

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

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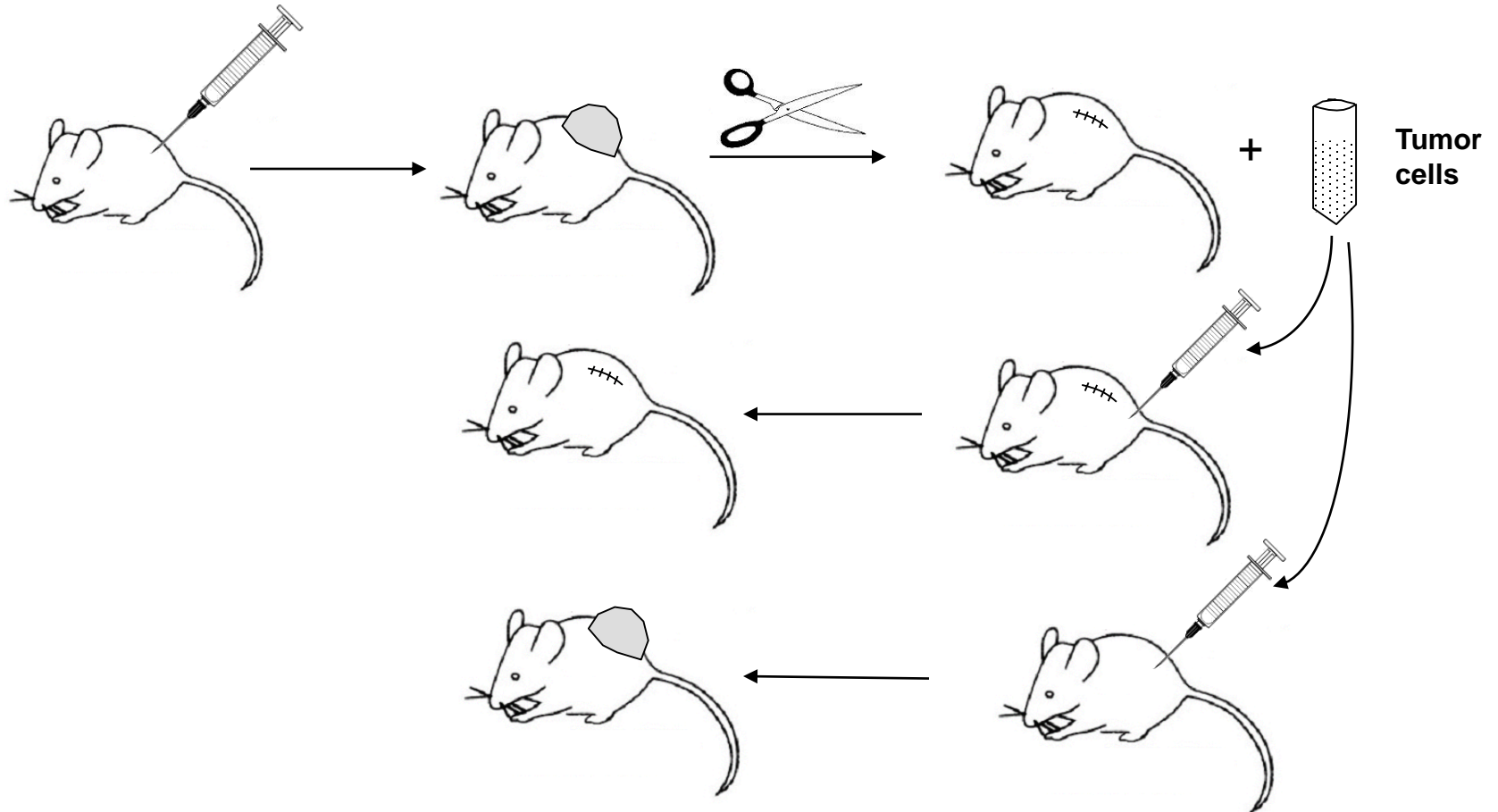
Conflict of Interest

