

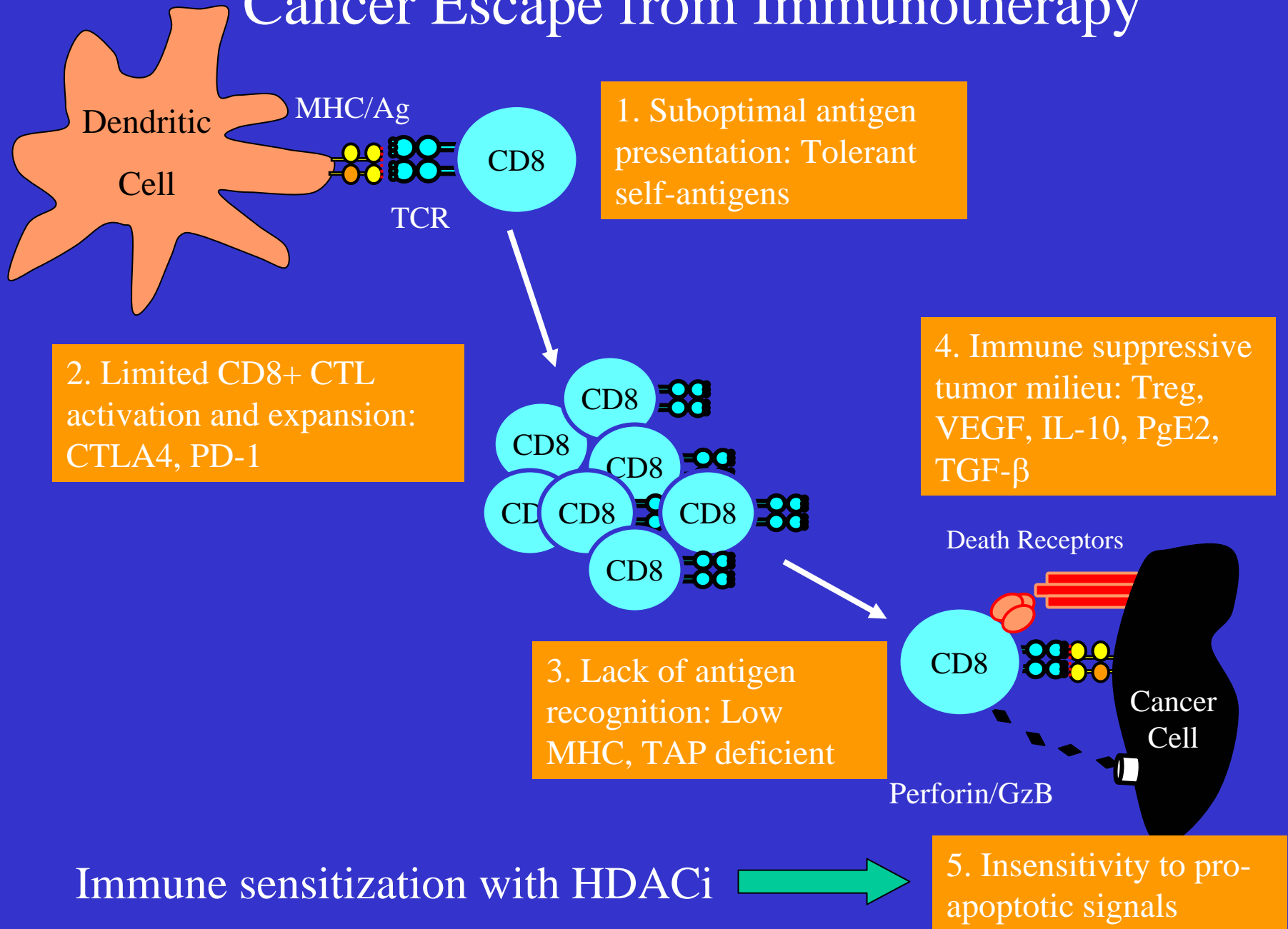
Immunosensitization of Melanoma Tumor to Adoptive Immunotherapy by a Histone Deacetylase Inhibitor

Dan Danh Vo
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Metastatic Melanoma Treatment

- Multiple forms of immunotherapy have been proposed over the years
 - Dendritic cell vaccine
 - IL2
 - Adoptive cell transfer therapy
- Patient response rate remained low, about (5%-15%)
- Tumor resistance possibly due to mechanisms of immune escape

Cancer Escape from Immunotherapy



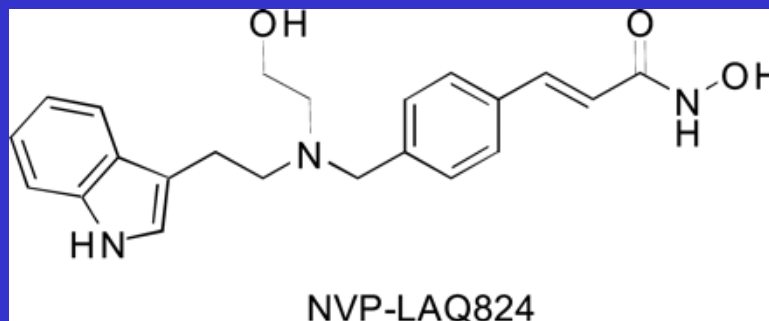
HDAC Inhibitors as Potential Immunostimulators

- Effects on tumor cells:
 - Increase death receptor expression.
 - Increase tumor antigen expression.
 - Increase expression of ligands for NK activating receptors.
- Effects on immune system cells:
 - Little cytotoxic effects on immune system cells.

