Adoptive T-cell Transfer

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Professor and Chairman
Melanoma Medical Oncology

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Disclosures

None
Adoptive Cell Therapy (ACT) with Antigen Specific T-cells

Surgical Removal of Cancer Nodule

Single Cell Suspension Incubated with IL-2

T Cells Proliferate

Cancer Cells Die

IL-2
Clinical Response following Lymphodepletion + T-lymphocyte Infusion
Response to TIL Therapy

pre-treatment

4 weeks post-treatment

18 months post-treatment durable response noted
Clinical Response Data from MDACC TIL Clinical Trial

Best overall response:

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>CR*</th>
<th>PR*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>2 (4%)</td>
<td>21 (41%)</td>
<td>23 (45%)</td>
</tr>
</tbody>
</table>

*Some patients are still undergoing clinical response

Radvanyi … Hwu
# Progression-free and Overall Survival

<table>
<thead>
<tr>
<th>Best Overall Response (n=51)</th>
<th>(\text{irRC Responders (45%)})</th>
<th>(\text{irRC Non-Responders (55%)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2</td>
<td>38+, 7, 6+, 6+, 6, 6, 5, 4, 4, 4, 3, 3, 2+, 1</td>
</tr>
<tr>
<td>PR</td>
<td>21</td>
<td>38+, 7, 6+, 6+, 6, 6, 5, 4, 4, 4, 3, 3, 2+, 1</td>
</tr>
<tr>
<td>SD</td>
<td>17</td>
<td>38+, 7, 6+, 6+, 6, 6, 5, 4, 4, 4, 3, 3, 2+, 1</td>
</tr>
<tr>
<td>PD</td>
<td>11</td>
<td>3, 3, 3, 2, 2, 2, 1, 1, 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>2</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>37+, 37+, 36+, 33+, 31+, 30+, 29+, 27+, 22+ 22+, 22, 11+, 11, 10, 9, 9, 8, 8, 3, 3</td>
<td>38+, 7, 6+, 6+, 6, 6, 5, 4, 4, 4, 3, 3, 2+, 1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression-free survival (months)</th>
<th>29, 20+</th>
<th>38+, 37+, 37+, 36+, 33+, 31+, 30+, 29+, 27+, 27+, 25+, 23+, 22+, 22+ 15, 12+, 11+, 10+, 9+, 9+, 3+</th>
<th>38+, 25, 14+, 14, 11+, 10+, 8, 8, 7+, 6+, 6+, 6, 6, 5, 4, 2+</th>
<th>21, 18, 14, 10+, 6, 5, 4+, 4, 3+, 3, 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (months)</td>
<td>29+, 20+</td>
<td>38+, 37+, 37+, 36+, 33+, 31+, 30+, 29+, 27+, 27+, 25+, 23+, 22+, 22+ 15, 12+, 11+, 10+, 9+, 9+, 3+</td>
<td>38+, 25, 14+, 14, 11+, 10+, 8, 8, 7+, 6+, 6+, 6, 6, 5, 4, 2+</td>
<td>21, 18, 14, 10+, 6, 5, 4+, 4, 3+, 3, 2</td>
</tr>
</tbody>
</table>
Numbers of Total TIL Infused and Type of Clinical Response

Clinical Response

- CR/PR
- PD/SD

Total TILs infused (x 10^9)

P = 0.003

Radvanyi ... Hwu
CD8+ TIL are Critical

Radvanyi ... Hwu
Higher Proportion of CD8+ TILs Co-expressing BTLA in Responders

% PD-1 in CD8+

% BTLA in CD8+

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CD8 by IHC in Original Metastases is Associated with CD8 % in Expanded TIL and Survival

\[ P = 0.049, \ r^2 = 0.305 \]

Jie Qing Chen
Overall Survival of Patients Receiving TILs with the Chemotherapy Preparative Regimen Alone (no TBI) or plus 2 or 12 Gy TBI.

