New Tumor Immunotherapy Strategies on the Horizon: Adoptive Cell Therapy for Metastatic Melanoma

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Conflict of Interest

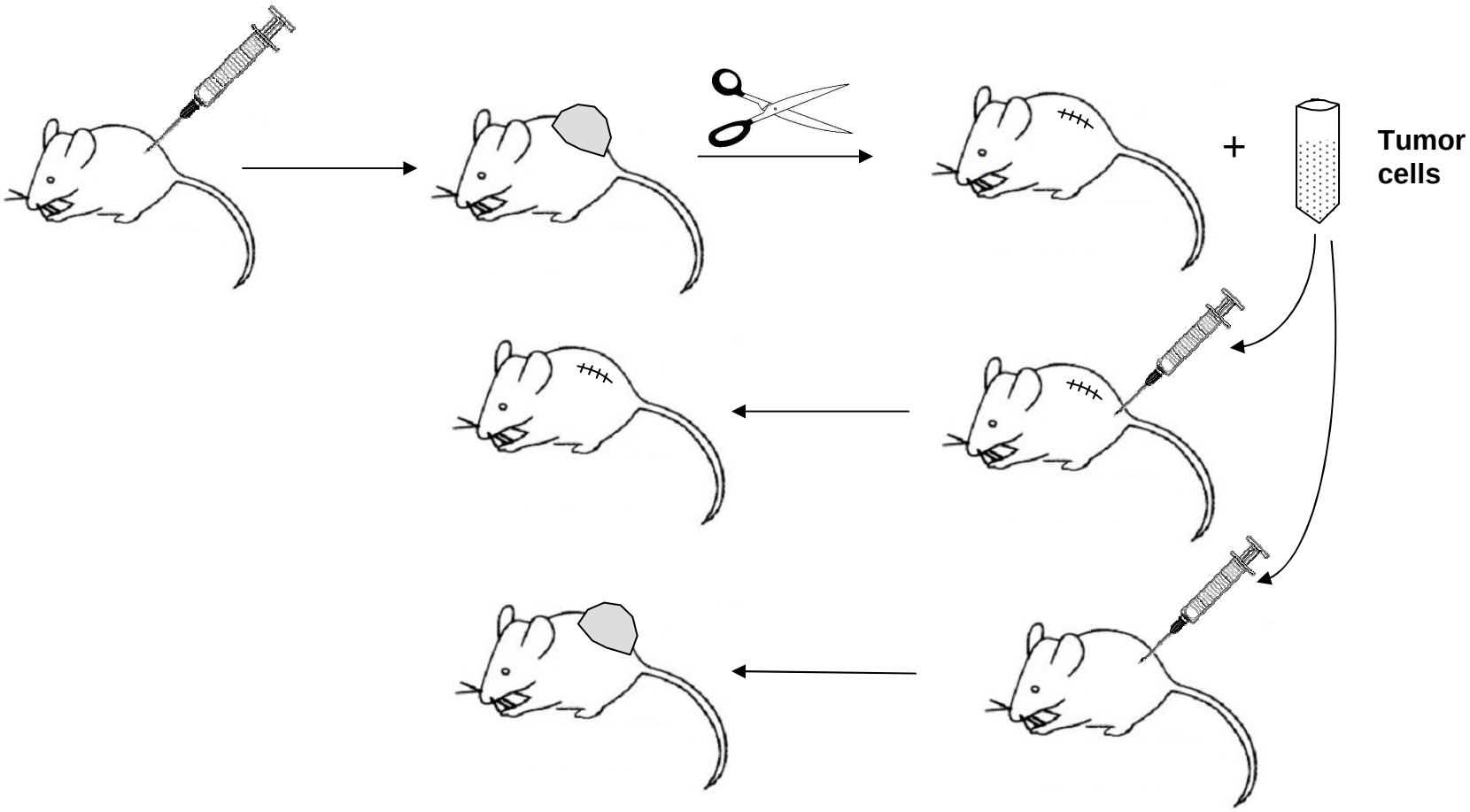
- **None**

Outline

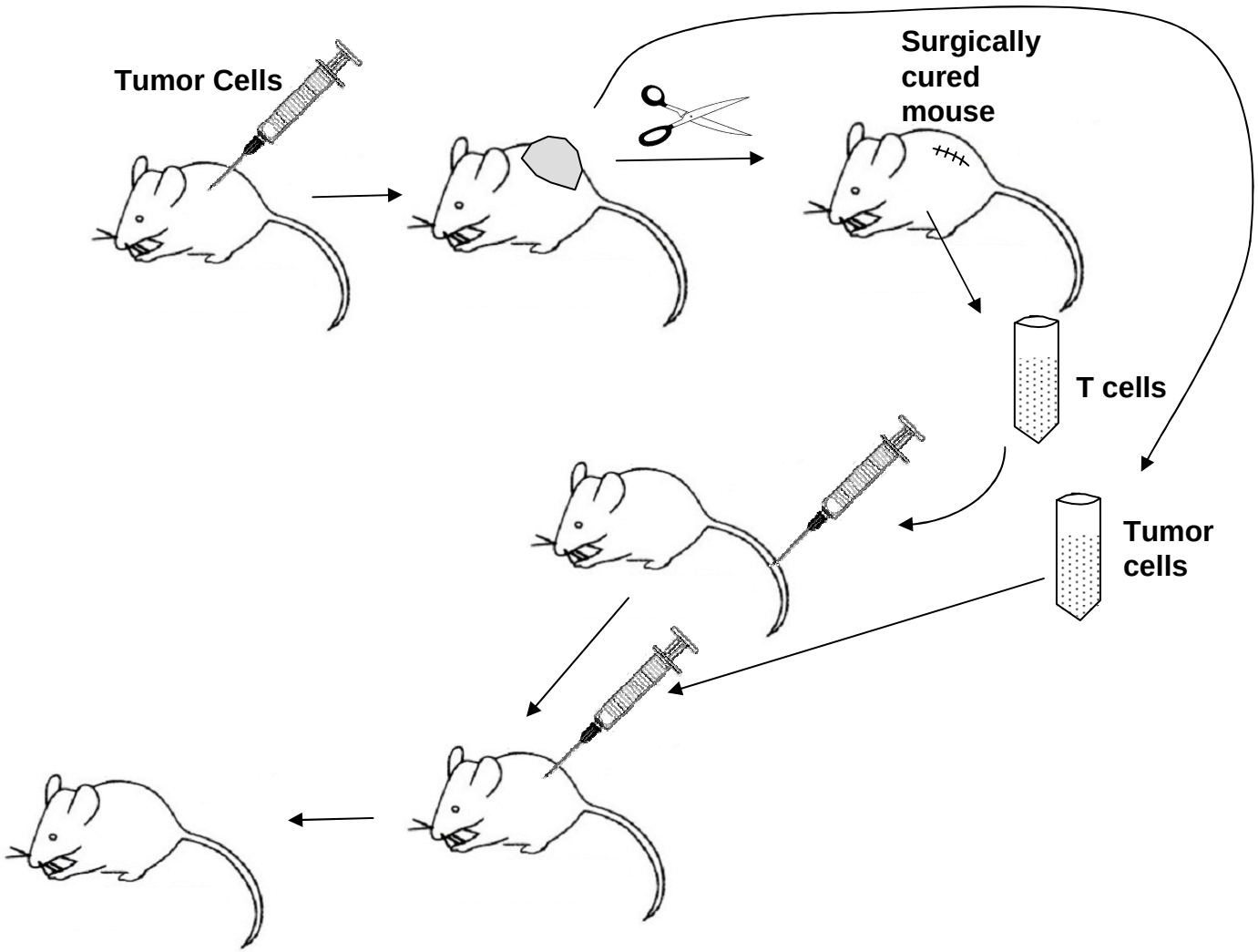
- **Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy: introduction and preliminary clinical trial results**