Insinga *et al.* **Nat Med** 2005.
Nebbioso *et al.* **Nat Med** 2005.
Skov *et al.* **Cancer Res** 2005.
Armeanu *et al.* **Cancer Res** 2005.

The HDACi NVP-LAQ824

- LAQ824: A synthetic cinnamic acid HDACi.
- HDACi class: Hydroxamic acid group, which includes SAHA (Vorinostat, Zolinza), trichostatin A and pyroxamide.
- Pan-HDAC class I (HDAC1, 2, 3 and 8) and II (HDAC4, 5, 6, 7, 9, 10) inhibitor.

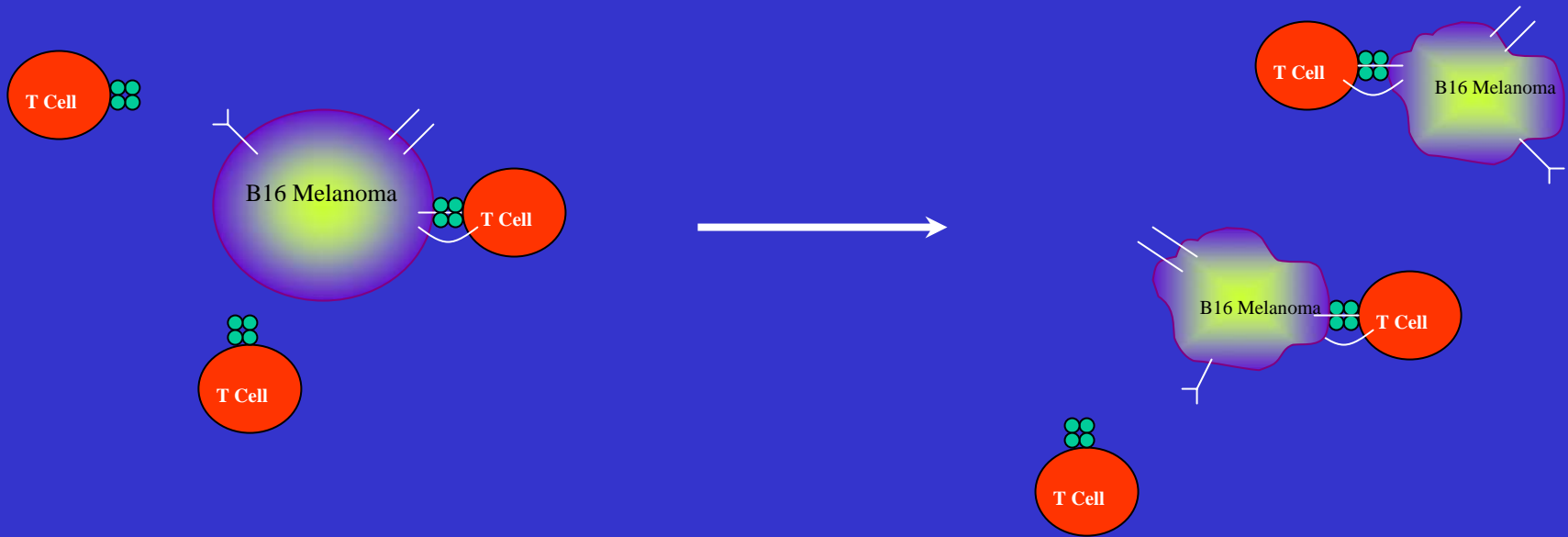


Atadja *et al.* Selective growth inhibition of tumor cells by a novel histone deacetylase inhibitor, NVP-LAQ824. **Cancer Res** 2004.

Weisberg *et al.* Histone deacetylase inhibitor NVP-LAQ824 has significant activity against myeloid leukemia cells *in vitro* and *in vivo*. **Leukemia** 2004.

Hypothesis

Treatment of melanoma tumor with histone deacetylase inhibitor may cause tumor cells to be more sensitive to immunotherapy.