Rosenberg SA et al. CCR 2011
### Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using T-Cell Transfer Immunotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (% of patients)</th>
<th>n (% of patients)</th>
<th>n (% of patients)</th>
<th>OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>PR</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>No TBI</td>
<td>43</td>
<td>16 (37)</td>
<td>5 (12)</td>
<td>21 (49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84, 36, 29, 28, 14, 12, 11, 7, 7, 7, 4, 4, 2, 2, 2</td>
<td>82+, 81+, 79+, 78+, 64+</td>
<td></td>
</tr>
<tr>
<td>200 TBI</td>
<td>25</td>
<td>8 (32)</td>
<td>5 (20)</td>
<td>13 (52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14, 9, 6, 6, 5, 4, 3, 3</td>
<td>68+, 64+, 60+, 57+, 54+</td>
<td></td>
</tr>
<tr>
<td>1,200 TBI</td>
<td>25</td>
<td>8 (32)</td>
<td>10 (40)</td>
<td>18 (72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21, 13, 7, 6, 6, 5, 3, 2</td>
<td>48+, 45+, 44+, 44+, 39+, 38+, 38+, 38+, 37+, 19</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>32 (34)</td>
<td>20 (22)</td>
<td>52 (56)</td>
</tr>
</tbody>
</table>

Rosenberg SA et al, CCR Jul 2011

*Note: The table shows the number of patients (n) and the percentage (%) of complete responses (CR) and partial responses (PR) for different treatments, along with the duration in months (mo) and the overall response (OR) percentages.*
## Treatment Characteristics During TIL Therapy and Clinical Outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>PS</th>
<th>Lactate dehydrogenase</th>
<th>Stage</th>
<th>Site of biopsy*</th>
<th>Evaluable metastasis</th>
<th>IL-2 doses</th>
<th>Resp.</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responders (n = 10)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>05-LA</td>
<td>41/M</td>
<td>0</td>
<td>Normal</td>
<td>M1a</td>
<td>SC</td>
<td>SC nodules</td>
<td>10</td>
<td>CR</td>
<td>20†</td>
<td>20†</td>
</tr>
<tr>
<td>19-NS</td>
<td>66/M</td>
<td>1</td>
<td>Normal</td>
<td>M1c</td>
<td>Perito.</td>
<td>Peritoneum</td>
<td>3</td>
<td>CR</td>
<td>4†</td>
<td>4†</td>
</tr>
<tr>
<td>03-MG</td>
<td>36/M</td>
<td>0</td>
<td>Normal</td>
<td>M1c</td>
<td>LN</td>
<td>Soft tissue, lung, bone</td>
<td>15</td>
<td>PR</td>
<td>9</td>
<td>21†</td>
</tr>
<tr>
<td>06-TS</td>
<td>60/M</td>
<td>0</td>
<td>Normal</td>
<td>M1b</td>
<td>Lung</td>
<td>Lung</td>
<td>5</td>
<td>PR</td>
<td>18†</td>
<td>18†</td>
</tr>
<tr>
<td>09-SD‡</td>
<td>45/M</td>
<td>0</td>
<td>Normal</td>
<td>M1b</td>
<td>LN</td>
<td>Lung</td>
<td>7</td>
<td>PR</td>
<td>13†</td>
<td>13±</td>
</tr>
<tr>
<td>13-BS</td>
<td>61/M</td>
<td>0</td>
<td>Normal</td>
<td>M1b</td>
<td>Lung</td>
<td>Lung</td>
<td>9</td>
<td>PR</td>
<td>10†</td>
<td>10†</td>
</tr>
<tr>
<td>14-SV‡</td>
<td>71/M</td>
<td>0</td>
<td>Above</td>
<td>M1a</td>
<td>SC</td>
<td>SC, LN</td>
<td>9</td>
<td>PR</td>
<td>3†</td>
<td>9†</td>
</tr>
<tr>
<td>16-SH</td>
<td>41/M</td>
<td>1</td>
<td>Normal</td>
<td>M1c</td>
<td>SC</td>
<td>Liver, adrenal, lung, LN</td>
<td>8</td>
<td>PR</td>
<td>6†</td>
<td>6†</td>
</tr>
<tr>
<td>18-WR</td>
<td>70/F</td>
<td>0</td>
<td>Normal</td>
<td>M1a</td>
<td>LN</td>
<td>SC, LN</td>
<td>8</td>
<td>PR</td>
<td>4†</td>
<td>4†</td>
</tr>
<tr>
<td>20-TY</td>
<td>58/M</td>
<td>0</td>
<td>Normal</td>
<td>M1a</td>
<td>SC</td>
<td>SC, LN</td>
<td>7</td>
<td>PR</td>
<td>3†</td>
<td>3†</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.1 ± 3.2</td>
<td></td>
<td>(7.3)</td>
<td>(9.3)</td>
</tr>
<tr>
<td><strong>Nonresponders (n = 10)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01-AY</td>
<td>56/M</td>
<td>0</td>
<td>Normal</td>
<td>M1c</td>
<td>Lung</td>
<td>Lung, SC, bone</td>
<td>9</td>
<td>SD</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>07-ZR</td>
<td>22/M</td>
<td>0</td>
<td>Normal</td>
<td>M1b</td>
<td>Lung</td>
<td>Lung</td>
<td>7</td>
<td>SD</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>08-RM</td>
<td>34/F</td>
<td>0</td>
<td>Normal</td>
<td>M1c</td>
<td>Liver</td>
<td>Liver</td>
<td>14</td>
<td>SD</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>12-VS‡</td>
<td>41/F</td>
<td>0</td>
<td>Normal</td>
<td>M1a</td>
<td>SC</td>
<td>SC, LN</td>
<td>11</td>
<td>SD</td>
<td>11†</td>
<td>11†</td>
</tr>
<tr>
<td>02-PE</td>
<td>36/M</td>
<td>0</td>
<td>Above</td>
<td>M1c</td>
<td>LN</td>
<td>LN, adrenal, periton.</td>
<td>9</td>
<td>PD</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>04-BA‡</td>
<td>57/M</td>
<td>0</td>
<td>Normal</td>
<td>M1c</td>
<td>Lung</td>
<td>LN, lung, adrenal,</td>
<td>13</td>
<td>PD</td>
<td>3</td>
<td>20†</td>
</tr>
<tr>
<td>10-BE</td>
<td>53/F</td>
<td>0</td>
<td>Normal</td>
<td>M1c</td>
<td>LN</td>
<td>SC, LN, adrenal</td>
<td>6</td>
<td>PD</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>11-KB</td>
<td>57/M</td>
<td>1</td>
<td>Above</td>
<td>M1c</td>
<td>LN</td>
<td>Lung, LN</td>
<td>6</td>
<td>PD</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>15-SM‡</td>
<td>52/M</td>
<td>1</td>
<td>Above</td>
<td>M1c</td>
<td>Liver</td>
<td>Bone, liver</td>
<td>10</td>
<td>PD</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>17-ZD‡</td>
<td>68/F</td>
<td>1</td>
<td>Above</td>
<td>M1c</td>
<td>Pleura</td>
<td>Lung, pleura, bone</td>
<td>5</td>
<td>PD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.0 ± 3.1</td>
<td></td>
<td>2.7</td>
<td>5.7</td>
</tr>
</tbody>
</table>