- **Methods to improve TIL Cell Therapy**
  - **4-1BB agonistic antibody *in vitro***
  - **PD-1 abrogating antibody *in vivo***

The Cure for Cancer (in mice)



Tumor immunity in mice is mediated by T lymphocytes



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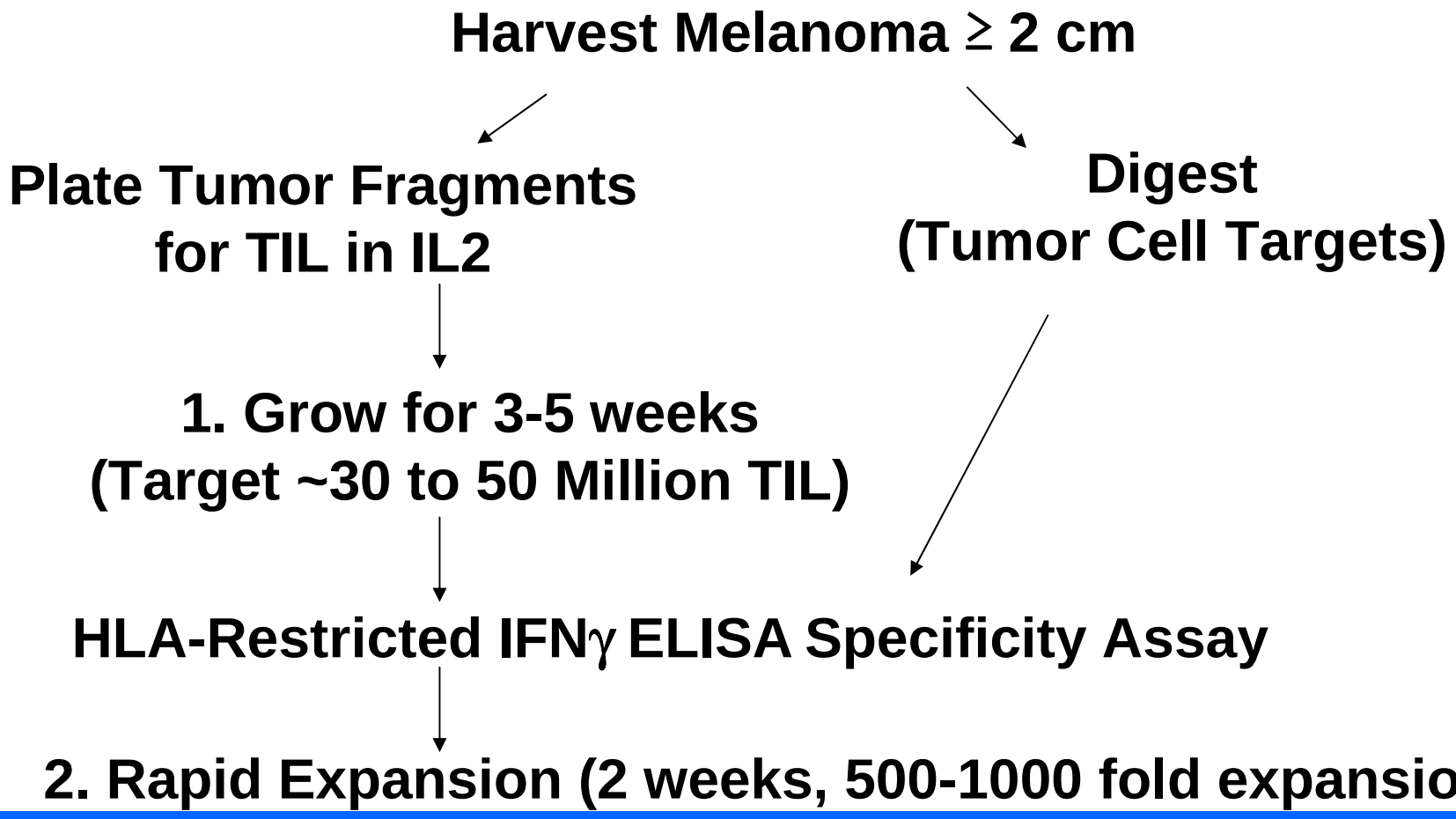
Tumor-Infiltrating Lymphocytes (TIL) Adoptive Cell Therapy

- **TIL can be expanded *in vitro* and adoptively transferred as a treatment for metastatic melanoma**
- **Preparative chemotherapy and post transfer high dose bolus IL-2**
- **56% Objective Response Rate (treated patients)**
  22% Complete Response Rate (treated patients)
  CRs: 93% 5 year survival *unrivaled results

