Treatment of Solid Cancers by Adoptive Cell Transfer of Tumor-Infiltrating Lymphocytes Targeting Mutated Tumor Antigens

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Outline

- Background
- Targeting neoantigens to extend adoptive cell therapy for the treatment of solid cancers
Three Main Approaches to Cancer Immunotherapy

1. Non-specific stimulation of immune reactions
   - Stimulate effector cells (IL-2, IL-12)
   - Inhibit regulatory factors (PD-1, CTLA-4)

2. Active immunizations to enhance anti-tumor reactions
   - Cancer vaccines

3. Passively transfer activated immune cells with anti-tumor activity
   - Adoptive cell transfer
A Critical Challenge Confronting the Development of Human Cancer Immunotherapy is the Identification of Antigens to Target

1. Differentiation antigens overexpressed on cancers compared to normal tissue (MART-1, gp100, CEA, Her-2, Mesothelin)

2. Antigens expressed on cancers and on non-essential normal tissues (CD19, thyroglobulin)

3. Shared antigens unique to cancer (cancer-testes antigens, NY-ESO-1, MAGE-A)

4. Critical components of the tumor stroma (VEGFR2, FAP)

5. Mutations unique to each cancer (EGFRvIII, Neoantigens)
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Adoptive Cell Transfer for Patients with Breast Cancer

• About 1 in 8 (12%) women in the US will develop invasive breast cancer during their lifetime.

• Each year, approximately 41,000 people die of metastatic breast cancer (ACS Facts and Figures 2017).

• Breast TIL are a prognostic indicator associated with improved pathologic complete response to neoadjuvant therapy (Salgado et al, JAMA Oncol 2015) and survival (Adams et al, J Clin Oncol 2014).

A strategy for Assessing T-cell reactivity Against Mutated Antigens in Solid Tumors

1) IFN-γ ELISPOT
2) 4-1BB/OX40 upregulation

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<th>Age</th>
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<th>PR</th>
<th>Her2</th>
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CD4/CD8 Ratios of Breast TIL

![Graph showing CD4+ and CD8+ cell percentages in ressected tumor IDs.](chart.png)

- CD4+ cell percentages range from 10% to 80%.
- CD8+ cell percentages range from 20% to 100%.

Resected tumor ID: 4051, 4062, 4099, 4125, 4130, 4131, 4136, 4180, 4186.
Pt J.A. (4136) – Patient History

• 49 year old woman
• 2003 – diagnosed with DCIS, mastectomy (L) and axillary dissection
• 2013 – relapsed with widespread invasive cancer ER+, PR+, Her2-
• Multiple treatments:
  – chemotherapy regimens: paclitaxel, capecitabine, vinorelbine, docetaxel, doxorubin, and cyclophosphamamide
  – Multiple endocrine regimens
  – Progressed through trial of lucitanib (last dose July 28, 2015)
• 2015 (August) – resection of right breast tumor for TIL generation and mutation analysis
• Interim treatment: Everolimus
• 2015 (December) – progressive disease (liver, LN, soft tissue and bony tumors)
  – Adoptice cell transfer (mutation-reactive TIL, 7.9e10 cells)
Targeting Immunogenic Mutations in Breast Cancer (Pt 4136)

Screen I (peptide pools)

71 mutations screened

- OKT3
- TIL only
- PP6
- PP5
- PP4
- PP3
- PP2
- PP1
- P0

IFN-γ spots / 2x10⁴ cells
Regression of Metastatic Breast Cancer After Adoptive Cell Transfer of Tumor Infiltrating Lymphocytes and Checkpoint Blockade
Summary

• 6/8 patients with breast cancer had mutation-reactive TIL
• TIL targeting nonsynonymous mutations may be able to mediate objective tumor regressions
  • PT 4136 is experiencing an ongoing response and is now a CR at 14+ months
• Efforts are underway to treat patients using gene-engineered T cells directed against tumor-specific neoantigens
Future Clinical Efforts: To Genetically Engineer T-Cells to Express Receptors Reactive Against Mutated Neoantigens in Patients with Metastatic Cancer

Clone mutation-reactive TCRs

Gene-engineer PBL

- Gammaretroviral vectors
- Transposons
- Gene editing and Targeted insertion
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