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

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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

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Cancer Escape from Immunotherapy

1. Suboptimal antigen presentation: Tolerant self-antigens

2. Limited CD8+ CTL activation and expansion: CTLA4, PD-1

3. Lack of antigen recognition: Low MHC, TAP deficient

4. Immune suppressive tumor milieu: Treg, VEGF, IL-10, PGF2, TGF-β

5. Insensitivity to pro-apoptotic signals

Immune sensitization with HDACi
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.

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.

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

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Pmel-1 gp100 TCR Transgenic Mice

Pmel-1 TCR

Clone 9

T Cell

B16

hgp100 > mgp100

0 10 20 30 40 50 60 70 80 90 100

Days After Treatment

Tumor Size (mm²)

A

B

no treatment

pml-1 (fresh) + rFPVhgp100 + IL-2

pml-1 (cultured) + rFPVhgp100 + IL-2

0 6 12 18 24 30 36 42 48 54 60

381
s.c. B16 melanoma treatment by adoptive transfer of pmel-1 splenocyte + HDACi results in initial tumor regression and slower growth rate

* P-value < .00001

Tumor Growth Curves
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

* P-value < .05
Immunohistochemical Staining
CD8+ T Cell Intratumoral infiltration

Pmel-1 Adoptive Transfer

Pmel-1 Adoptive Transfer + HDACi
T Cell Activation by IFNγ Staining

Pmel-1 Adoptive Transfer

Pmel-1 Adoptive Transfer + HDACi

Day 28 Post Adoptive Transfer

% IFNγ+ CD8+ T Cell

IFN-γ-FITC vs C8-PE

R3

59.95%

17.48%

Day 28

Spleen Day 7

Spleen Day 14

Spleen Day 28

% IFNγ+ CD8+ T Cell
HDACi enhances pmel-1 cytotoxic activity in vitro
Immune Sensitization with HDACi

1. Antigen presentation and CD8+ CTL activation

2. CD8+ CTL expansion and circulation

3. Antigen recognition on cancer cells

4. Pro-apoptotic signals to cancer cells
   - Perforin/GzB
   - Death Receptors

HDACi
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