- **None**

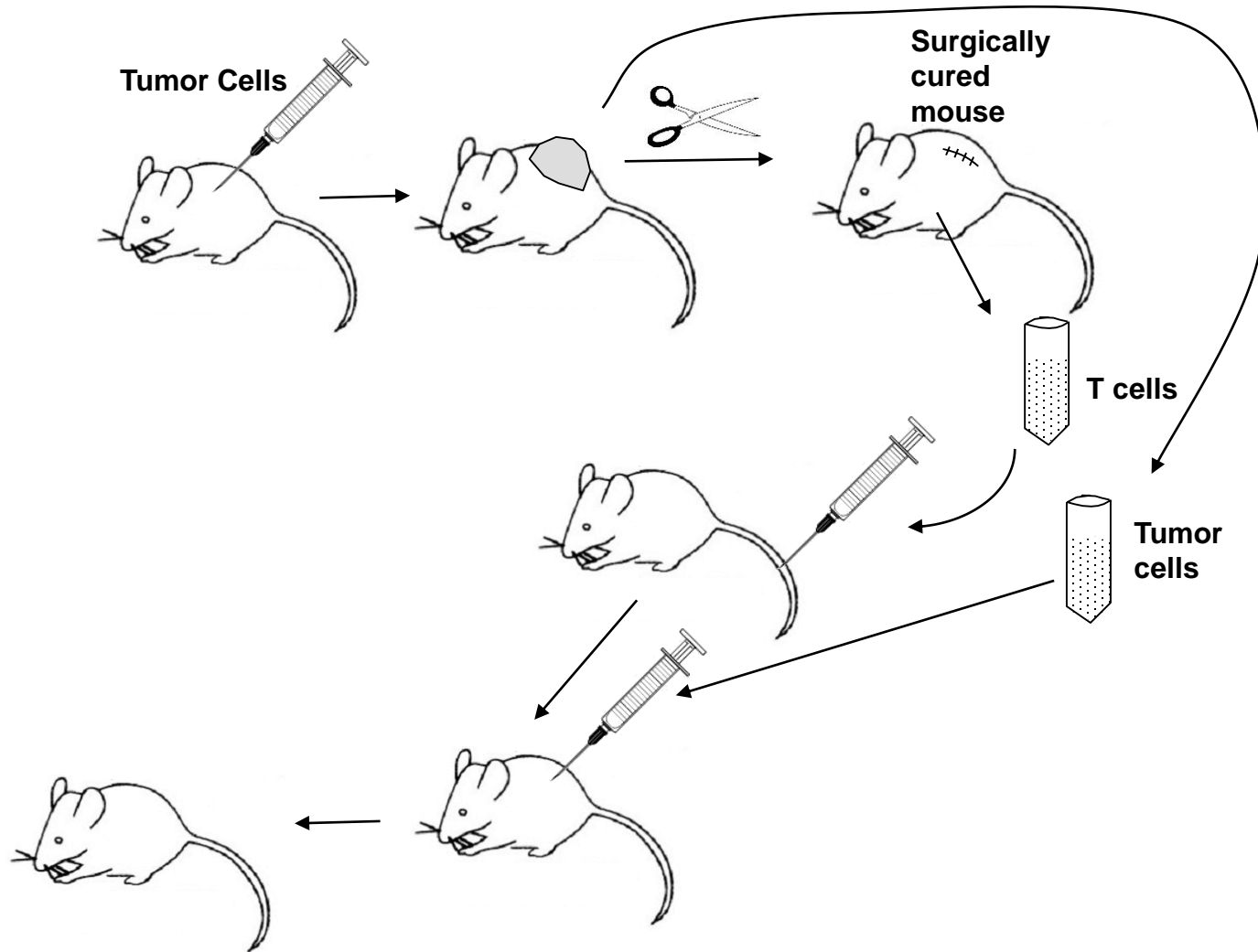
Outline

- **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

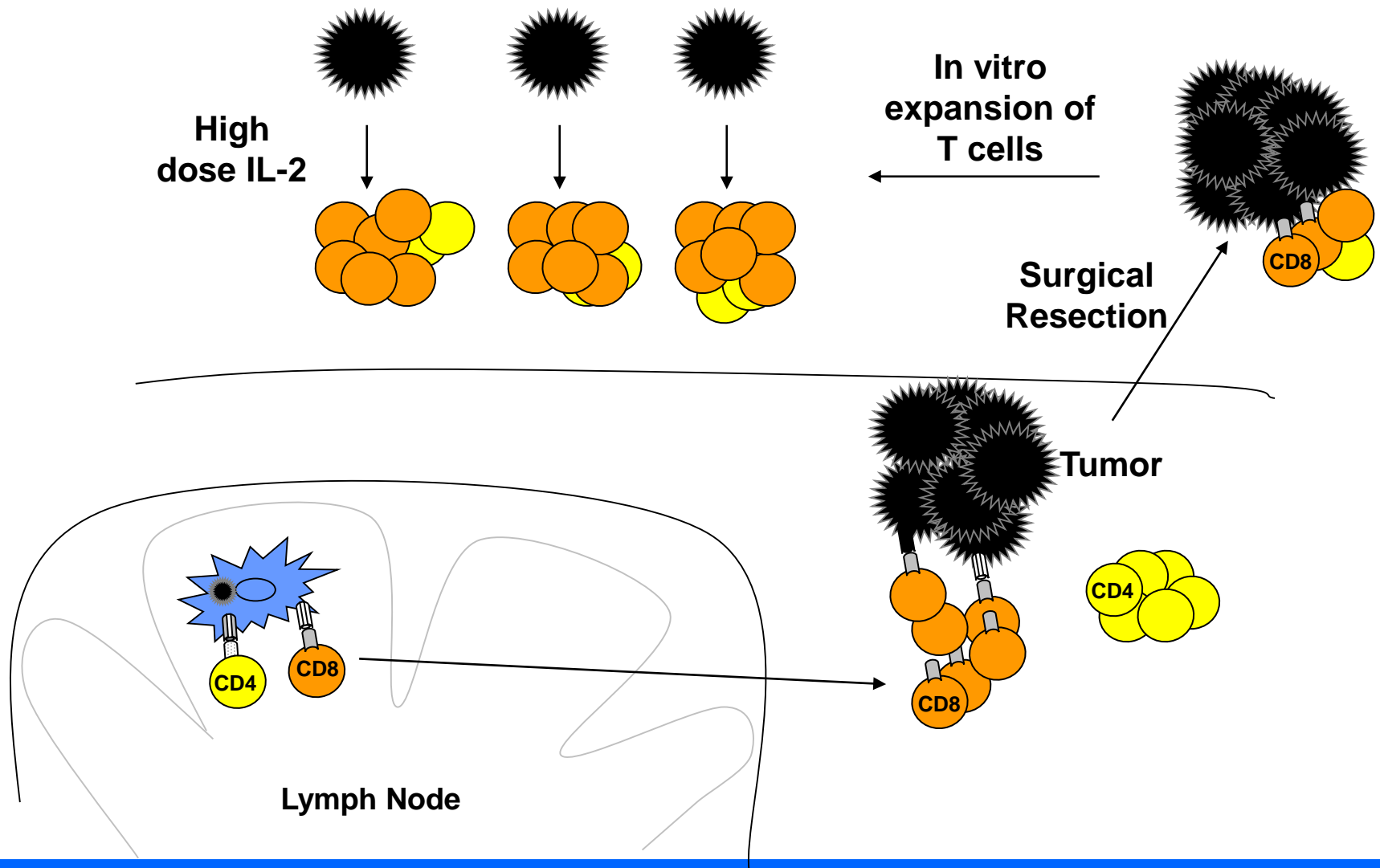


Tumor-Infiltrating Lymphocytes (TIL) Adoptive Cell Therapy

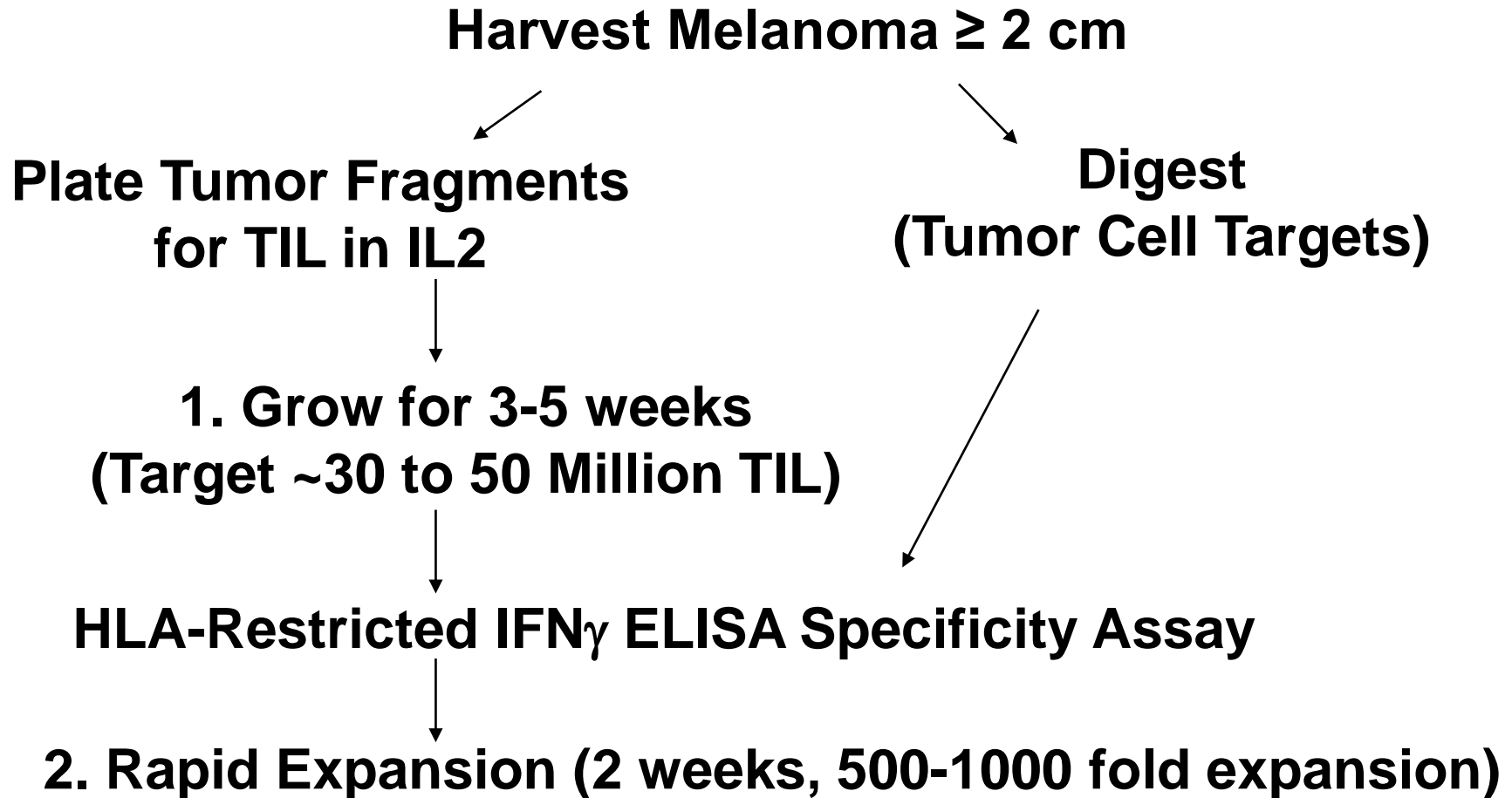
