Chimeric antigen receptor (CAR) modified T cells as a novel approach to immunotherapy of B cell malignancies.

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Conflict of Interest Disclosure

Renier Brentjens MD PhD

Has no real or apparent conflicts of interest to report.
Generation of a tumor specific chimeric antigen receptor (CAR)

α-tumor mAb

α-tumor scFv-CD28-ζ

TCR complex

CAR retroviral vector
Advantages of chimeric antigen receptors (CARs)

• HLA-independent antigen recognition
• CARs active in both CD4$^+$ and CD8$^+$ T cells
• Target antigens include proteins, carbohydrates and glycolipids
• Significant quantities of tumor specific T cells are rapidly generated
• Minimal risk of generating undesired autoimmunity or GvHD
CD19

• CD19 expression is restricted to B cells and possibly follicular dendritic cells
• CD19 is not expressed on pluripotent bone marrow stem cells
• CD19 is expressed on the surface of most B cell malignancies
Expression of CD19 and other B cell markers on B lineage cells

- Stem Cell
- pro B
- pre B
- immature B
- mature B
- plasma cell

CD19

CD22

CD20

preB-ALL

B cell lymphomas and leukemias

myelomas
Generation of CD19-targeted T cells for treatment of B cell malignancies

1. Construct a chimeric antigen receptor (CAR)

2. Subclone CAR gene into a retroviral vector (SFG)

3. Transduce and expand patient T cells \textit{ex vivo}

4. Infuse transduced T cells to eradicate CD19$^+$ tumor

\begin{align*}
\text{SFG-19z1} & \quad \text{SD} \quad \Psi \quad \text{SA} \\
\text{VH} & \quad \text{VL} \quad \text{CD8} \quad \zeta \text{ chain} \quad \text{3' LTR}
\end{align*}
Expansion of CD19-targeted T cells with \textit{in vivo} anti-tumor activity

**A**

![Graph showing cell count over time for different conditions](image)

**B**

![Flow cytometry plots showing CAR expression before and after expansion](image)

**C**

![Graph showing percentage survival of Raji tumor](image)

Brentjens et al. Nat Med 2003
19z1+ T cells require in vivo co-stimulation

NALM6

NALM6/CD80

% Survival

Time (days)

% Survival

Time (days)

19z1

Pz1

P<0.001

P=0.029

Brentjens et al Nat Med 2003
T cell co-stimulation

- T cell activation and proliferation requires both signaling through the TCR (signal 1) and signaling through a co-stimulatory receptor (signal 2) (i.e. CD28 binding to CD80)

- In the absence of co-stimulation (signal 2), the T cell will either become unresponsive (anergic) or undergo activation-induced cell death (AICD/apoptosis)
Second generation 19-28z CAR

Moving into the clinic. . . .
1928z+ T cell Manufacturing Flow

Day 0
Thaw/Wash
Cytomate

Incubation
Dynabeads
CD3/28

CLL patient
T cells

Selection
ClinExVivo MPC

CD3+ enriched
activated
T cells

Day 3-4
Transduction
SFG-1928z
Vector

1928z+ transduced
T cells

Day ≥10
Debeading
ClinExVivo MPC

1928z+ expanded T cells

Biosafety/
QC release tests

Infusion

Wash/Formulation
Cytomate

Effector/Memory phenotype
In vitro CTL assay
In vivo antitumor activity in
SCID Beige mice

Hollyman et al, J. Immunother, 2009
A Clinical Trial in Patients with Chronic Lymphocytic Leukemia (CLL)

IRB #06-138
A Phase I Trial for the Treatment of Purine Analog-Refractory Chronic Lymphocytic Leukemia using Autologous T cells Genetically Targeted to the B cell Specific Antigen CD19

FUNDED: STRAP Supplement 5R01CA138738-03, MSKCC ETC program project grant
Enrollment Criteria:
   Patients with purine analog-refractory CLL disease

Treatment Protocol Step 1:
   Dose escalation of 19-28z T cells:
      3 dose levels (3 x 10^7 T cells/kg, 1 x 10^8 T cells/kg, and 3 x 10^8 T cells/kg)

