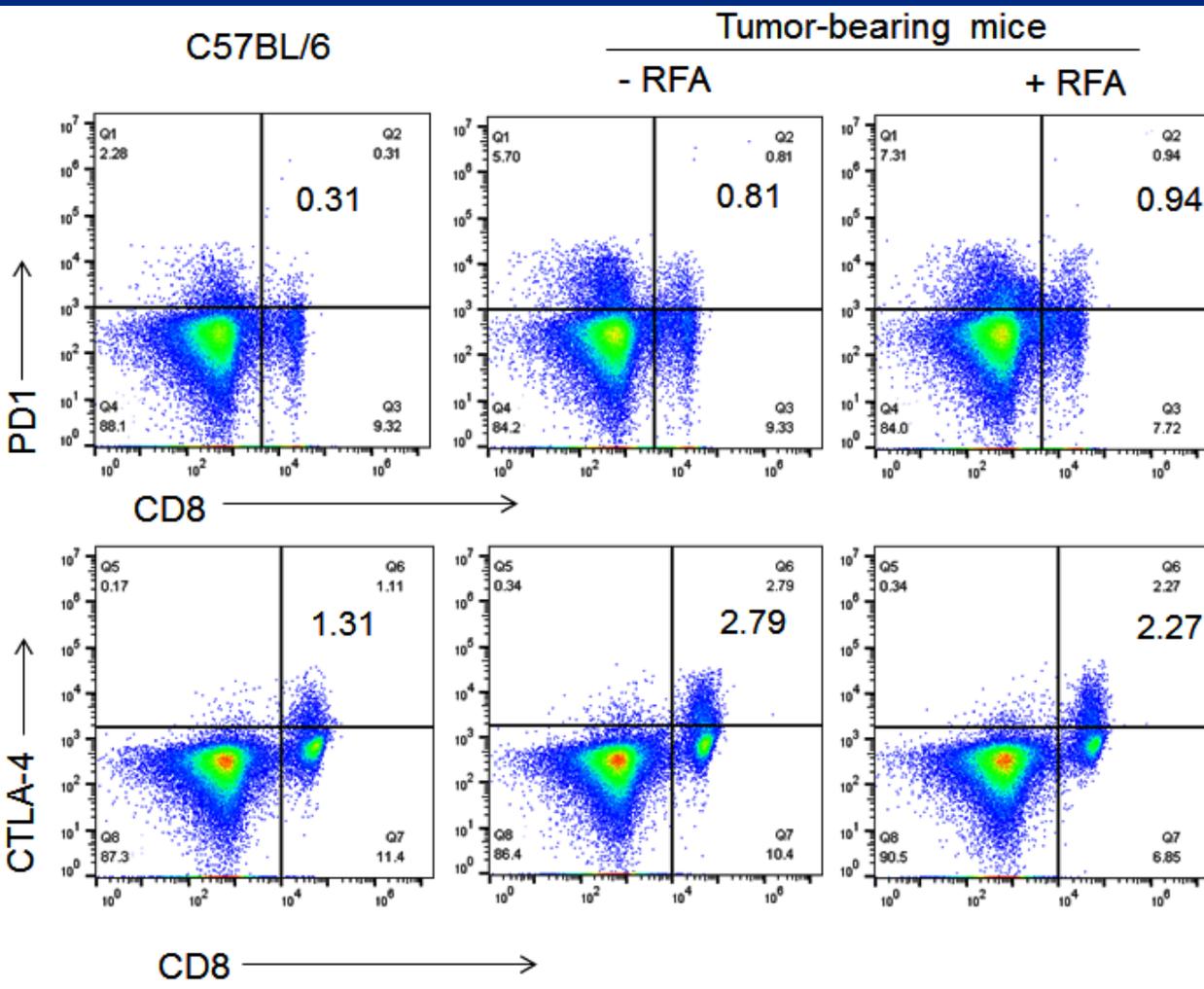
RFA does not increase the frequency of CD8 T cells secreting IFN- γ in response to stimulation with for Tag-epitope-I in tumor-bearing mice



RFA impacts the frequency of CD8 T cells secreting TNF- α in response to stimulation with for Tag-epitope-I in tumor-bearing mice