- **TIL can be expanded *in vitro* and adoptively transferred as a treatment for metastatic melanoma**
- **Preparative chemotherapy and post transfer high dose bolus IL-2**
- **56% Objective Response Rate (treated patients)
22% Complete Response Rate (treated patients)
CRs: 93% 5 year survival *unrivaled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

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

TIL-based Immunotherapy Schematic



Moffitt's TIL Trial for Unresectable Melanoma



Rapid Expansion



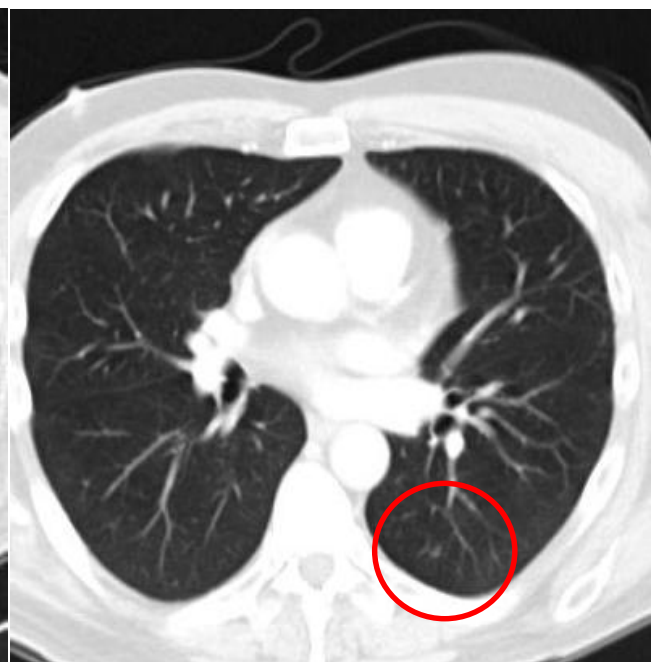
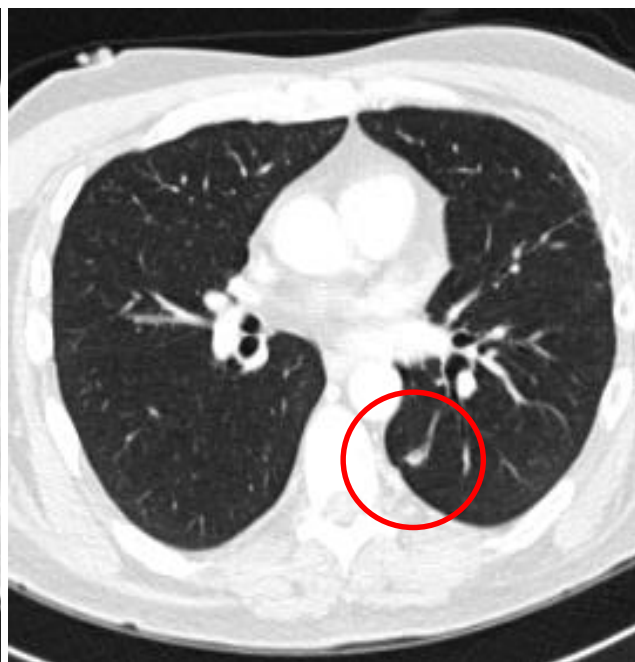
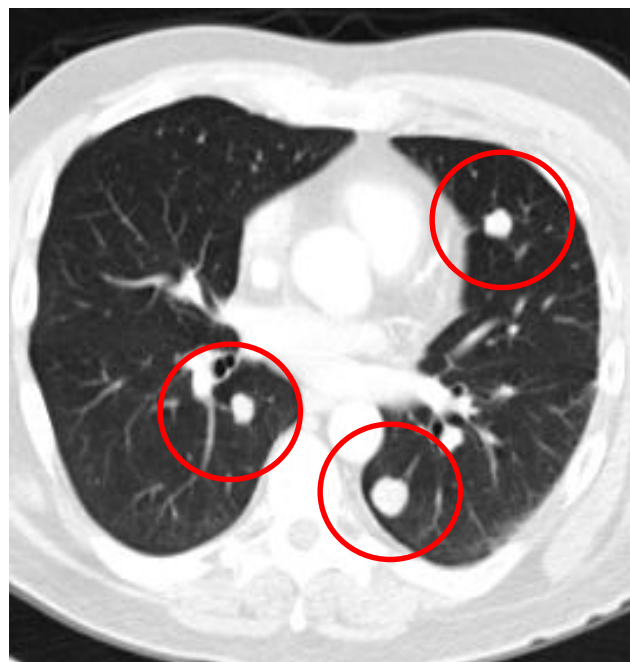
**30-60 bags
required**