  Rosenberg, et al. CCR 2011
- **Expensive, technically challenging, toxic**

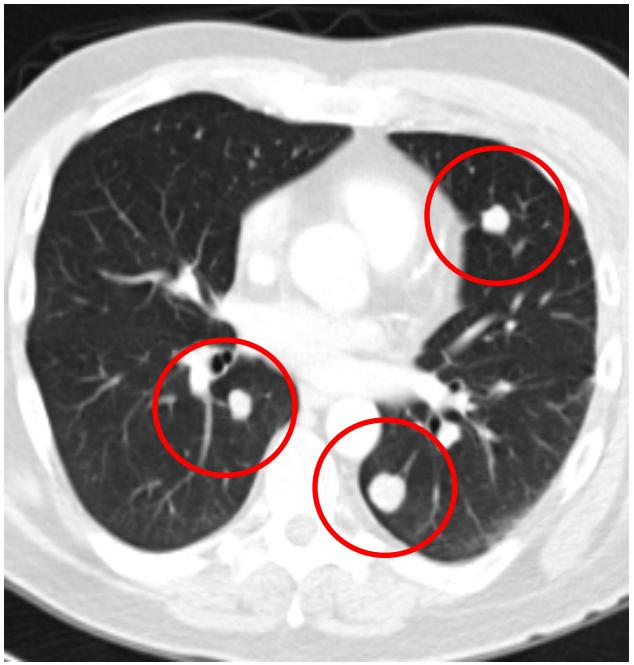
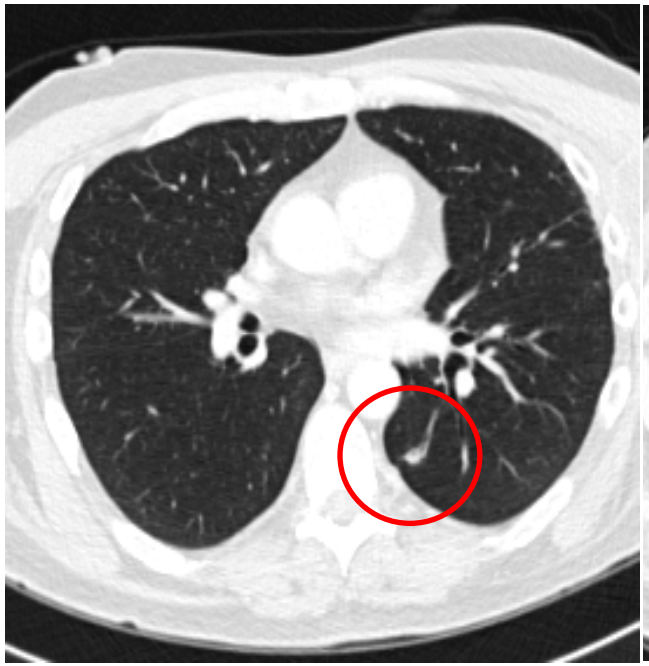
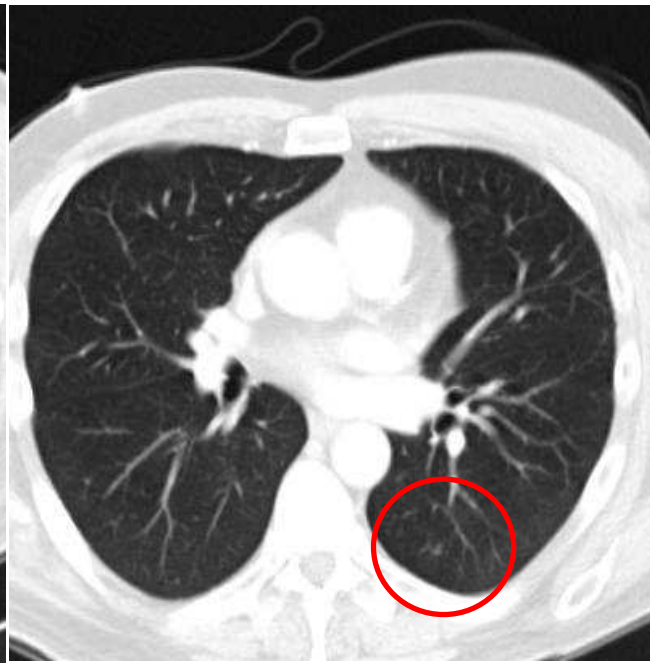
Moffitt's TIL Trial for Unresectable Melanoma