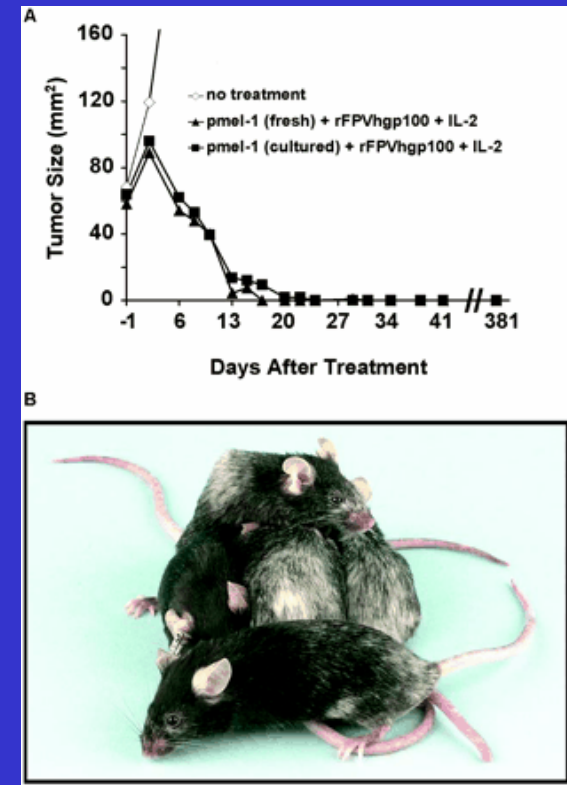
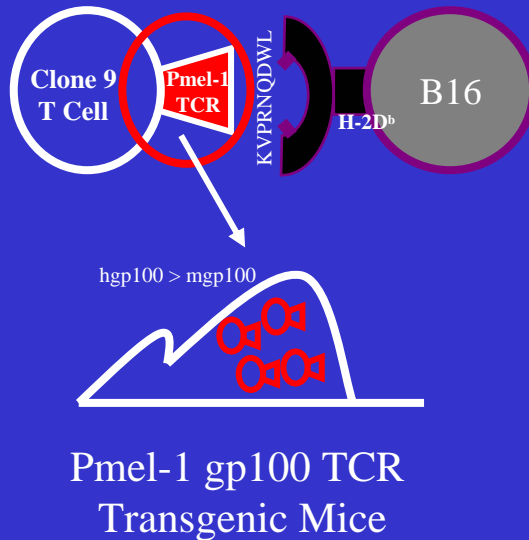


Pmel-1 Model of TCR Transgenic Cell Adoptive Transfer

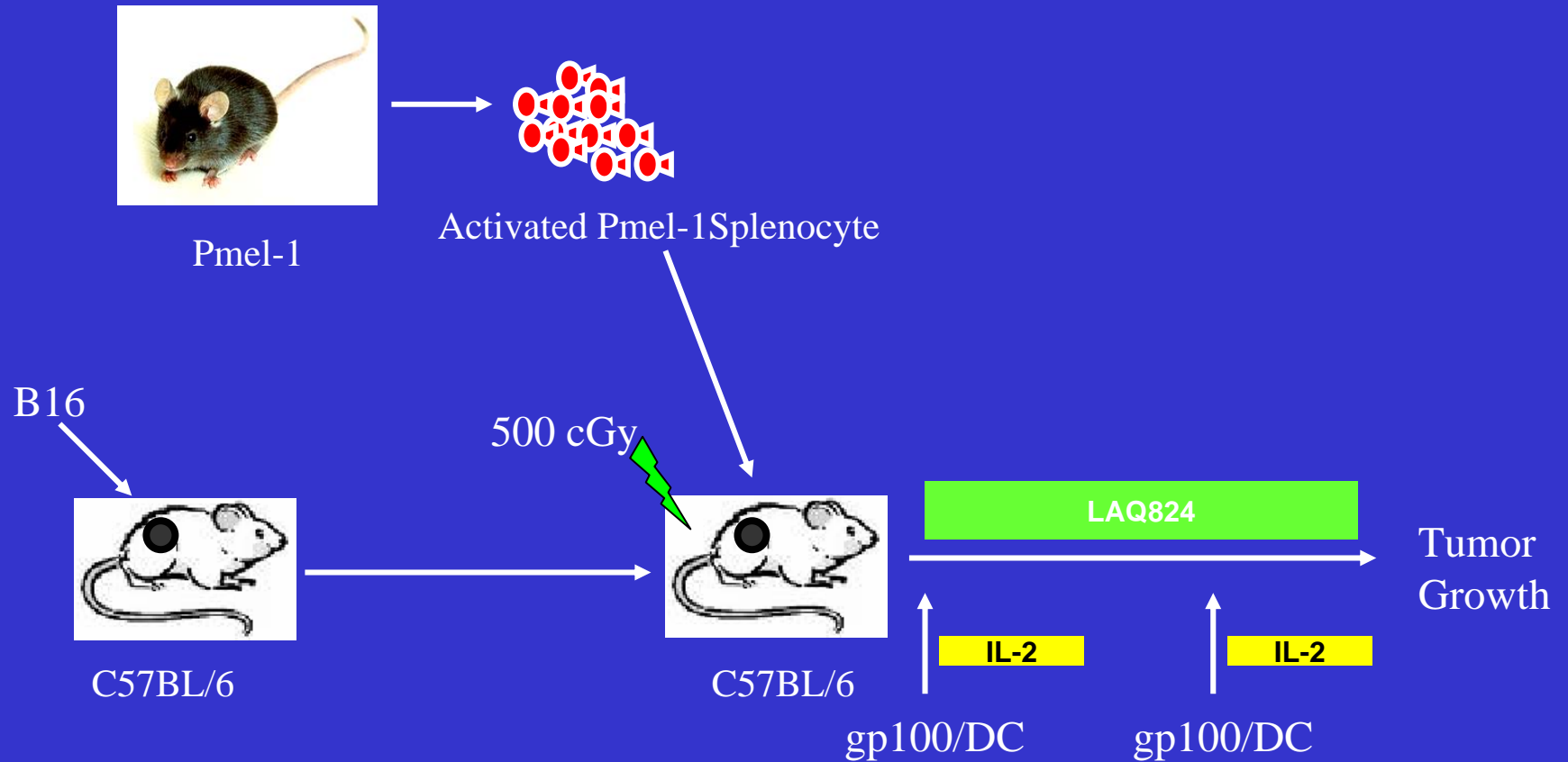
Tumor Regression and Autoimmunity after Reversal of a Functionally Tolerant State of Self-reactive CD8⁺ T Cells