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

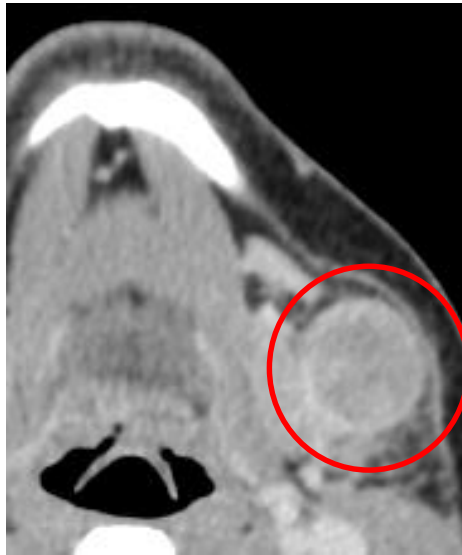


0 x 0 cm

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

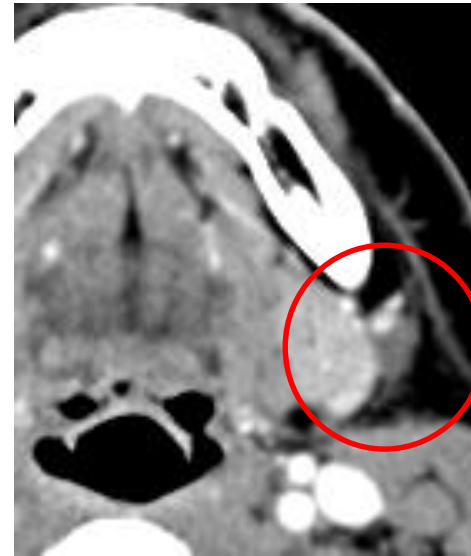
Lower Jaw Metastasis

PRE



2.4 x 2.2 cm

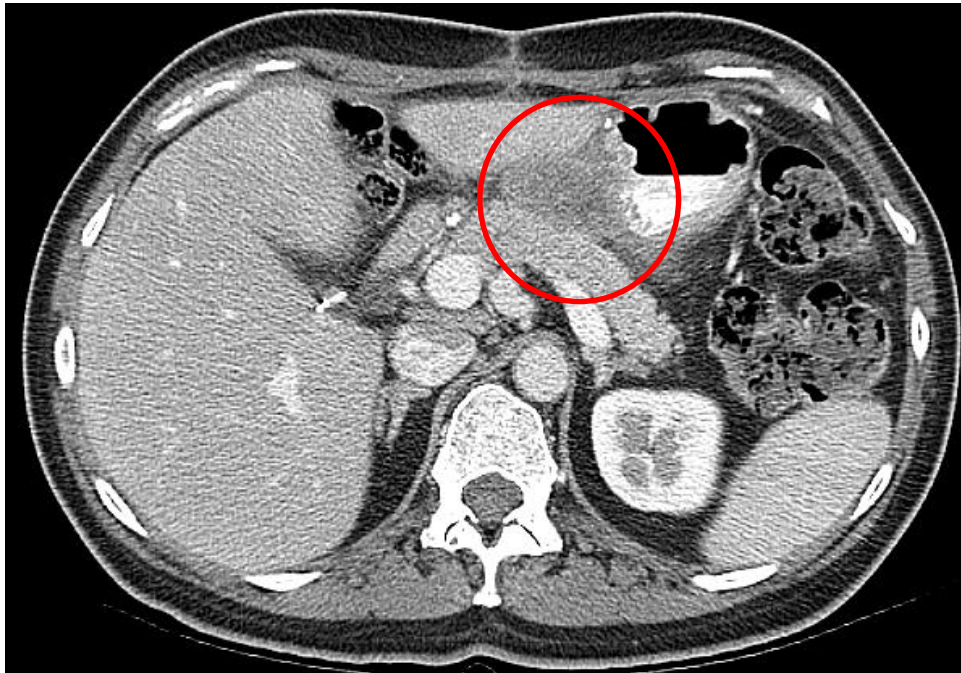
4 MONTHS POST



0.9 x 0.5 cm

Visceral Metastasis

PRE



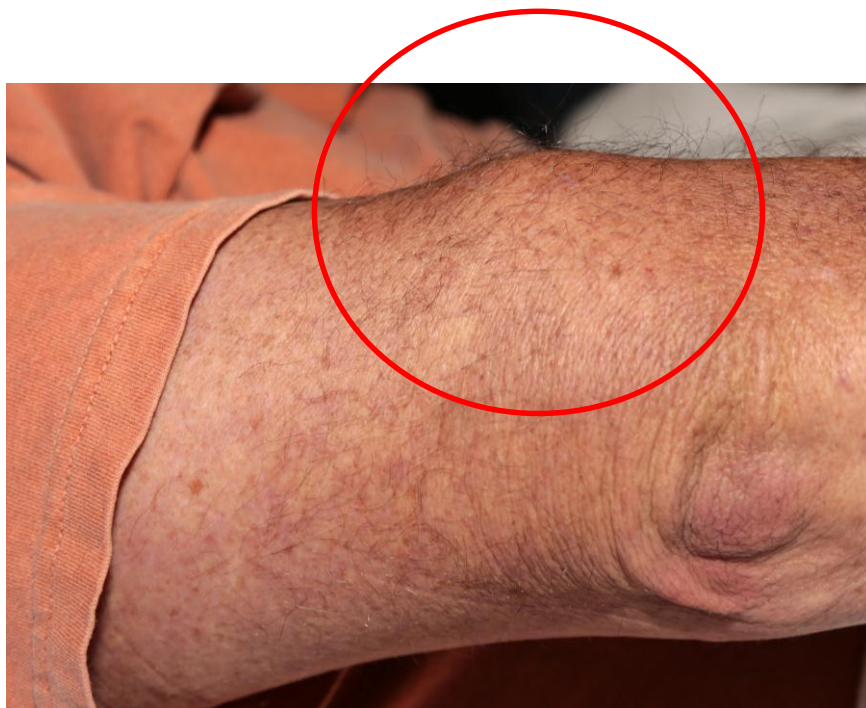
2.8 X 6 cm

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



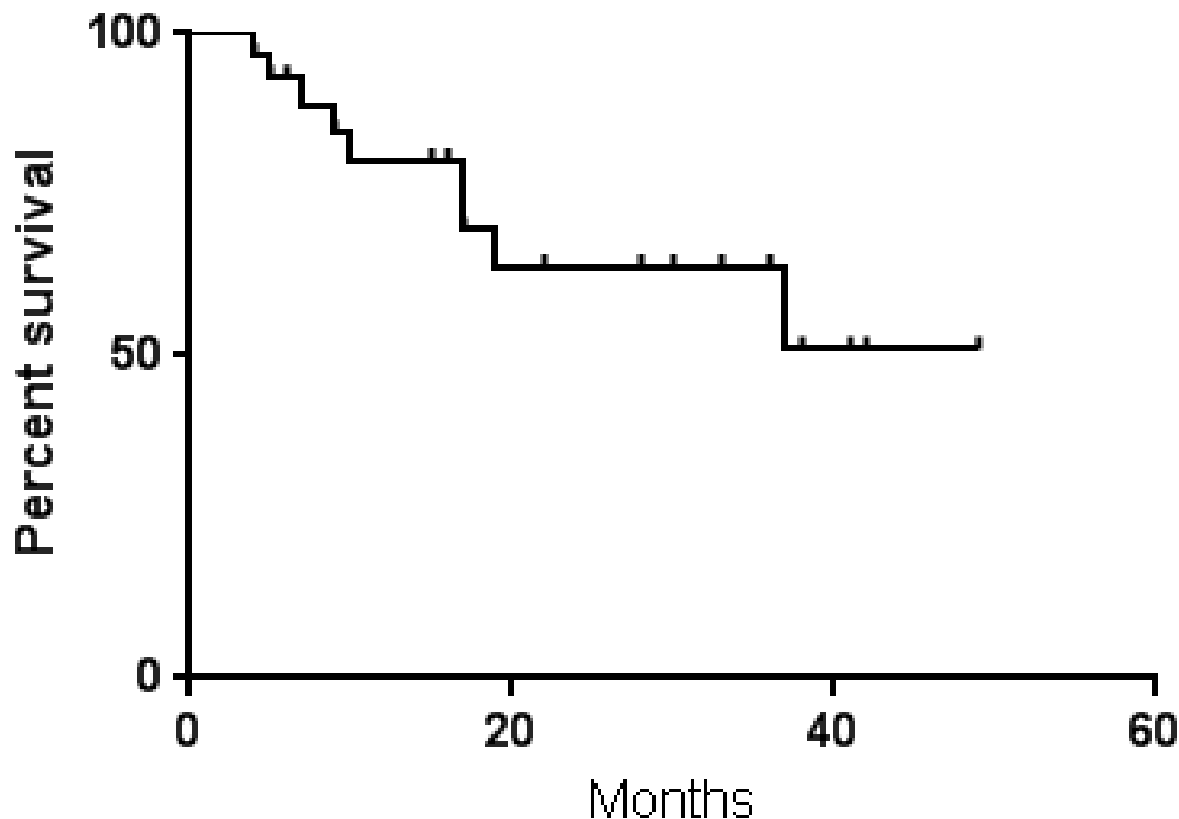
12/13/2010
2.1 x 3.0 cm

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

Overall Survival of Patients Treated at Moffitt



Median overall survival not reached at median follow up of 33 months (n= 30)