* Site of tumor sample  
† Ongoing  
‡ Patients with HLA-A*0201.
Does PD-1 inhibition enhance T-cell therapy?
Increased Number of Transferred T-cells at the Tumor Site in Tumor-bearing Mice Receiving anti-PD-1 and ACT Treatment

Delayed Tumor Progression in Tumor-bearing Mice Receiving anti-PD-1 and ACT Treatment

Question?

Does BRAF inhibition enhance T-cell therapy?
Combination of PLX4720 with Adoptive T-cell Therapy Leads to Enhanced Anti-tumor Activity (B6 nude mice)

Administration of PLX4720 Increases Tumor Infiltration of Adoptively Transferred pmel-1 T-cells \textit{in vivo}

Liu C…Hwu P.
Combining BRAF(V600E) Inhibition and Immunotherapy

Immunotherapy Alone

Immunotherapy Plus BRAF(V600E) Inhibition

Jahan Khalili / Greg Lizee
Insertion of Genes into Lymphocytes to Enhance Antitumor Properties

Native TCR genes to direct cell specificities against the tumor

Chimeric receptors to enhance T-Cell activation and costimulation

Chemokine receptors to enhance migration of T-cells to tumor

Retroviral vectors can insert novel genes into lymphocytes
Chimeric Antibody/T Cell Receptor: Combines Antibody V Region and T-cell Signaling Chains

Antibody

TCR

scFv-γ

Fc-γ

extracellular

intracellular
Transduction of T-cells with Chimeric Receptor Genes to Direct T-cell Specificity

Transduced T-cell

Insert Chimeric Receptor Gene

Tumor cell
Brief Definitive Report

Lysis of Ovarian Cancer Cells by Human Lymphocytes Redirected with a Chimeric Gene Composed of an Antibody Variable Region and the Fc Receptor Gamma Chain.