Willem W. Overwijk,^{1,2} Marc R. Theoret,³ Steven E. Finkelstein,¹
Deborah R. Surman,¹ Laurina A. de Jong,² Florry A. Vyth-Dreese,²
Tees A. Dellemijn,² Paul A. Antony,¹ Paul J. Spiess,¹ Douglas C. Palmer,¹
David M. Heimann,¹ Christopher A. Klebanoff,³ Zhiya Yu,¹ Leroy N. Hwang,¹
Lionel Feigenbaum,⁴ Ada M. Kruisbeek,² Steven A. Rosenberg,¹
and Nicholas P. Restifo¹

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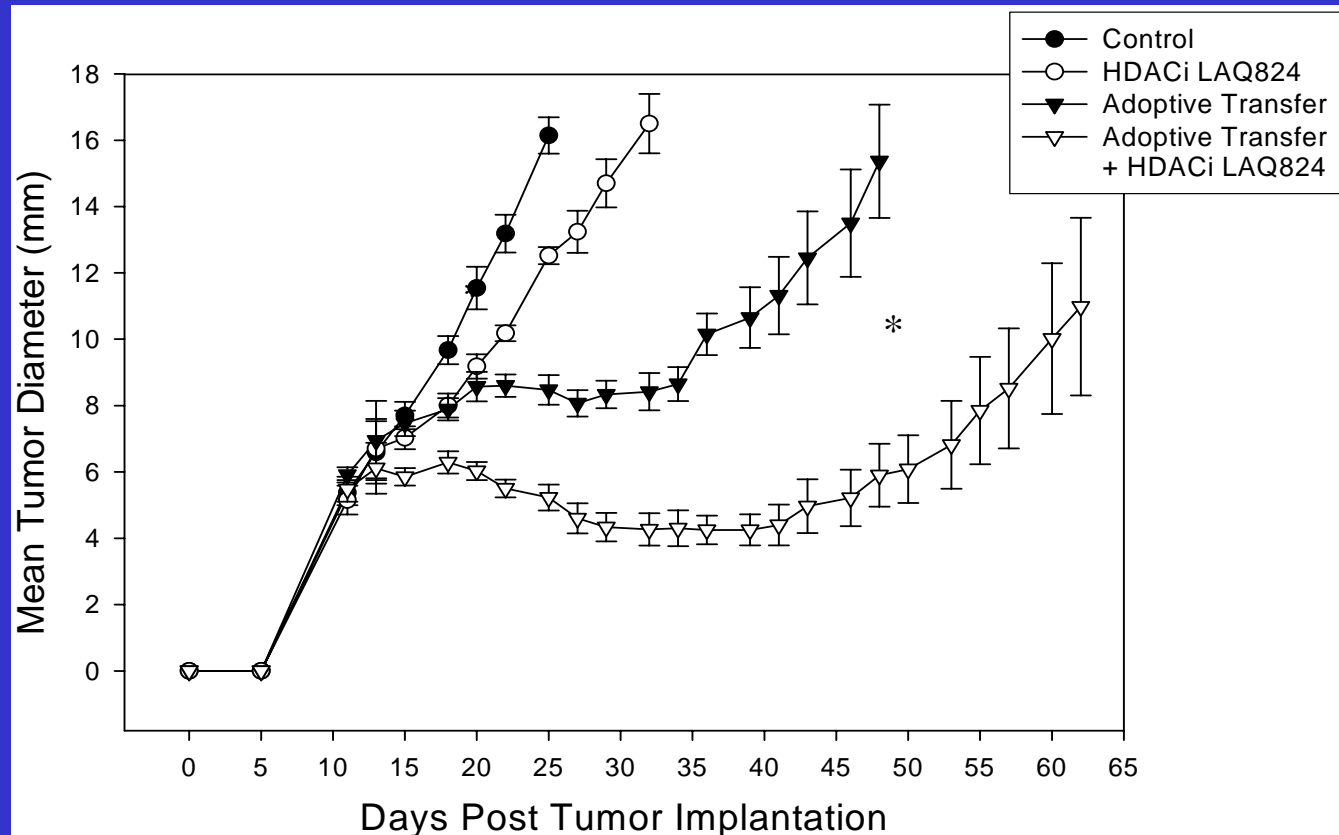


Experimental Outline



s.c. B16 melanoma treatment by adoptive transfer of pmel-1 splenocyte + HDACi results in initial tumor regression and slower growth rate

