Adoptive Cell Therapy Using Tumor Infiltrating Lymphocytes (TIL) and Application to Bladder Cancer

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Disclosures

Research Funding and IP Licensing Agreement from Iovance Biotherapeutics Inc.

Prometheus Inc supplies *in vitro* IL-2

Bristol Myers Squibb Inc. provides *in vitro* 4-1BB for Moffitt research and adoptive cell therapy trials
Learning Objectives

1. Understand the principles of ACT with TIL

2. Understand the effect of neoadjuvant chemotherapy on TIL expansion from bladder tumors

3. Understand how targeting 4-1BB can improve TIL expansion from bladder tumors
T cell Activation

Tumor cells → Antigen Presenting Cell: Dendritic Cell (DC)

MHC class I
MHC class II

CD8+ → Cytotoxicity

CD4+ → Helper functions
Inflammation
Regulation
Tumor-specific T cells can be detected in the blood and tumors of patients with cancer.
Tumor Infiltrating Lymphocytes (TIL)

• TIL associated with improved prognosis

• TIL are functionally impaired due to suppressive factors in the tumor microenvironment

• When cultured \textit{in vitro}, TIL regain effector functions

• Can be expanded to high numbers and used in adoptive cell therapy (ACT) for the treatment of metastatic cancers
Isolation and Expansion of TIL

Surgical Resection

In vitro expansion of T cells

High dose IL-2

Tumor

CD4

CD8

CD8

CD4

Lymph Node
Specificity of TIL Grown from Melanoma Tumor

IFN-γ pg/ml

Target
- No tumor
- tumor 1
- tumor 2

Fragment Number

1 2 3 4 5 6 7 8 9 10 11 12
Adoptive Cell Therapy with TIL

6-8 weeks

Restifo and Rosenberg Science 2015
Pilot Trial – Efficacy of TIL in Patients with Metastatic Melanoma

19 patients enrolled

6 patients not treated
- 1 did not grow TIL
- 1 adverse event to lymphodepleting chemotherapy
- 1 death, 3 progressive disease

13 patients treated – 38% overall response rate
- 3 complete responders (CR)
- 2 partial responders (PR)
- 4 stable disease (SD)
- 4 progressive disease (PD)

Pilon-Thomas, *J Immunother* 2012
Patient Clinical Results - CR

Pre TIL

2 months post

24 months post

1.6 x 1.5 cm

0.8 x 0.6 cm

0 cm

Pilon-Thomas, J Immunother 2012
Example of Prolonged Stable Disease

Pre-TIL

2.1 x 3.0 cm

27 months Post

2.0 x 1.5 cm

Pre-TIL

2.6 x 1.7 cm

27 months Post

1.7 x 1.3 cm
Lower Jaw Metastasis - PD

* Tumor mass on left face resolved

Pre-TIL  |  4 months post  |  11 months post
---|---|---
2.4 x 2.2 cm | 0.9 x 0.5 cm | 0.6 x 0.5 cm
Survival Results After Adoptive Cell Therapy with TIL at Moffitt

- 44 of 47 successful TIL expansions (94%)
- 40 treated with TIL of 47 resected patients (85%)
- Median PFS 12 months; projected median OS is 60 months
- 14 deaths
Hypothesis:

Tumor-specific TIL can be isolated and expanded from bladder tumors

30 patients consented
  5 patients NED
  21/25 successful TIL expansions from primary or lymph node metastases
  10 patients were chemo-naïve
  11 patients received neoadjuvant chemotherapy
Expansion of TIL from Bladder Tumors

![Graph showing the number of TIL before treatment with or without chemotherapy.](image-url)
Phenotype of TIL Expanded from Primary Bladder Tumors

CD8+ T cells

p<0.02
Phenotype of TIL Expanded from Primary Bladder Tumors

CD4+ T cells

NK cells

Pre-Treatment
Immune Infiltrates in Primary Bladder Tumors

Bladder Tumor Digest - Chemo

Bladder Tumor Digest - No Chemo

% of Live Cells in Digest

T cells, NK, B cells, Myeloid, Tregs
Expansion of Tumor-Specific TIL from Bladder Tumors

IFN-gamma (pg/ml)

CM
Autologous Tumor
K562

Fragment
Improving TIL Expansion

Hypothesis: Increased expansion of TIL from primary bladder tumors can be achieved by targeting checkpoint receptors on T cells
Anti-4-1BB Agonistic Antibody Increases Melanoma TIL Expansion

N=4 patients
Bladder TIL Expresses 4-1BB

Percent of T cells

Percentage of CD3+ TIL (%)

Percent of T cells

CD4⁺ 41BB⁺

CD8⁺ 41BB⁺
## Addition of Agonistic 4-1BB Antibody Improves Expansion of Bladder TIL

<table>
<thead>
<tr>
<th>Sample #</th>
<th>Number of Expanded Fragments</th>
<th>Total TIL Number</th>
<th>Neoadjuvant chemo</th>
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<tr>
<td></td>
<td>IL-2</td>
<td>IL-2</td>
<td>IL-2 + 4-1BB</td>
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<tr>
<td>19</td>
<td>4</td>
<td>1.23E+07</td>
<td>2.65E+07</td>
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</table>
Expansion of CD8+ T cells after Addition of Agonistic 41BB

![Graph showing percentage of CD8+ cells pre-treatment with IL-2 and IL-2 + anti-4-1BB.](image-url)
Rapid Expansion of Bladder TIL

Patient Number

Fold Expansion

2
19
20
26
27
Summary

• Tumor-reactive TIL can be expanded from primary bladder tumors and LN mets

• TIL can be expanded from bladder tumors of patients treated with chemotherapy

• TIL expansion and specificity is improved with the addition of agonistic 4-1BB antibody

• Bladder TIL can be expanded to clinically relevant numbers for ACT
Future Directions

• Local delivery of TIL
  Murine models of bladder cancer to evaluate feasibility and efficacy

• Systemic delivery of TIL in metastatic bladder cancer patients
  Xenograft models of bladder cancer to evaluate efficacy

• Clinical Trial
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