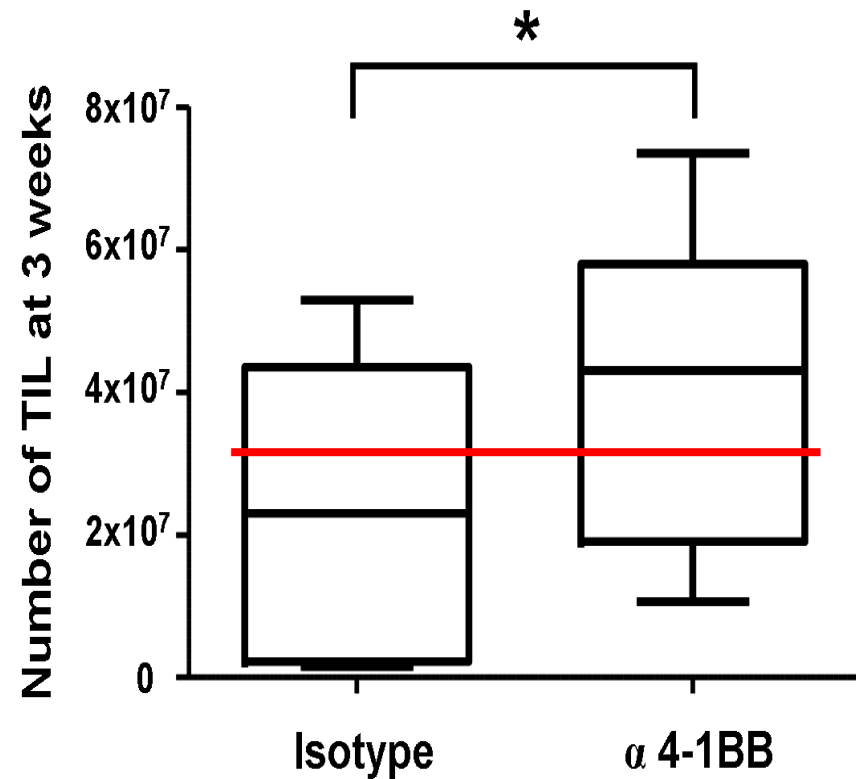
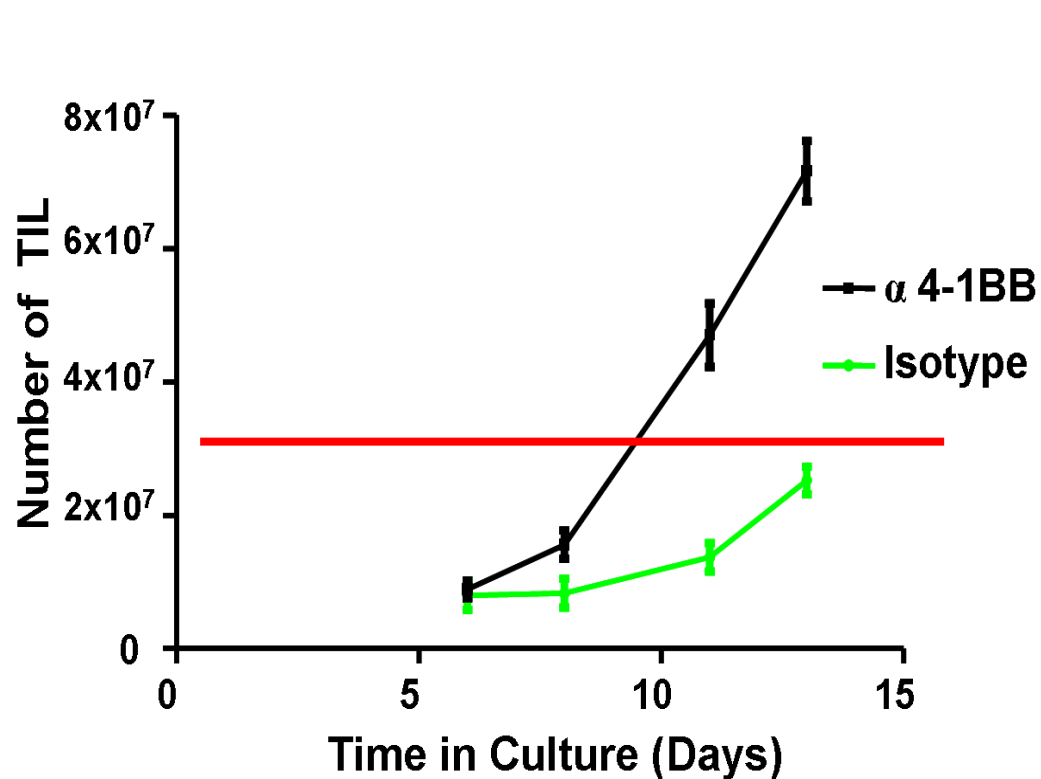
Moffitt ACT Clinical Results Summary

- 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

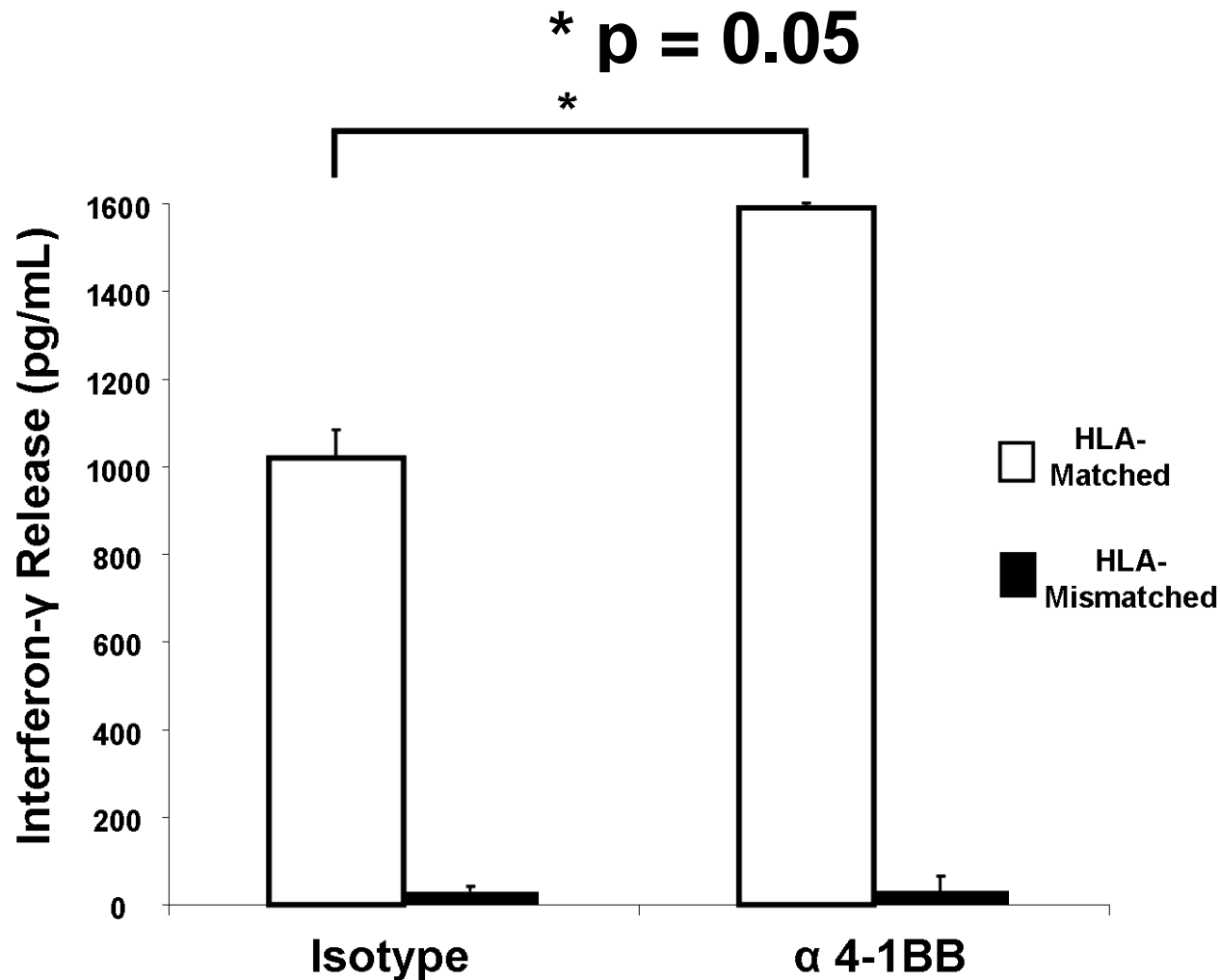
Current direction: Immunomodulatory antibodies to accelerate TIL growth and improve anti-tumor efficacy