Treatment Protocol Step 2:
   Dose escalation of cyclophosphamide prior to MTD dose of T cells established in phase I:
      3 dose levels of cyclophosphamide (1.5g/m^2, 2.2g/m^2, and 3.0g/m^2)

Anticipated patient enrollment
   24-36 patients
Meanwhile, back in the lab. . . .
Generation of a syngeneic hCD19$^+$ tumor model to study modified T cell biology

- Xenograft SCID-Beige murine tumor models have distinct limitations:
  - Tissues (tumor and T cells) are xenogeneic to the host
  - Mice lack a competent immune system
- A syngeneic murine tumor model has distinct advantages:
  - T cells are syngenic to the host
  - Mice are immune competent
  - Normal B cells will express the hCD19 targeted antigen
Syngeneic EL4(hCD19) tumor model

- IV injection
- Harvest splenocytes
- Retroviral transduction with chimeric receptor
- EL4(hCD19)

**Assessments:**
- T cell eradication of tumor
- T cell homing to tumor
- Long-term survival of T cells
- Memory T cell response to rechallenge with tumor
- T cell proliferation in vivo
- Efficacy of suicide vectors
- T cell proliferation in vivo
- Determination of side effects of therapy
- Long-term survival of T cells
- Memory T cell response to rechallenge with tumor
- T cell proliferation in vivo
- Efficacy of suicide vectors
- Determination of side effects of therapy

**Results:**
- 53% cell kill
- M1 gate

**Graph:**
- Counts
- FL1-H

Syngeneic EL4(hCD19) tumor model

Percent Survival vs Days since tumor cell injection
Persistent B cell aplasias induced by lymphodepletion and 19z1+ T cells
Lymphodepletion: Mechanism(s)

- Promotion of homeostatic proliferation
- Depletion of cytokine “sinks” by reduction of endogenous lymphocytes
- Depletion of endogenous inhibitory CD4+ T regulatory cells (Tregs)
- Depletion of endogenous inhibitory myeloid derived suppressor cells (MDSCs)
- Decreased competition for access to antigen presenting cells such as dendritic cells (DCs)
- Translocation from the gut of bacterial products including LPS and other Toll-like receptor agonists (TLRs) induces activation and maturation of DCs and heighten levels of systemic inflammatory cytokines (IL-12p70)

Gattinoni et al Nat Rev Imm (2006), Paulos et al JCI (2007)
Lymphodepletion enhances anti-tumor efficacy of 19z1⁺ T cells.
Back to the clinic. . . .
Amended IRB #06-138

• **Enrollment Criteria:**
  Patients with purine analog-refractory CLL disease

• **Protocol Design:**
  – A 3 step design:
    • Step I: low dose modified T cells alone
    • Step II: combination with dose escalating lymphodepleting cyclophosphamide chemotherapy
    • Step III: escalating T cell dose at established cyclophosphamide MTD from Step II
A Clinical Trial in Patients with Acute B cell Lymphoblastic Leukemia (B-ALL)

IRB #09-114
A Phase I trial of precursor B cell Acute Lymphoblastic Leukemia (B-ALL) treated with autologous T cells genetically targeted to the B cell specific antigen CD19.
• **Enrollment Criteria:**
  Patients with relapsed B cell ALL

• **Protocol Design:**
  – A standard phase I dose escalation study:
    • Leukapheresis to obtain T cells
    • Relapsed patients receive salvage re-induction therapy (Prednisone, vincristine, PEG-Asparaginase)
    • Regardless of remission status, patients receive high dose cyclophosphamide (3 gm/m\(^2\))
    • Infusion of autologous 19-28z T cells
## MSKCC clinical trial results

