Anti-PD-1 antibody enhances the potency of GM-CSF-secreting tumor cell immunotherapy (mGVAX)

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GVAX™ Platform: Proposed Mechanism of Action Based on Preclinical Models

PD-1: Facts

- Negative regulator of T cell activation that shares structural properties with members of the CD28 family

- PD-1 blockade reverses T-cell exhaustion, restores cytokine production and augments the expansion of antigen specific T cells

-> Based on mechanism of PD-1 action, blockade of this pathway should potentially enhance the potency of cancer immunotherapies
Combination Therapy:
GM-CSF-secreting tumor cell Immunotherapy and anti-PD-1

**Study Schematics**

- **Day 0**
  - Challenge
  - Live B16F10

- **Day 3, 7 or 11**
  - Immunization
  - mGVAX

- **Day 10-24**
  - Immune Monitoring

- **Day 3**
  - Anti-PD-1
  - 200 μg

- **Day 4**
  - Anti-PD-1
  - 100 μg

*Chimeric anti-mouse PD-1 antibody provided by Medarex*
Anti-PD-1 prolongs survival of mGVAX treated animals

*Anti-PD-1 monotherapy does not provide any therapeutic benefit in the non-immunogenic B16 model*
Anti-PD-1 prolongs survival of mGVAX treated animals

Survival (CT26 model): Day 3 treatment
Anti-PD-1 enhances mGVAX induced antigen-specific T-cell responses

IFN\(\gamma\) ELISPOT (7 days post immunotherapy)

![Graph showing number of events (per 5e5 splenocytes) for F10 and trp2 antigens in HBSS, mGVAX, mGVAX + anti-PD-1 conditions.](image)

\*p=0.01 for F10 and p=0.02 for trp2
Anti-PD-1 enhances mGVAX immunotherapy induced cytokine production by splenocytes

Cytokine Analysis (7 days post immunotherapy)

- TNFa: *p<.005
- IFNg: *p=.002
- IL5: *p=.01
- IL6: *p=.0001
- IL10: *p=.002
- MCP: *p<.0001
Anti-PD-1 increases the percentage of CD8 memory T-cells in mGVAX treated animals

Ly6C⁺/CD69⁻ (CD8 subpopulation)
Anti-PD-1 enhances mGVAX induced, antigen-specific cytolytic T-cell responses

In vivo CTL (ovalbumin as surrogate antigen)

![Graph showing percent lysis over days post immunotherapy with HBSS, mGVAX, and combination treatments, with significance markers for p<0.05.](image-url)
Anti-PD-1 enhances mGVAX induced, intratumoral CD8 T-cell infiltration

**TIL kinetics**

**CD4**

- HBSS
- mGVAX
- Combination

**CD8**

- HBSS
- mGVAX
- Combination

**CD8^{+}IFN_{\gamma}^{+}\**

- HBSS
- mGVAX
- Combination

**CD8^{+}CD107a^{+}\**

- HBSS
- mGVAX
- Combination
mGVAX + anti-PD-1 combination therapy results in enhanced survival (B16F10 and CT26 tumor models)

- Anti-PD-1 therapy augments mGVAX mediated CD8\(^+\) T cell responses (cytolytic activity, pro-inflammatory cytokine secretion)
- Anti-PD-1 allows the persistent survival of mGVAX activated cytolytic T cells
- Anti-PD-1 increases the percentage of mGVAX induced memory T-cells within the CD8 subpopulation
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