RFA impacts PD-1 expression in CD8 T cells from tumor-bearing mice



Ongoing RFA-based Immunotherapeutic Strategies

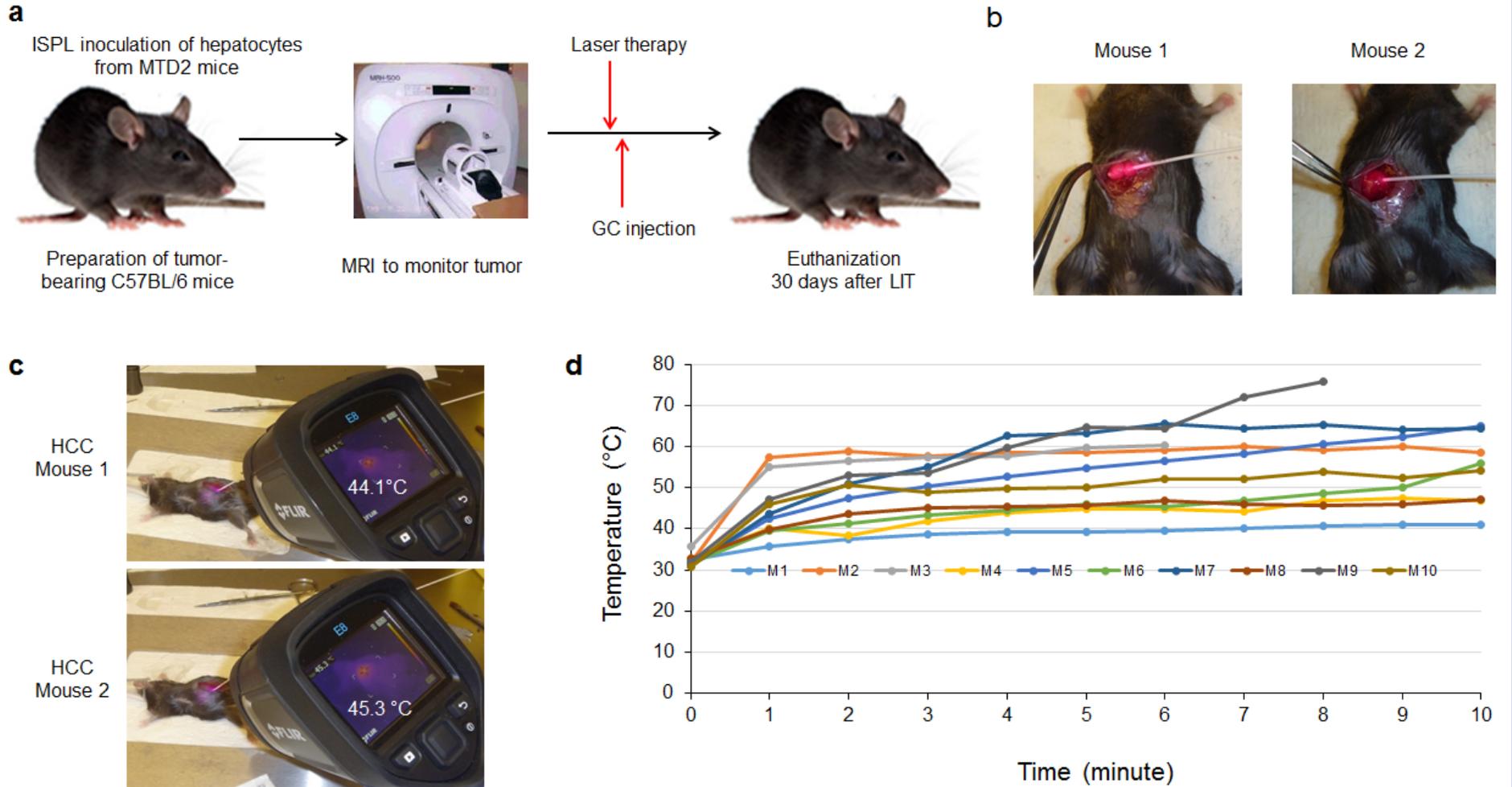
- 1. RFA in combination with Sunitinib for the treatment of HCC**
- 2. RFA in combination with anti-PD-1 antibodies for the treatment of HCC**
- 3. RFA in combination of sunitinib and anti-PD-1 antibodies for the treatment of HCC**

Future Direction:

Laser Ablation in Combination with

Immunotherapies in the Treatment of HCC

Development of Laser Ablation for the Treatment of HCC



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Kevin Staveley-O'Carroll, PhD, MD
ocarrollk@health.missouri.edu