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Diagnosis - Patient</th>
<th>Age at Diagnosis (years)</th>
<th>Age at Treatment (years)</th>
<th>Sex</th>
<th>Indication for Treatment</th>
<th>Prior Therapies</th>
<th>Genetic Abnormalities/ IgV&lt;sub&gt;H&lt;/sub&gt; Mutation Status</th>
<th>WBC (x10&lt;sup&gt;9&lt;/sup&gt;/ul)</th>
<th>ALC (x10&lt;sup&gt;9&lt;/sup&gt;/ul)</th>
<th>Hgb (g/dL)</th>
<th>PLT (x10&lt;sup&gt;9&lt;/sup&gt;/ul)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL-1</td>
<td>44</td>
<td>51</td>
<td>M</td>
<td>Bulky LAD</td>
<td>FCR, PCRM</td>
<td>del11q</td>
<td>200.6</td>
<td>196.6</td>
<td>7.1</td>
<td>26</td>
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<tr>
<td>CLL-2</td>
<td>66</td>
<td>72</td>
<td>M</td>
<td>Bulky LAD</td>
<td>FR, RCVP, PCRM</td>
<td>Unmutated IgV&lt;sub&gt;H&lt;/sub&gt;</td>
<td>4.2</td>
<td>3.4</td>
<td>9.9</td>
<td>60</td>
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<tr>
<td>CLL-3</td>
<td>62</td>
<td>73</td>
<td>F</td>
<td>Bulky LAD</td>
<td>Chlorambucil, PCR, PCRM</td>
<td>Normal karyotype</td>
<td>136.4</td>
<td>132.3</td>
<td>8.9</td>
<td>100</td>
</tr>
<tr>
<td>CLL-4</td>
<td>63</td>
<td>69</td>
<td>M</td>
<td>Bulky LAD</td>
<td>R, PCRM</td>
<td>del11q</td>
<td>187.1</td>
<td>174</td>
<td>9.9</td>
<td>189</td>
</tr>
<tr>
<td>CLL-5</td>
<td>65</td>
<td>68</td>
<td>M</td>
<td>Bulky LAD</td>
<td>PCR</td>
<td>del11q, trisomy 12</td>
<td>76.3</td>
<td>66.4</td>
<td>10</td>
<td>162</td>
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<tr>
<td>CLL-6</td>
<td>56</td>
<td>68</td>
<td>M</td>
<td>Bulky LAD</td>
<td>RCVP, PCR, Bendamustine</td>
<td>del11q, inv, unmutated IgV&lt;sub&gt;H&lt;/sub&gt;</td>
<td>97.1</td>
<td>92.2</td>
<td>8.9</td>
<td>174</td>
</tr>
<tr>
<td>CLL-7</td>
<td>52</td>
<td>62</td>
<td>M</td>
<td>Bulky LAD</td>
<td>CVP, RC, PCRM, PCRM</td>
<td>del17p, unmutated IgV&lt;sub&gt;H&lt;/sub&gt;</td>
<td>1.9</td>
<td>1</td>
<td>10</td>
<td>61</td>
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<tr>
<td>CLL-8</td>
<td>58</td>
<td>61</td>
<td>M</td>
<td>Bulky LAD</td>
<td>RCVP, Alemtuzumab</td>
<td>del17p, monosomy 14, monosomy 15</td>
<td>5.4</td>
<td>3.3</td>
<td>11.6</td>
<td>41</td>
</tr>
<tr>
<td>ALL-1</td>
<td>66</td>
<td>67</td>
<td>M</td>
<td>Relapsed disease</td>
<td>C, Mitoxantrone, vincristine, etoposide</td>
<td>Normal karyotype</td>
<td>2.9</td>
<td>0.7</td>
<td>8.6</td>
<td>126</td>
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<tr>
<td>ALL-2</td>
<td>45</td>
<td>48</td>
<td>F</td>
<td>Relapsed disease</td>
<td>HyperCVAD, mitoxantrone, cytarabine, vincristine</td>
<td>Normal karyotype</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

CLL, chronic lymphocytic leukemia; ALL, acute lymphoblastic leukemia; M, male; F, female; LAD, lymphadenopathy; FCR, fludarabine, cyclophosphamide, rituximab; PCRM, pentostatin, cyclophosphamide, rituximab, mitoxantrone, FR, fludarabine, rituximab; RCVP, rituximab, cyclophosphamide, vincristine, prednisone; C, cyclophosphamide; PCR, pentostatin, cyclophosphamide, rituximab; R, rituximab; RC, rituximab, cyclophosphamide; HyperCVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; IgV<sub>H</sub>, immunoglobulin heavy chain; WBC, white blood cell counts; ALC, absolute lymphocyte counts; Hgb, hemoglobin; PLT, platelet counts; *: This patient is yet to be treated with modified T cells