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

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



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

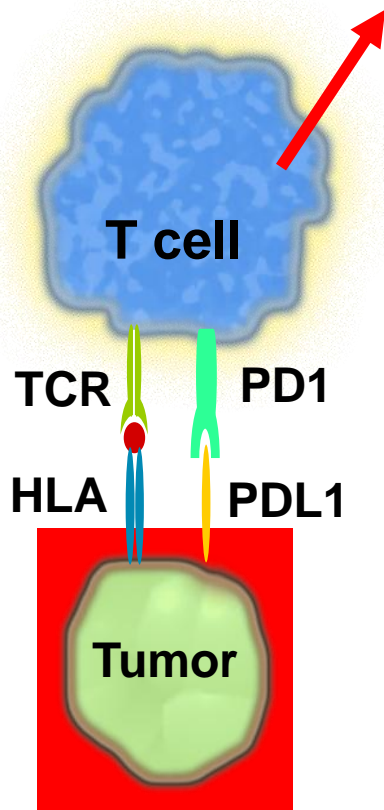


4-1bb Agonistic Antibody Summary

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

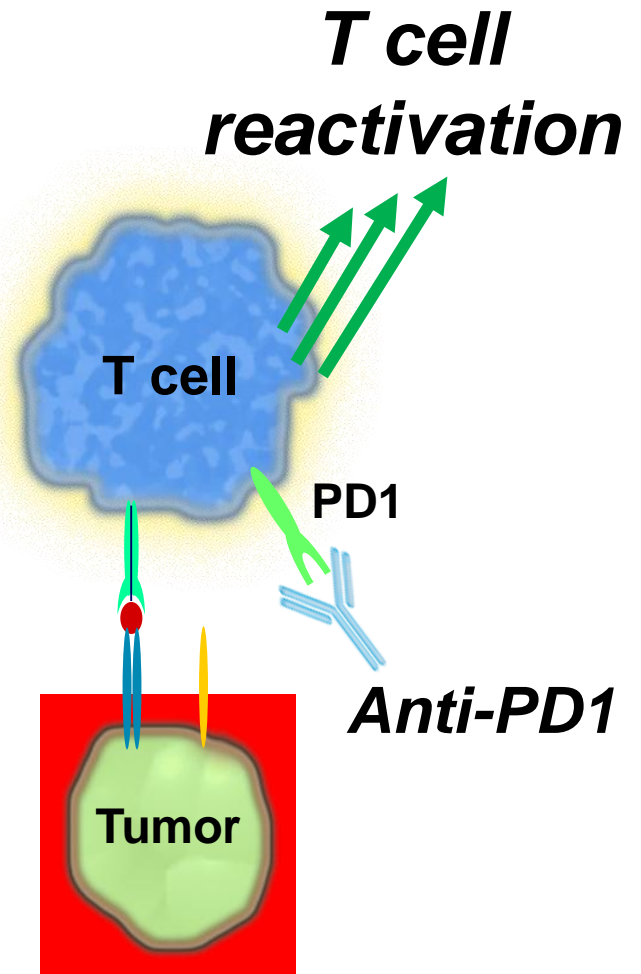
PD1 Blockade: Reviving Exhausted T Cells