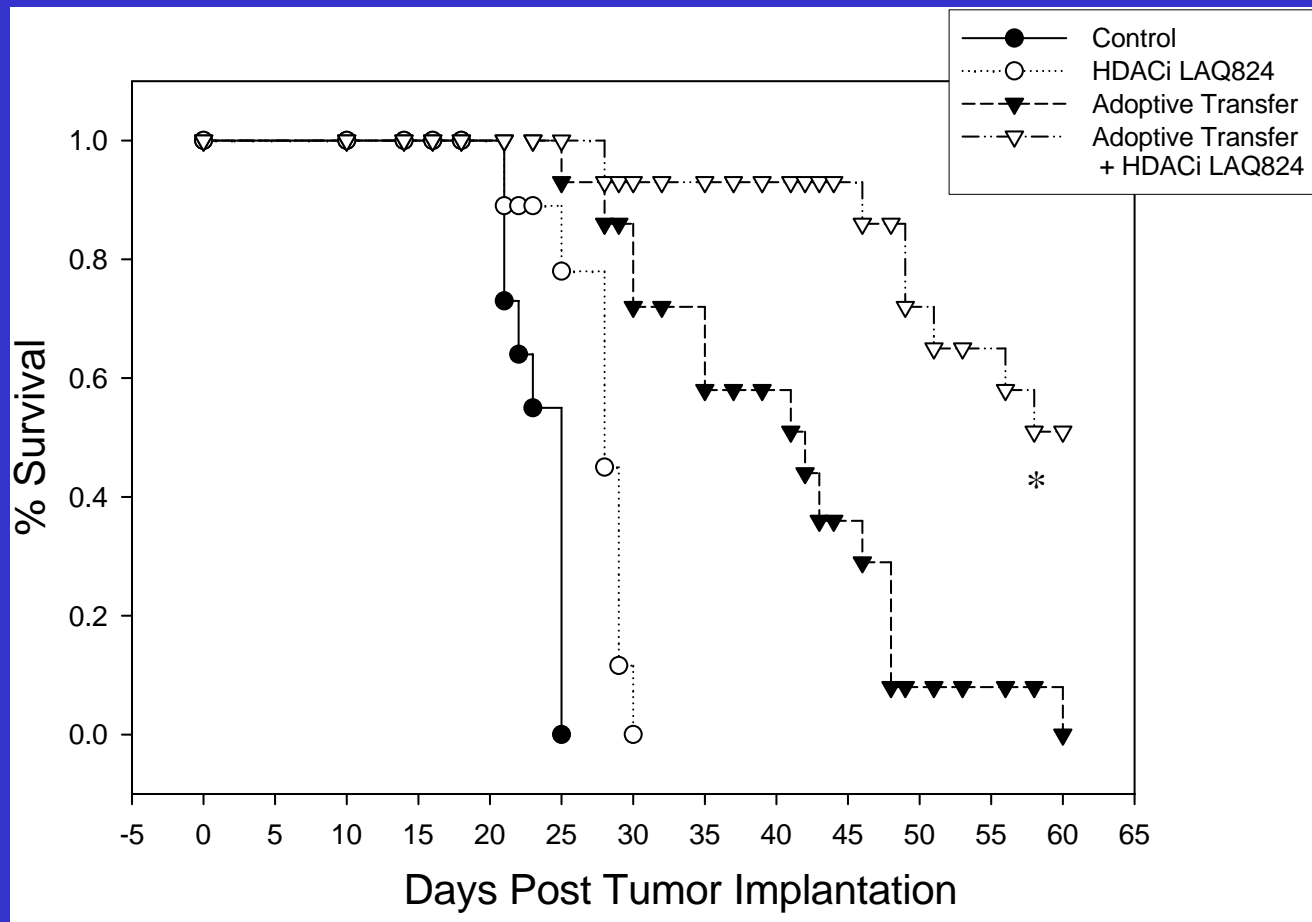
Tumor Growth Curves



* P-value < .00001

s.c. B16 melanoma treatment by adoptive transfer of pmel-1 splenocyte + HDACi results in increase survival

Survival Curves



* P-value < .05

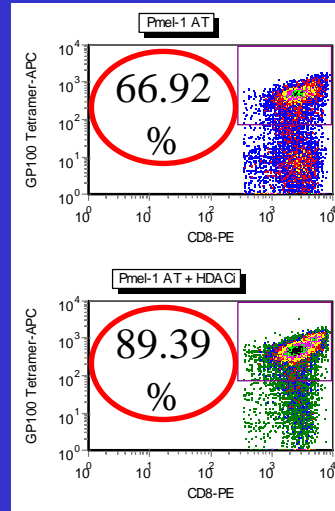
Pool from 3
independent
experiments

HDACi causes increase in gp100+ CD8+ T cell proliferation and intratumoral infiltration in vivo