By Patrick Hwu,* G. E. Shafer,* J. Treisman,* G. Schindler,‡ G. Gross,‡ R. Cowherd,* S.A. Rosenberg,* and Z. Eshhar‡

From the *Surgery Branch, National Cancer Institute, National Institutes of Health Bethesda, Maryland 20892; and the ‡Department of Chemical Immunology, Weizmann Institute of Science, Rehovot 76100, Israel
The Human Ovarian Carcinoma Cell Line IGROV-1 is Specifically Lysed by Mov-γ TIL

Hwu et al JEM 1993
A T cell-independent antitumor response in mice with bone marrow cells retrovirally transduced with an antibody / Fc-γ chain chimeric receptor gene recognizing a human ovarian cancer antigen

Gang Wang, Rajesh K. Chopra, Richard E. Royal, James C. Yang, Steven A. Rosenberg & Patrick Hwu

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.
Tumor Growth in $MO\nu\gamma$-Reconstituted Mice after T-cell Depletion
Chimeric Antigen Receptor Domains

T-cell activation domain → Co-stimulatory domain → Hinge and transmembrane region → Antibody-derived recognition moiety

CAR genes inserted into T cell via vector

CAR-expressing T cell → Anti-CD19 CAR protein

CD19 Cancer cell

Kochenderfer JN, Rosenberg SA
Nature Review | Clinical Oncology 2013
## Summary of Published anti-CD19 CAR Clinical Trial Results

### Table 1 | Summary of published anti-CD19 CAR clinical trial results

<table>
<thead>
<tr>
<th>Institution</th>
<th>Gene-transfer vector used</th>
<th>Antibody*</th>
<th>Co-stimulatory domain in CAR</th>
<th>Chemotherapy administered before cell infusion</th>
<th>Normal B-cell depletion†</th>
<th>Regression of malignancy reported?</th>
<th>Cytokine-release-type toxicities§ reported?</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylor College of Medicine</td>
<td>Gamma-retrovirus</td>
<td>FMC63</td>
<td>CD28 or none</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>City of Hope</td>
<td>Plasmid electroporation</td>
<td>FMC63</td>
<td>None</td>
<td>Fludarabine before some T cell infusions</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Memorial Sloan–Kettering Cancer Center</td>
<td>Gamma-retrovirus</td>
<td>SJ25C1</td>
<td>CD28</td>
<td>None or cyclophosphamide</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>Gamma-retrovirus</td>
<td>FMC63</td>
<td>CD28</td>
<td>Cyclophosphamide and fludarabine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>Lentivirus</td>
<td>FMC63</td>
<td>4-1BB</td>
<td>Variable</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>3</td>
</tr>
</tbody>
</table>

*The antibody that CAR antigen-recognition moiety was derived from. †Reported for >3 months. §For example, hypotension. Abbreviation: CAR, chimeric antigen receptor.
Summary of the 1\textsuperscript{st} Patients Treated on the NCI Adult Autologous anti-CD19 CAR Trial

**Table 2 | Summary of the first patients treated on the NCI adult autologous anti-CD19 CAR trial\cite{KochenderferJN, RosenbergSA}**