**T cell
exhaustion**



PD1 Blockade: Reviving Exhausted T Cells

T cell

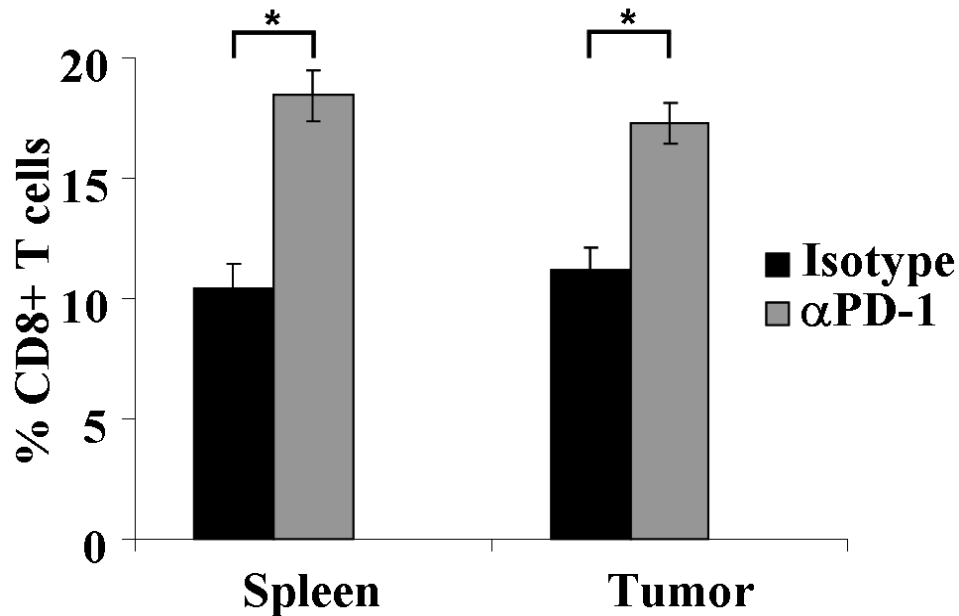


Aim

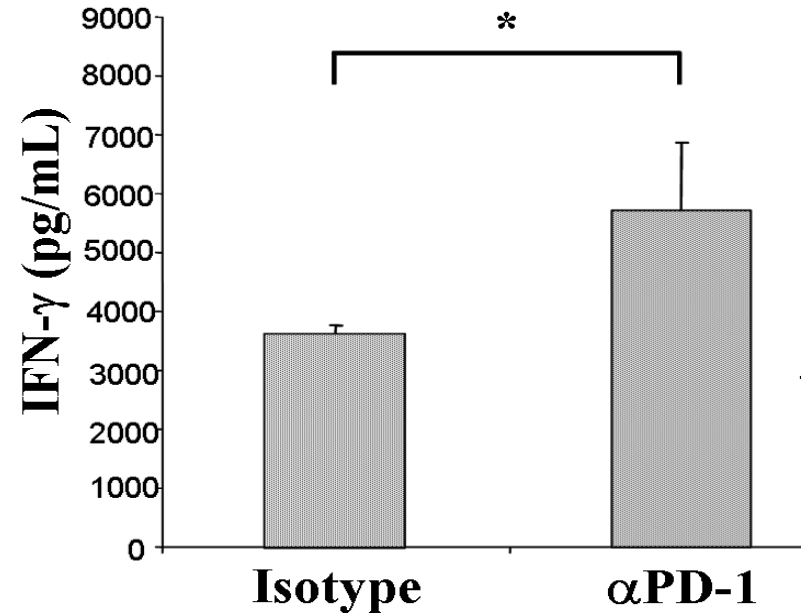
- To determine if a PD-1 abrogating antibody *in vivo* prior to tumor harvest may increase resulting CD8+ TIL and tumor-specific IFN- γ production

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

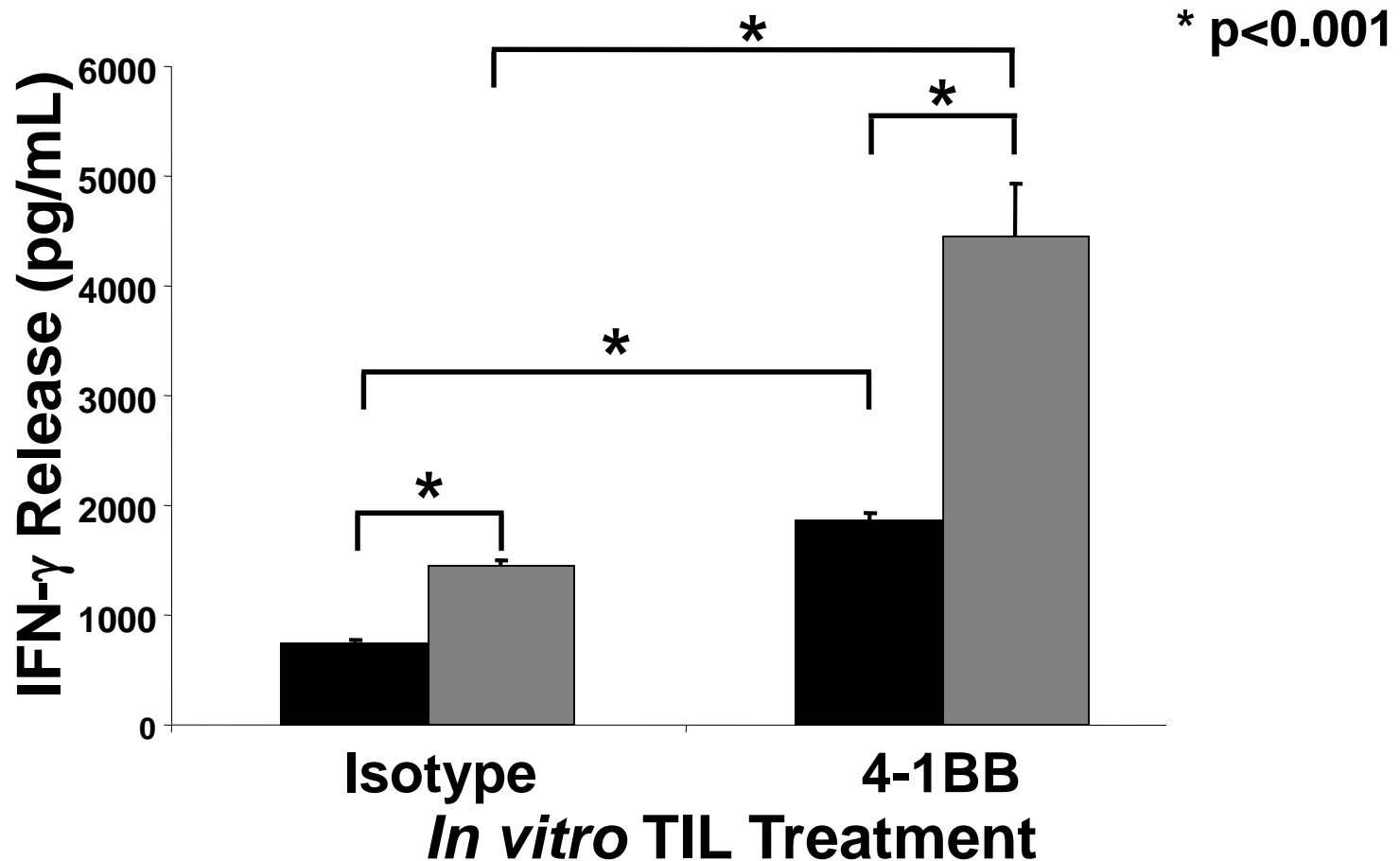
* $p < 0.05$



* $p < 0.05$



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



Key Takeaways

- **Adoptive T cell therapy for metastatic melanoma is feasible**
- **Efforts are ongoing for combination therapy to improve clinical outcomes**

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