Brentjens et al Blood 2011
# MSKCC clinical trial results

Table 5. Summary of patient responses

<table>
<thead>
<tr>
<th>Diagnosis-Patient</th>
<th>Response to T-cell infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL-1</td>
<td>No objective response</td>
</tr>
<tr>
<td>CLL-2</td>
<td>No objective response</td>
</tr>
<tr>
<td>CLL-3</td>
<td>No objective response</td>
</tr>
<tr>
<td>CLL-4</td>
<td>Not evaluable</td>
</tr>
<tr>
<td>CLL-5</td>
<td>Marked reduction in lymphadenopathy at 3 months subsequently stable for 6 months</td>
</tr>
<tr>
<td>CLL-6</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>CLL-7</td>
<td>Stable disease, lasting 4 months</td>
</tr>
<tr>
<td>CLL-8</td>
<td>Stable disease, lasting &gt;8 weeks</td>
</tr>
<tr>
<td>ALL-1</td>
<td>Persistent B cell aplasia in bone marrow and peripheral blood</td>
</tr>
</tbody>
</table>
MSKCC clinical trial results

Pretreatment

1 month following treatment

3 months following treatment

Brentjens et al Blood 2011
MSKCC clinical trial results
Other published clinical trial results with CD19-targeted CAR modified T cells: NCI and UPenn
NCI clinical trial results

Kochenderfer et al Blood 2010
NCl clinical trial results

Patient with relapsed follicular NHL

Prior Therapies:  PACE, idiotype vaccine, ipilimumab, EPOCH-R

Conditioning: high dose cyclophosphamide with fludarabine

Post infusion:  IL-2 tid x 3 days

Response:  PR with persistent B cell aplasias

Kochenderfer et al Blood 2010

An additional 7 patients plus retreatment of patient 1 with low grade B cell malignancies

Prior Therapies: Not Reported

Conditioning: high dose cyclophosphamide with fludarabine

Post infusion:  IL-2 tid as tolerated

Response:  1/8 CR, 4/8 PR with persistent B cell aplasias in 4/8 patients treated

Kochenderfer et al Blood 2011
UPenn clinical trial results
## UPenn clinical trial results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prior Chemotherapy</th>
<th>Conditioning Chemotherapy</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fludarabine, Rituximab, Alemtuzumab, R-CVP, Lenolidomide, PCR</td>
<td>Bendamustine</td>
<td>CR (11+ months)</td>
</tr>
<tr>
<td>2</td>
<td>Alemtuzumab</td>
<td>Bendamustine/Rituximab</td>
<td>PR (7 months)</td>
</tr>
<tr>
<td>3</td>
<td>Rituximab/Fludarabine, Rituximab/Bendamustine, Alemtuzumab</td>
<td>Pentostatin/Cytoxan</td>
<td>CR (10+ months)</td>
</tr>
</tbody>
</table>
## Comparisons of published clinical data

<table>
<thead>
<tr>
<th>Center</th>
<th># patients</th>
<th>scFv</th>
<th>CAR design</th>
<th>Chemo-sensitive disease?</th>
<th>vector</th>
<th>B cell aplasia?</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI</td>
<td>8</td>
<td>FMC63</td>
<td>CD28-ζ</td>
<td>Yes†</td>
<td>retro-virus</td>
<td>Yes</td>
</tr>
<tr>
<td>UPenn</td>
<td>3</td>
<td>FMC63</td>
<td>4-1BB-ζ</td>
<td>Yes</td>
<td>lenti-virus</td>
<td>Yes</td>
</tr>
<tr>
<td>MSKCC</td>
<td>12</td>
<td>SJ25C1</td>
<td>CD28-ζ</td>
<td>No</td>
<td>retro-virus</td>
<td>Yes*</td>
</tr>
</tbody>
</table>