Rapid Expansion

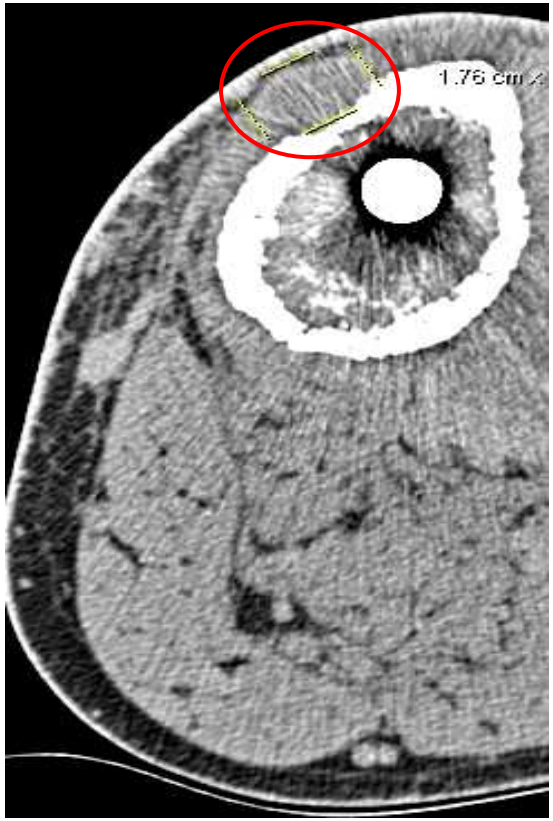
30-60 bags required

Patient Clinical Result

Pre TIL	2 MONTHS POST	24 MONTHS POST
		
02/03/11 1.6 x 1.5 cm	04/07/11 0.8 x 0.6 cm	02/07/13 0 cm

Pretibial Melanoma Metastasis

PRE

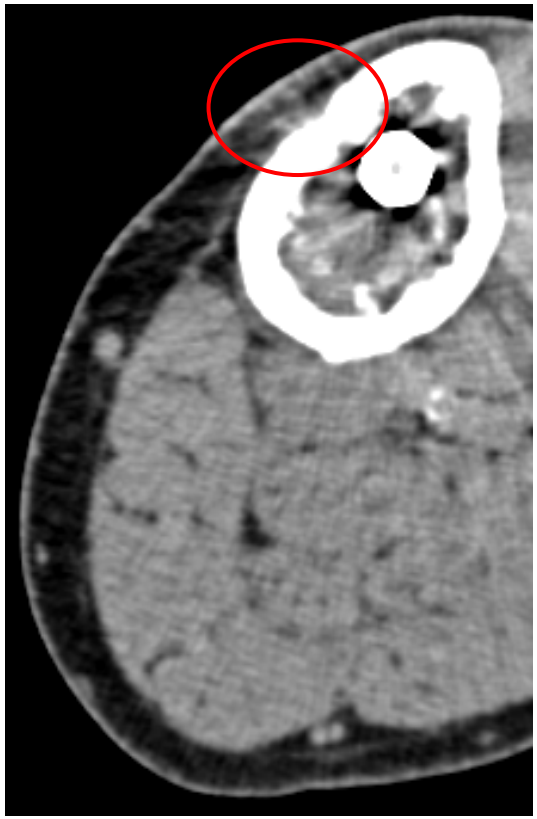


1.8 x 1.1 cm

1.5 MONTHS POST*

1.5 x 0.9 cm

12 MONTHS POST

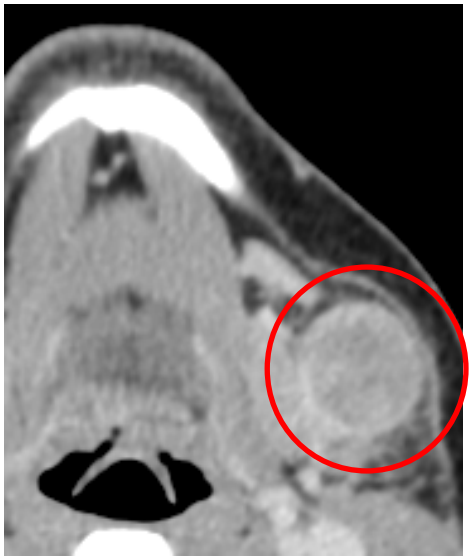


0 x 0 cm

*** Of note, the patient came off pain medications previously required for leg pain.**

Lower Jaw Metastasis

PRE



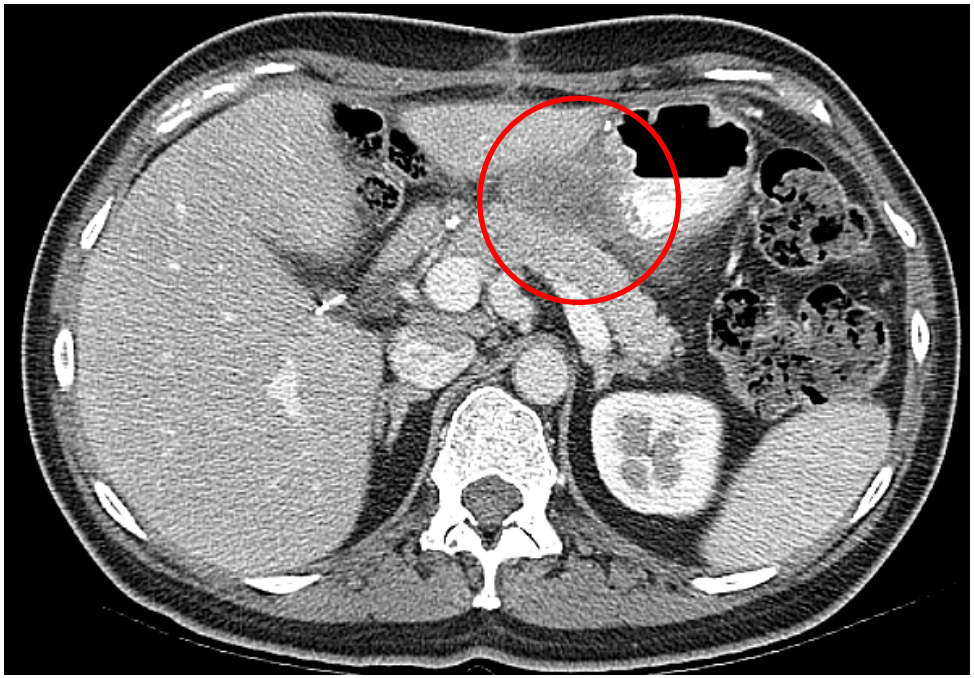
2.4 x 2.2 cm

4 MONTHS POST

0.9 x 0.5 cm

Visceral Metastasis

PRE

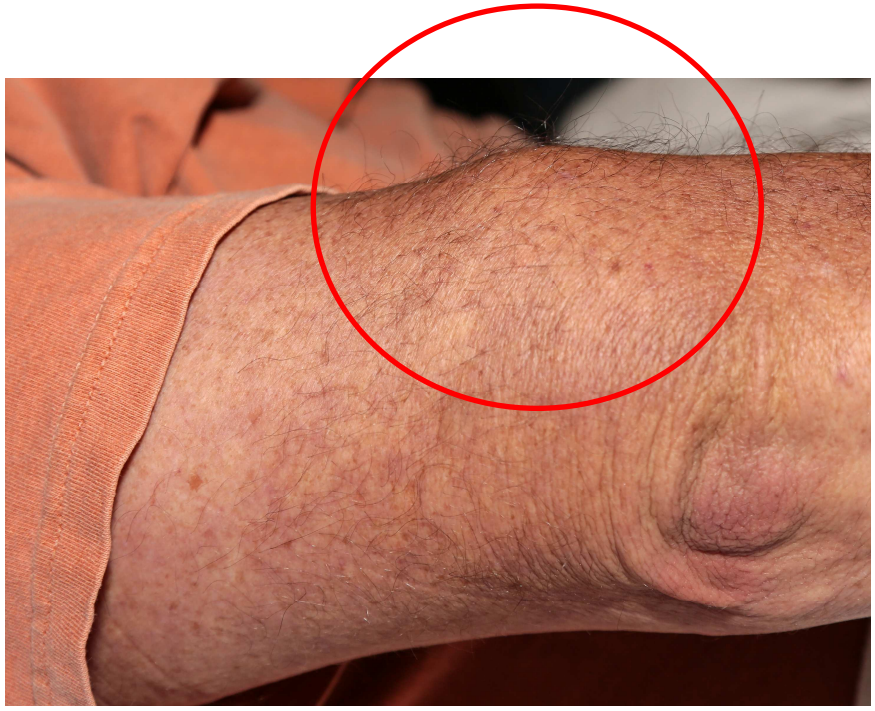


2.8 X 6 cm