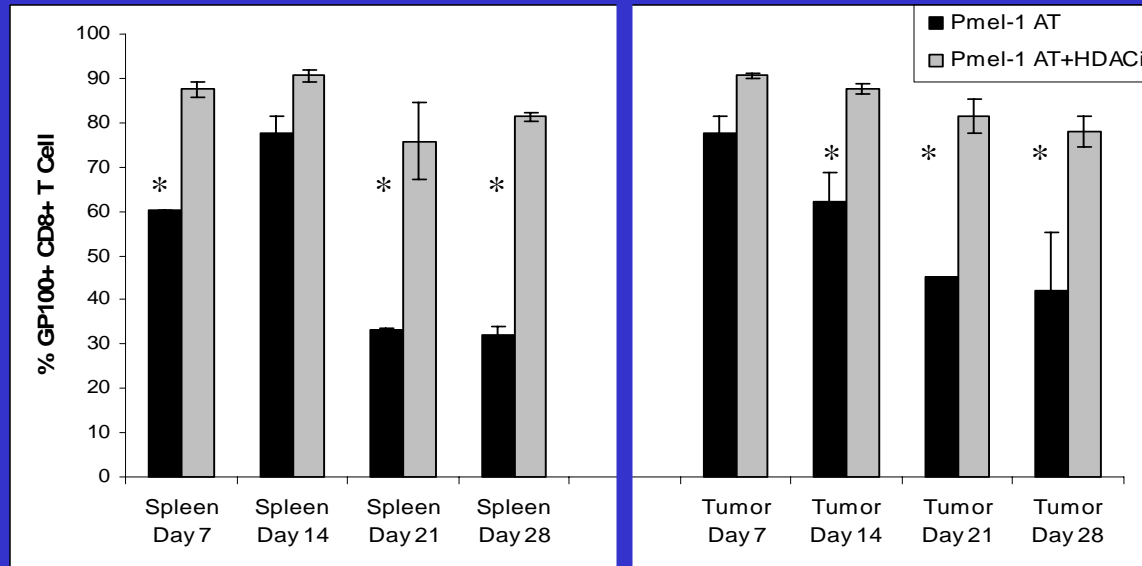
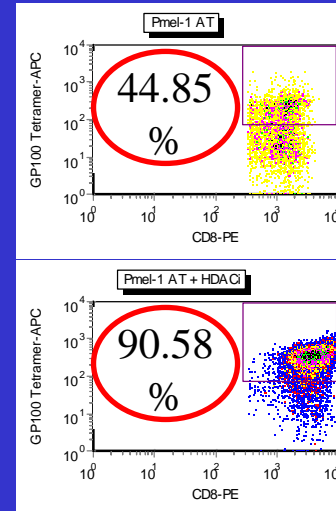
Pmel-1 Adoptive Transfer

