Functional reprogramming of the tumor stroma by IL-12 Engineered T cells is required for anti-tumor immunity

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Mouse B16/Melanoma Model of Adoptive Cell Transfer

A tripartite regimen is effective:

i) 1 million Pmel-1 CD8+ cells

ii) $2 \times 10^7$ plaque-forming units of rVV encoding hgp100

iii) administration of high-dose IL-2: 600,000 IU BID for 3 days

Tumor-Specific CD8+ T Cells Expressing Interleukin-12 eradicate established B16 melanomas with 10,000 cells and no IL-2 or Vaccine

Kerker SP et al. Cancer Res. 2010 Sept. 1\textsuperscript{st}, 70;6725
Treatment with IL-12 engineered CD8+ T cells leads to increased tumor infiltration of adoptively transferred cells stably expressing IL-12

Kerka SP et al. Cancer Res. 2010 Sept. 1st, 70;6725
IL-12 based anti-tumor immunity is dependent on endogenous factors
IL-12 based anti-tumor immunity is dependent specifically on host bone marrow derived cells

IL-12r⁻/⁻ / Il-12r⁻/⁻
IFN-γ expression and sensitization through host cells is critical for successful treatment.
Host NK, T and B cells are not necessary for tumor rejection

WT host
- NT
- P-IL-12

RAG\(^{-/-}\) host
- NT
- P-IL-12

Time (d) after transfer

Tumor area (mm\(^2\))
Majority of cells expressing IL-12Rβ2 within the tumor are CD11b+ myeloid derived cells.

PI-, CD3-, NK1.1-, B220- CD11b+
CD11b+ Myeloid Cells within tumors of IL-12 treated mice have higher expression of FAS (CD95)
 Adoptively transferred CD8+ T cells within the tumor have high FASL expression

Pmel Thy1.1+ cells expressing IL-12 were transferred into C56/BL6 mice
Summary

• Small numbers of tumor specific T cells overproducing IL-12 within the tumor microenvironment can eradicate large established tumors

• Anti-tumor immunity is dependant on IL-12 and IFN-γ dependent sensitization of host bone marrow derived myeloid cells

• IL-12 engineered T cells induce functional changes in the myeloid population residing within tumors

• Anti-tumor immunity is largely dependent on the ability of endogenous cells to cross-present tumor antigens in vivo
Clinical Applicability

• Clinical grade inducible vector designed by Ling Zhang and Richard Morgan

• Phase I/II Study of Metastatic Melanoma Using Lymphodepleting Conditioning Followed by Infusion of CD8 Enriched Tumor Infiltrating Lymphocytes Genetically Engineered to Express IL-12
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