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Age (years)</th>
<th>Malignancy</th>
<th>Number of unique prior therapies</th>
<th>Number of CAR-expressing T cells infused per kg</th>
<th>Response (duration in months after T-cell infusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a\textsuperscript{\dagger}</td>
<td>47</td>
<td>Follicular lymphoma</td>
<td>4</td>
<td>$0.3 \times 10^7$</td>
<td>PR (7)</td>
</tr>
<tr>
<td>1b\textsuperscript{\dagger}</td>
<td>48</td>
<td>Follicular lymphoma</td>
<td>5</td>
<td>$1.3 \times 10^7$</td>
<td>PR (33)</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>Follicular lymphoma</td>
<td>5</td>
<td>$0.3 \times 10^7$</td>
<td>NE</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>Chronic lymphocytic leukaemia</td>
<td>3</td>
<td>$1.1 \times 10^7$</td>
<td>CR (24)</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>Splenic, marginal zone lymphoma</td>
<td>3</td>
<td>$1.1 \times 10^7$</td>
<td>PR (12)</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>Chronic lymphocytic leukaemia</td>
<td>4</td>
<td>$0.3 \times 10^7$</td>
<td>SD (6)</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>Chronic lymphocytic leukaemia</td>
<td>7</td>
<td>$1.7 \times 10^7$</td>
<td>PR (7)</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>Chronic lymphocytic leukaemia</td>
<td>4</td>
<td>$2.8 \times 10^7$</td>
<td>CR (21+)</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>Follicular lymphoma</td>
<td>7</td>
<td>$3.0 \times 10^7$</td>
<td>PR (11\textsuperscript{\S})</td>
</tr>
</tbody>
</table>

\*All eight patients were male. \*Patient 1 was treated twice. \*Not evaluable for malignancy response beyond 11 months because the patient developed laryngeal carcinoma. Abbreviations: CAR, chimeric antigen receptor; CR, complete remission; NE, not evaluable for malignancy response because the patient died with influenza pneumonitis; PR, partial remission; SD, stable disease.

Kochenderfer JN, Rosenberg SA
Nature Review | Clinical Oncology 2013
Antitumor activity and long-term fate of chimeric antigen receptor-positive T-cells in patients with neuroblastoma

Chrystal U. Louis,1-3 Barabara Savoldo,1,3 Gianpietro Dotti,1,4 Martin Pule,1 Eric Yvon,1 G. Doug Myers,1 Claudia Rossig,1 Heidi V. Russell,2,3 Oumar Diouf,1,3 Enli Liu,1 Meng-Fen Wu,5 Adiran P. Gee,1 Zhuhong Mei,1 Cliona M. Rooney,1,3,6 Helen E. Heslop,1,4 and Malcolm K. Brenner,1,4

1Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children’s Hospital, The Methodist Hospital Houston, TX; 2Texas Children’s Cancer Center, Baylor College of Medicine, Houston, TX Departments of 3Pediatrics, and 4Medicine, Baylor College of Medicine, Houston, TX; 5Biostatistics Shared Resource Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX; and 6Department of Pathology and Immunology, Baylor College of Medicine, Houston TX

- Anti-GD2 CAR in EBV CTLs
- 3 of 11 patients with active disease experienced CR
- Persistence of CAR CTLs beyond 6 weeks was associated with superior clinical outcome.
Insertion of Genes into Lymphocytes to Enhance Antitumor Properties

Native TCR genes to direct cell specificities against the tumor

Chimeric receptors to enhance T-Cell activation and costimulation

Chemokine receptors to enhance migration of T-cells to tumor

Retroviral vectors can insert novel genes into lymphocytes
One of the Rate-limiting Steps in ACT is the Inefficient Migration of T-cells to Tumor
The Presence of CXCL1 in the Tumor Microenvironment
Melanoma Cells Produce CXCL1 which Serves as an Autocrine Growth Factor and Stimulates Angiogenesis
Transduction of T-cells with CXCR2 May Allow Them to Migrate to Tumor Sites

CXCL-1

Angiogenesis

Autocrine Growth Signal

CXCR2

Tumor Cells
CXCR2-expressing T-cells Display Enhanced Accumulation in Tumor Site

**CXCR2 T-Cells**

**Control T-cells**

**Tumor site**

**Peripheral blood**

The intensity of ROI (Photons’S⁻¹ cm⁻²) and Thy1.1+ cell/CD8⁺ T cell in peripheral blood (%): P=0.0182 and P=0.1126.
The Expression of CXCR2 in Pmel T-cells Delays Tumor Growth and Improves the Survival of Tumor-bearing Mice
Clinical Trial Plans

Tumor biopsy to determine if CXCR2-transduced T-cells preferentially migrate to the tumor
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