Pmel-1 Adoptive Transfer + HDACi LAQ824

Spleen

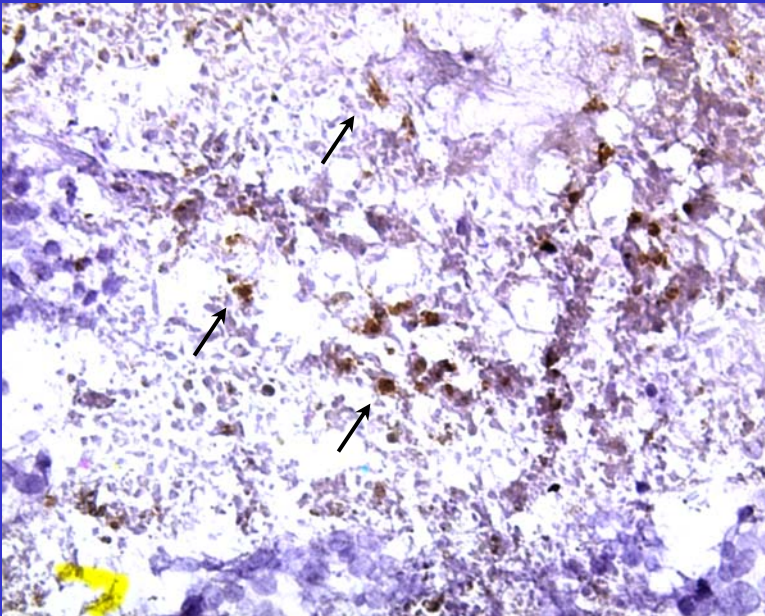


Tumor

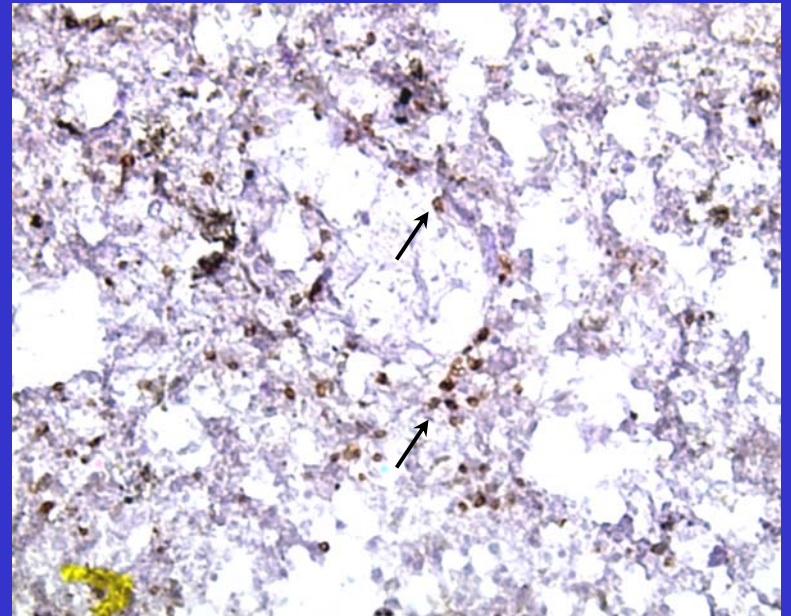


* P-value < .05

Immunohistochemical Staining CD8+ T Cell Intratumoral infiltration



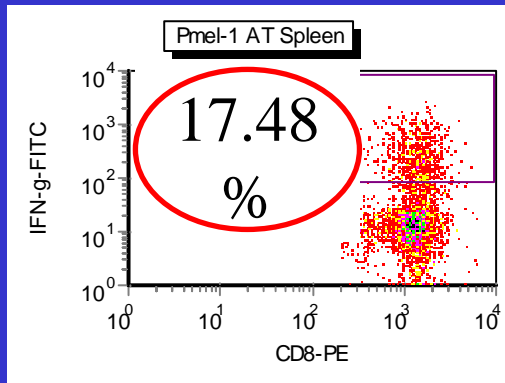
Pmel-1 Adoptive Transfer



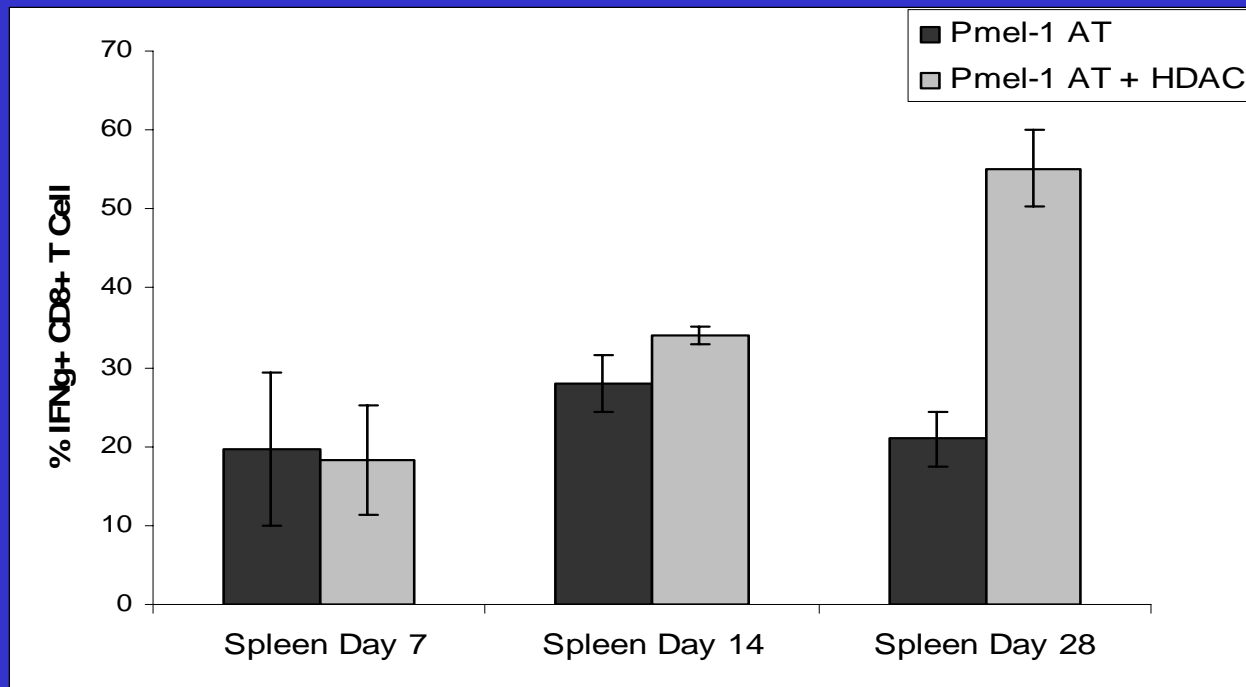
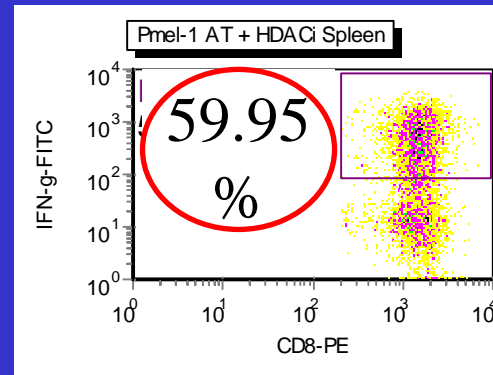
Pmel-1 Adoptive Transfer + HDACi