† Data available on only 1 of 8 patients  
* In the setting of B-ALL patients in CR
There are many current ongoing phase I clinical trials targeting CD19 with many clinically relevant variables:

- CAR gene transfer
  - Retrovirus
  - Lentivirus
  - Transposons
  - Electroporation
- Targeted disease
  - Leukemia (CLL ALL)
  - Lymphoma (NHL)
- Patient population
  - Pediatric
  - Adult
- Prior lymphodepletion/chemotherapy sensitive disease (+/-)
- CAR design
  - First generation CARs
  - Second and third generation CARs
Variables in CAR design

First-Generation CAR  
scFv-CD3ζ

Second-Generation CAR  
scFv-CD28-CD3ζ

Third-Generation CAR  
scFv-CD28-4-1BB-CD3ζ  
scFv-CD28-OX40-CD3ζ
## The Result

<table>
<thead>
<tr>
<th>Center</th>
<th>Disease</th>
<th>CAR Endodomain</th>
<th>Vector to Express CAR</th>
<th>Conditioning Regimen</th>
<th>Target</th>
<th>Status</th>
<th>ClinicalTrials.Gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC</td>
<td>CLL –refractory</td>
<td>Zeta/28</td>
<td>RV</td>
<td>Cyclophosphamide</td>
<td>CD3-selected</td>
<td>Open. 6 treated</td>
<td>NCT00466531</td>
</tr>
<tr>
<td>MSKCC</td>
<td>B ALL-relapsed</td>
<td>Zeta/28</td>
<td>RV</td>
<td>Cyclophosphamide</td>
<td>CD3-selected</td>
<td>Open. 1 treated</td>
<td>NCT01044069</td>
</tr>
<tr>
<td>BCM</td>
<td>B NHL and CLL</td>
<td>Zeta/28 vs. Zeta</td>
<td>RV</td>
<td>NA</td>
<td>PBMC (OKT3 and IL-2)</td>
<td>Open. 5 treated: 4 DLBCL 1 B-CLL</td>
<td>NCT00586391</td>
</tr>
<tr>
<td>BCM</td>
<td>B NHL and CLL</td>
<td>Zeta/28 vs. Zeta-EBV</td>
<td>RV</td>
<td>NA</td>
<td>PBMC and EBV CTL</td>
<td>2 treated</td>
<td>NCT00608270</td>
</tr>
<tr>
<td>BCM</td>
<td>B ALL, S/P HSCT</td>
<td>Zeta/28</td>
<td>RV</td>
<td>+30 days after allo-HSCT</td>
<td>Multi-virus CTL</td>
<td>open</td>
<td>NCT00709033</td>
</tr>
<tr>
<td>NCI</td>
<td>Lymphoma, CLL</td>
<td>Zeta/28</td>
<td>RV</td>
<td>Fludarabine and Cyclophosphamide</td>
<td>PBMC (anti-CD3 + REP)</td>
<td>Open. 4 treated</td>
<td>NCT00924326</td>
</tr>
<tr>
<td>U Penn</td>
<td>Refractory B Leukemia/ Lymphoma</td>
<td>Zeta/41BB vs. Zeta</td>
<td>LV</td>
<td>Variable</td>
<td>Auto PBMC (CD3/CD28 beads)</td>
<td>To open</td>
<td>NCT00891215</td>
</tr>
<tr>
<td>U Penn</td>
<td>Relapsed ALL, S/P HSCT</td>
<td>Zeta/41BB</td>
<td>LV</td>
<td>Variable</td>
<td>Allo DLI</td>
<td>To open</td>
<td></td>
</tr>
<tr>
<td>MDACC</td>
<td>B-NHL, S/P autologous HSCT</td>
<td>Zeta/CD28</td>
<td>Electroporation/SB plasmids</td>
<td>BEAM-R</td>
<td>Auto PBMC (+/- IL-2)</td>
<td>To open</td>
<td>NCT00968760</td>
</tr>
<tr>
<td>MDACC</td>
<td>B-lineage malignancy, S/P allogeneic HSCT</td>
<td>Zeta/CD28</td>
<td>Electroporation/SB plasmids</td>
<td>Conditioning regimen for HSCT</td>
<td>Allogeneic PBMC or umbilical cord blood</td>
<td>To open</td>
<td></td>
</tr>
<tr>
<td>COH</td>
<td></td>
<td>Zeta</td>
<td>Plasmid</td>
<td>Fludarabine or +28 days S/P HSCT</td>
<td>PBMC</td>
<td>Closed. 3 treated</td>
<td>NCT00182650</td>
</tr>
<tr>
<td>COH/FHCRC</td>
<td>Recurrent LCL/MCL, S/P Autologous HSCT</td>
<td>Zeta</td>
<td>LV</td>
<td>Tcm: CD8+/CD4-CD45RA-/CD62+</td>
<td>To open</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kohn et al Mol Ther (2011)
To generate a multi-center consortium utilizing harmonized pre-existing ongoing clinical trials to address variables in gene transfer and CAR design, as well as validate this therapeutic approach in larger multi-center clinical trials. To directly compare retroviral and lentiviral vectors for gene transfer of CARs into patient T cells.