11 MONTHS POST

0 X 0 cm

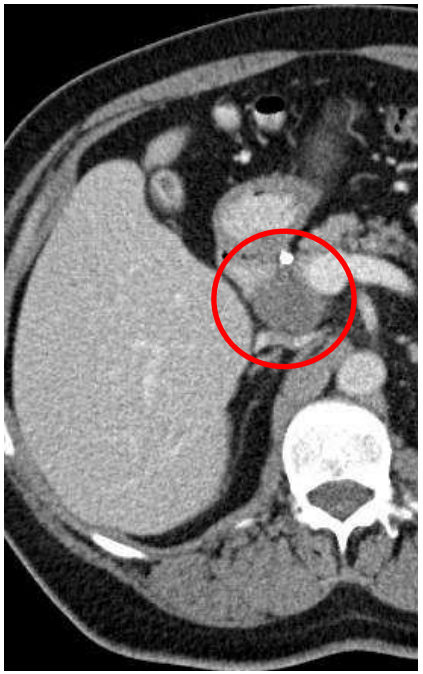
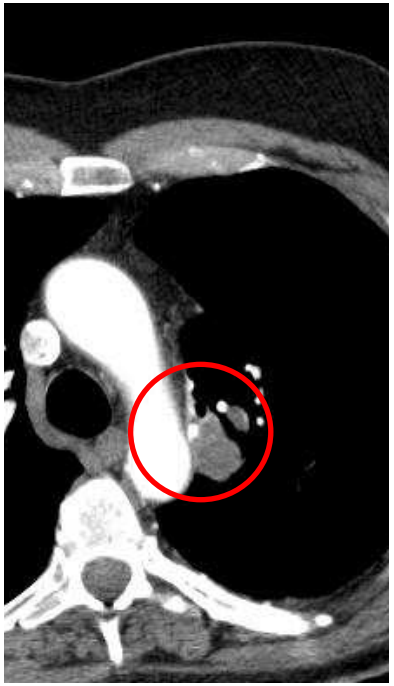
Symptomatic Arm Lesion



Pre

8 Days Post

Example of Prolonged Stable Disease

Pre-TIL	27 months Post	Pre-TIL	27 months Post
			
12/13/2010 2.1 x 3.0 cm	3/26/2013 2.0 x 1.5 cm	12/13/2010 2.6 x 1.7 cm	3/26/2013 1.7 x 1.3 cm

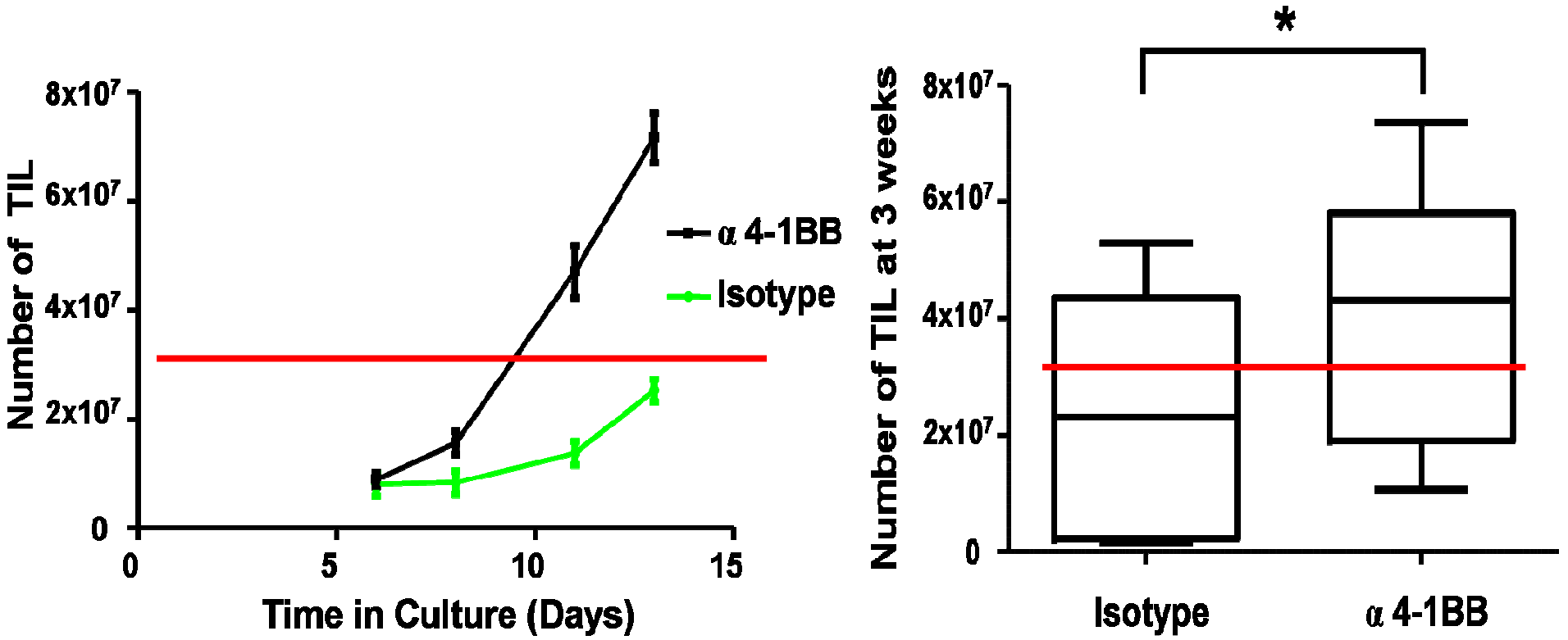
Moffitt ACT Clinical Results Summary

- 13 of 20 (65%) enrolled patients were successfully treated
- 4 (20%) enrolled patients dropped out prior to treatment due to progression
- 3 (15%) dropped out due to other reasons
- 3 (23%) had Complete Responses
- 6 (46%): Progression-Free Survival > 1 yr