T Cell Activation by IFN γ Staining

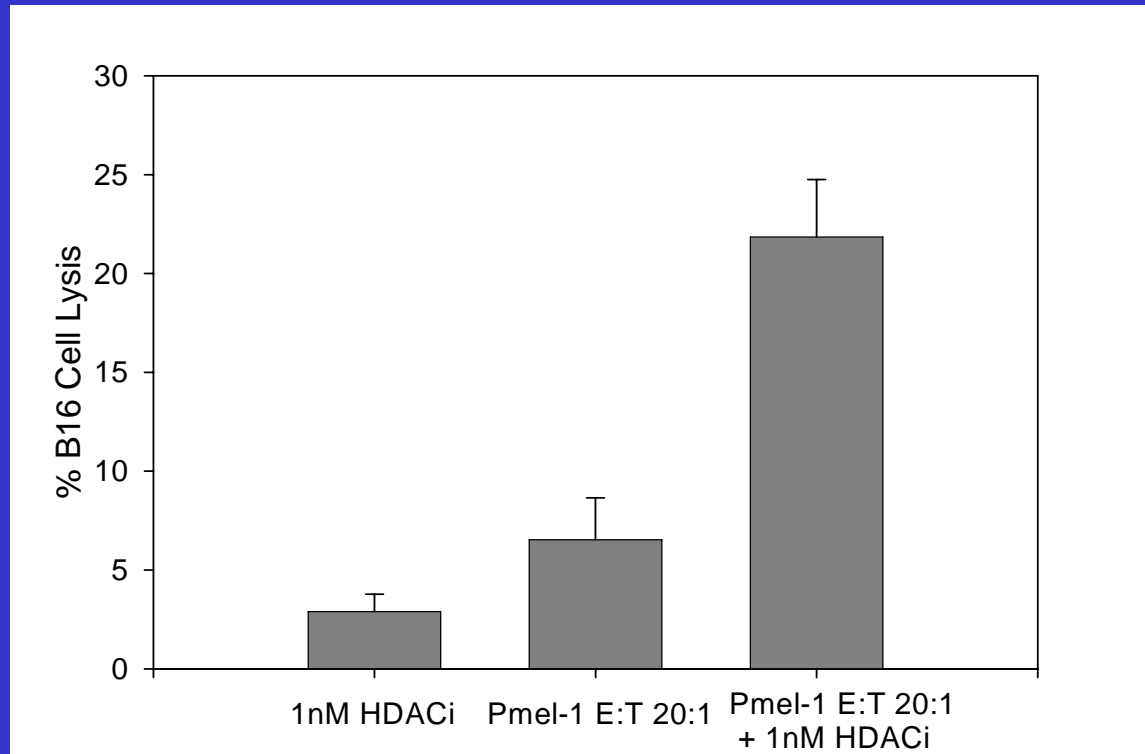
Pmel-1 Adoptive Transfer



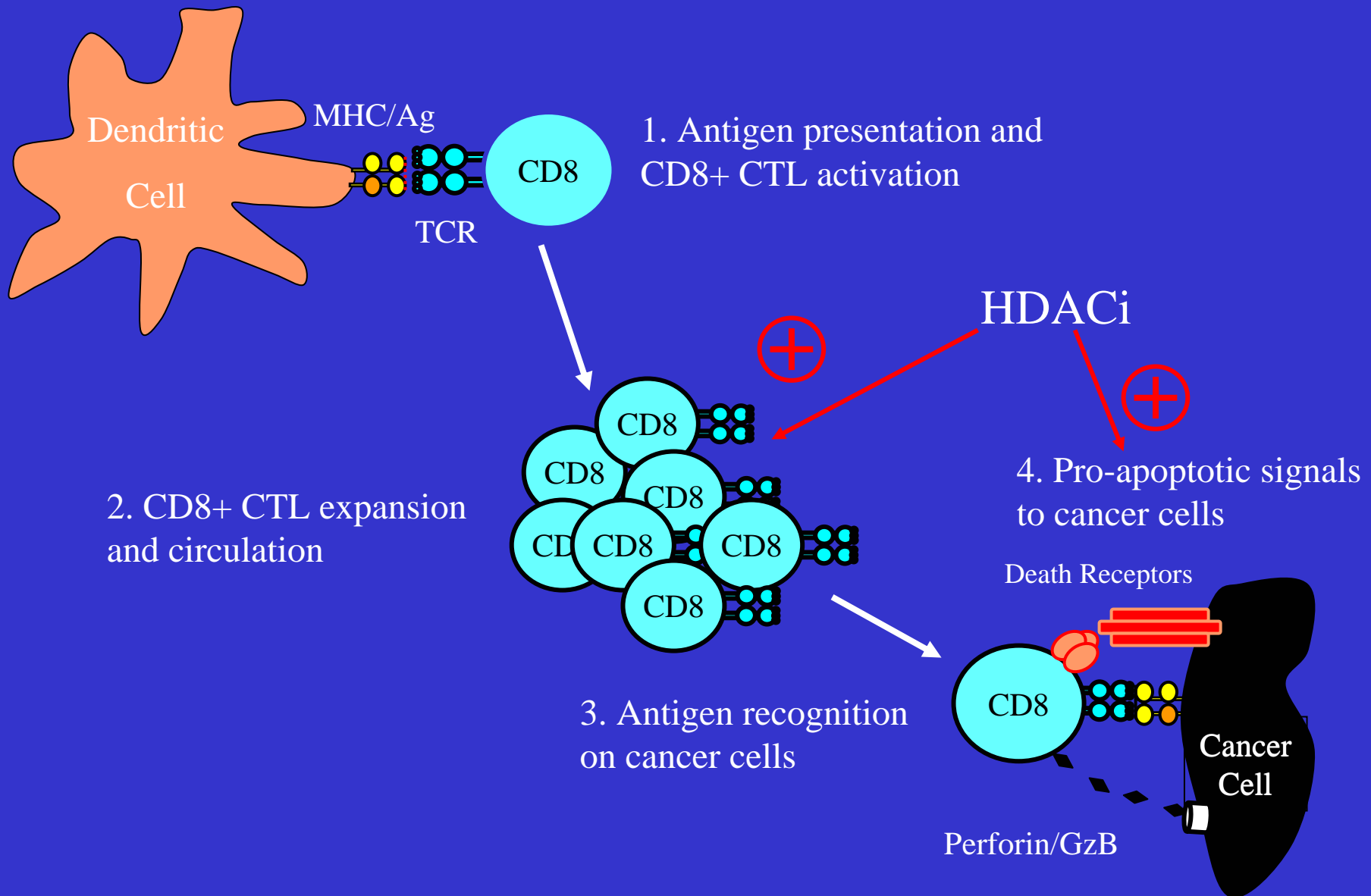
Pmel-1 Adoptive Transfer
+ HDACi



HDACi enhances pmel-1 cytotoxic activity in vitro



Immune Sensitization with HDACi



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