Current direction: Immunomodulatory antibodies to accelerate TIL growth and improve anti-tumor efficacy

Pilon-Thomas et al., *J Immunother* 2012

4-1BB Agonistic Antibody Increases TIL Expansion *in vitro*



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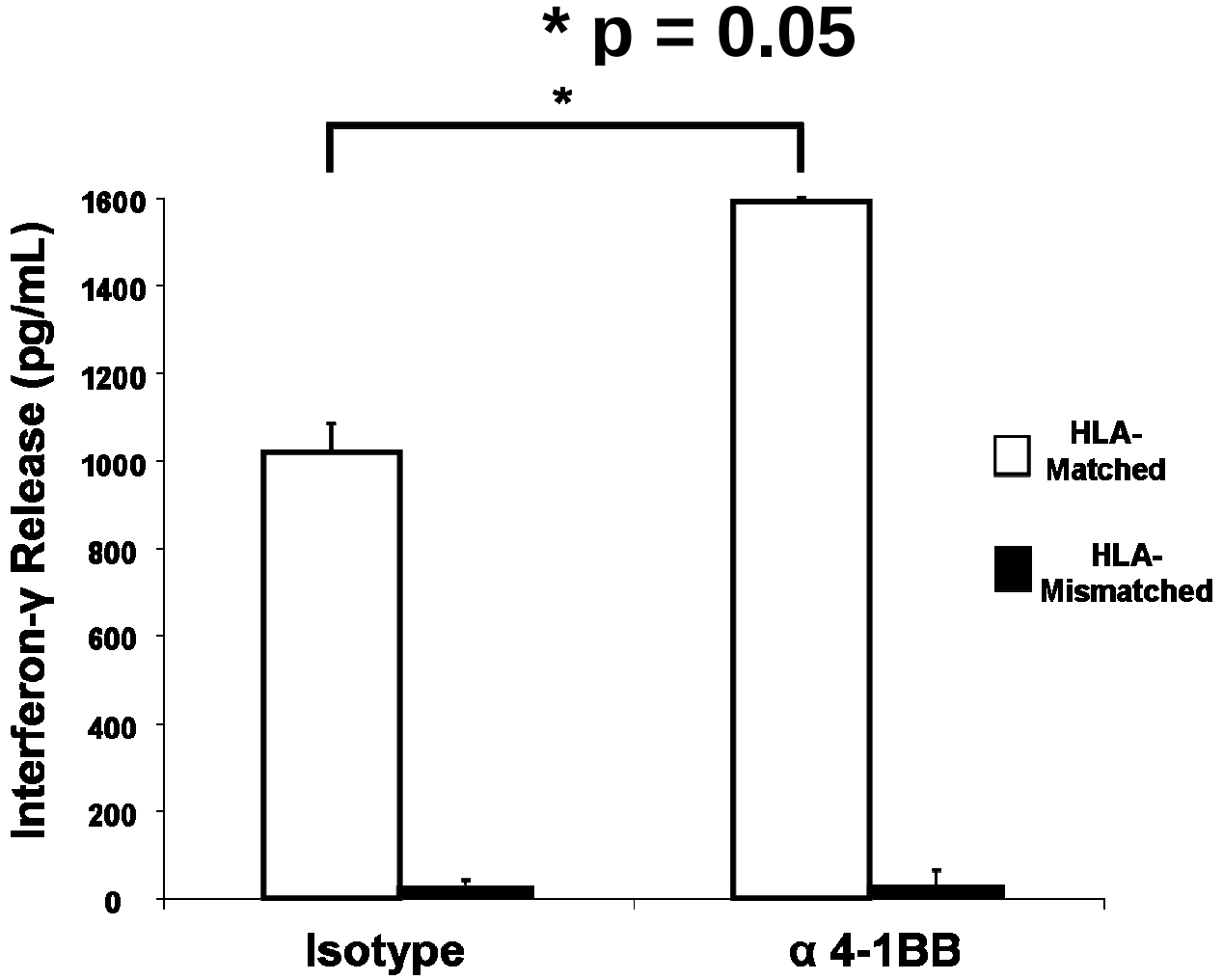
4-1BB Ab Enhances HLA-Restricted, Tumor-Specific Cytokine Release



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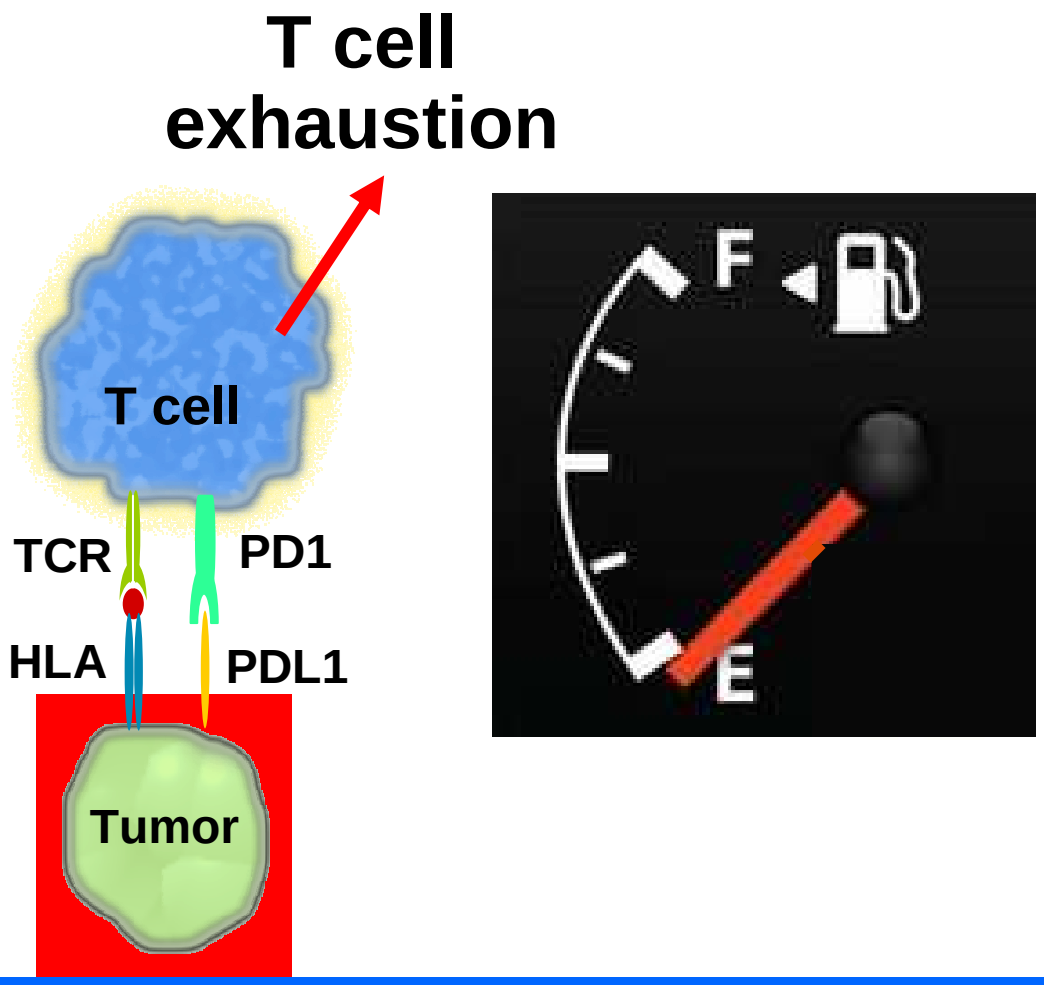
4-1bb Agonistic Antibody Summary

- **Enhances TIL numbers**
- **Enhances CD8+ effector T cell phenotype**
- **Enhances tumor-induced IFN-γ production**

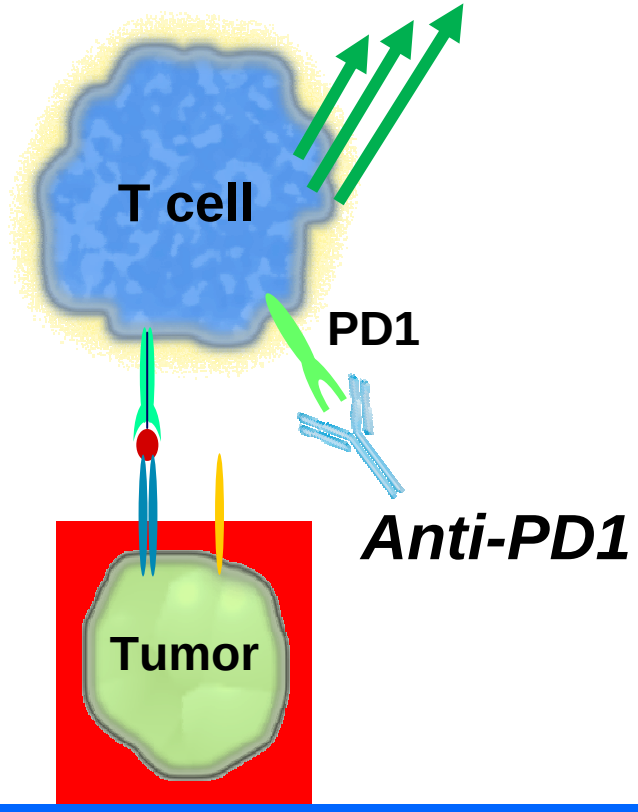
PD1 Blockade: Reviving Exhausted T Cells



PD1 Blockade: Reviving Exhausted T Cells

T cell

T cell reactivation

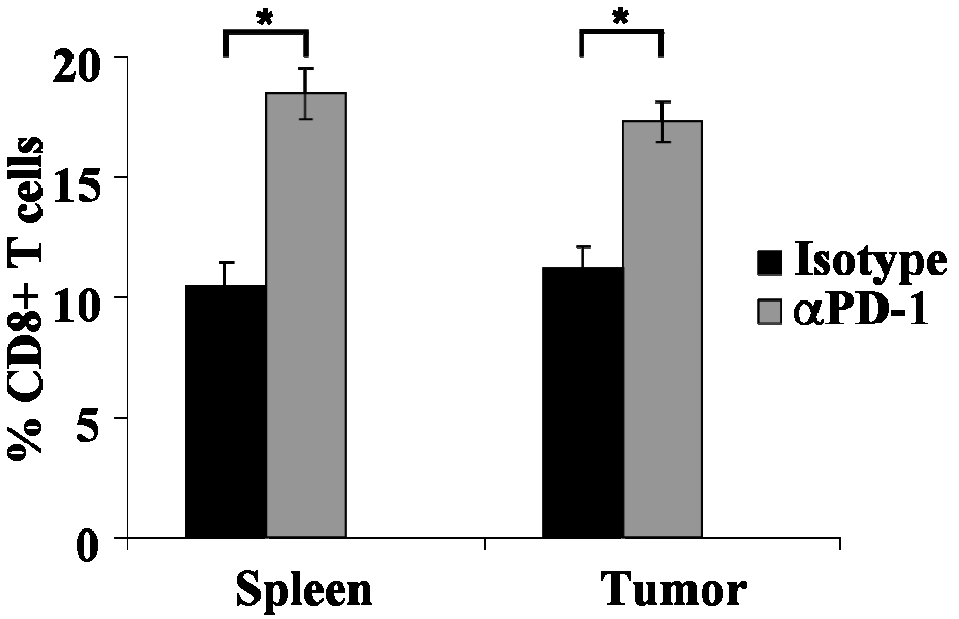


Aim

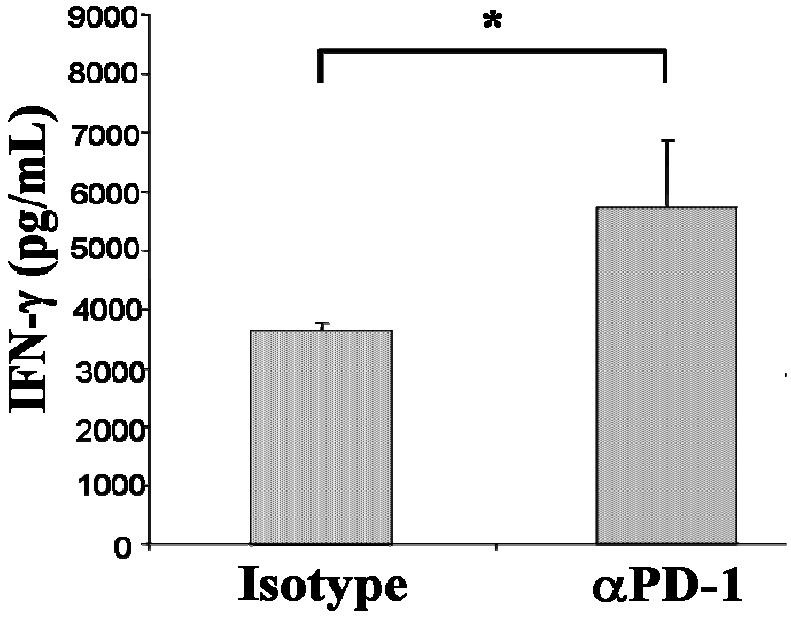
- **To determine if a PD-1 abrogating antibody *in vivo* prior to tumor harvest may increase resulting CD8+ TIL and tumor-specific IFN-γ production**

PD-1 Blockade *in vivo* Prior to TIL Harvest Augments Adoptive Cell Therapy in a Murine B16 Model

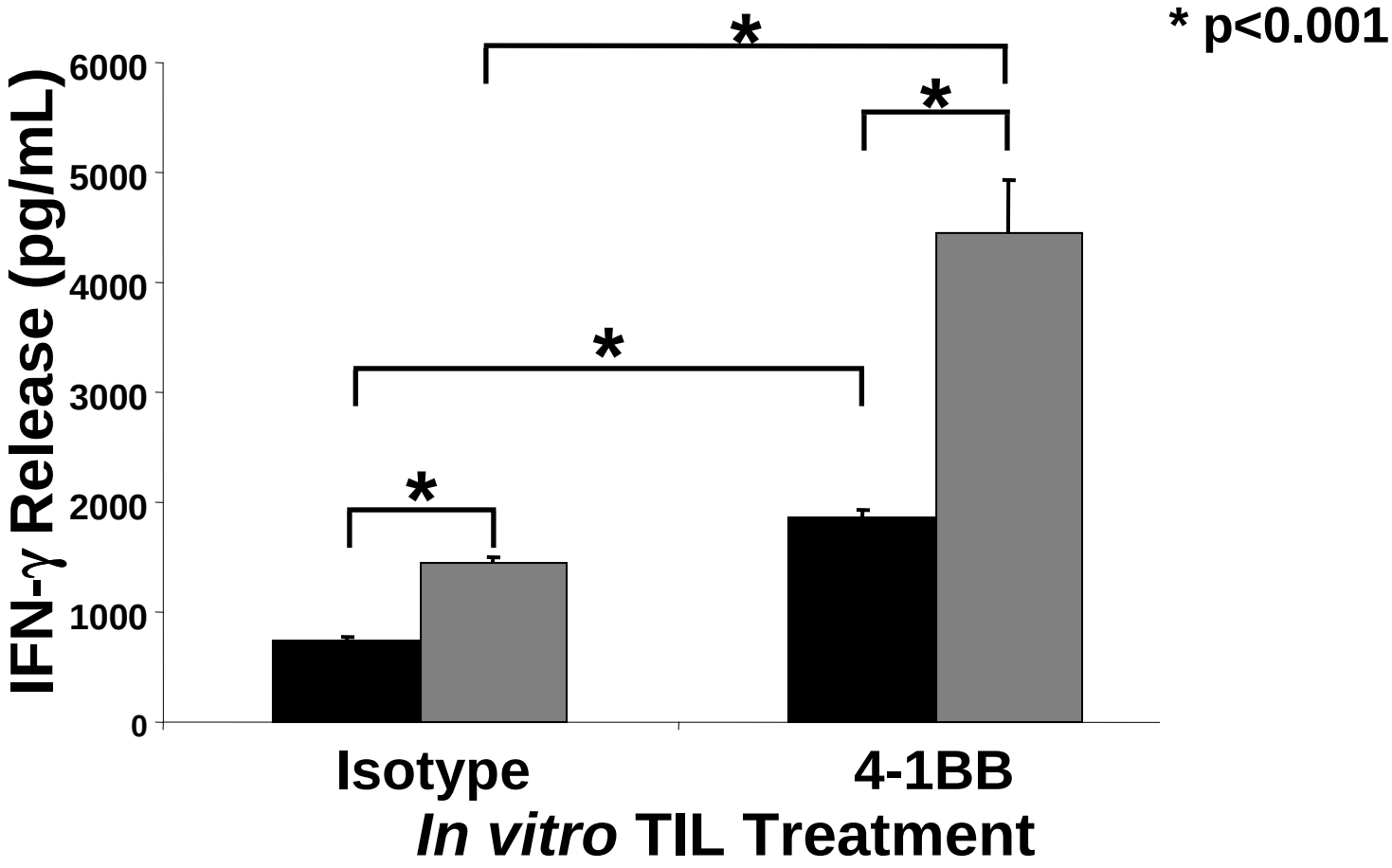
* p < 0.05



* p < 0.05



Combination of αPD-1 *in vivo* and 4-1BB *in vitro* Enhances Anti-Melanoma Reactivity



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