1) To directly compare *in vivo* persistence and anti-tumor efficacy of second generation CD19 targeted CARs containing either the CD28 or 4-1BB co-stimulatory domains.

2) To more rapidly generate statistically relevant data regarding these variables.

3) To further demonstrate the “exportability” of this technology between academic institutions suitably endowed with requisite GMP facilities validating the feasibility of conducting future planned phase II-III clinical trials utilizing this technology.
Meanwhile, back in the lab. . . .
Syngeneic EL4(hCD19) tumor model

- IV injection
- mCD19+-/- hCD19+/-
- Assess T cell eradication of tumor
- Assess T cell homing to tumor
- Assess long-term survival of T cells
- Assess memory T cell response to rechallenge with tumor
- Assess T cell proliferation in vivo
- Assess the efficacy of suicide vectors
- Determine the side effects of therapy
- Retroviral transduction with chimeric receptor
- Harvest splenocytes
- 53%
- Determine the side effects of therapy
Cyclophosphamide lymphodepletion reduces Tregs and induces IL-12 and IFNγ secretion

A

B

Pegram et al Blood 2012 (on line)
IL-12

• A heterodimeric cytokine secreted by activated APCs, neutrophils and macrophages.
• Induces Th1 CD4⁺ T cell response enhancing IL-2 and IFN-γ secretion
• Enhances T cell clonal expansion and effector function in concert with TCR signaling (signal 1) and CD28 co-stimulation (signal 2), serving as a signal 3.
• Avoids/reverses T cell anergy
• May overcome Treg mediated effector T cell inhibition
• Recruits and activates NK cells
• Clinical trials in cancer using systemic IL-12 therapy has been limited by severe inflammatory side effects
19z1IRESIL-12 modified T cells secrete biologically active IL-12 and exhibit enhanced targeted cytotoxic function and resistance to Tregs
Syngeneic IL-12 secreting CD19 targeted T cells induce B cell aplasias and tumor eradication in the absence of prior lymphodepletion.
Conclusions

• Based on recently published clinical trial outcomes, treatment with autologous CAR modified T cells targeted to CD19 is a promising novel approach for patients with B cell malignancies

• Multiple variables in clinical trial designs complicates the interpretation of published results

• Variables relevant to the \textit{in vivo} biology of modified T cells as well as clinical outcomes remain to be defined

• Optimal application of this approach will require well designed multicenter clinical trials to generate data for an optimized clinical trial design suitable to phase III clinical trials

• Modification of tumor targeted CAR$^+$ T cells with additional genes encoding pro-inflammatory cytokines, delivered directly to the hostile tumor microenvironment may markedly enhance the anti-tumor efficacy of these T cells, overcome the need for prior conditioning chemotherapy, and therefore expand the application of this approach to a broader patient population
Enhanced CM phenotype, enhanced cytotoxicity, enhanced persistence

NK cell
Recruitment and activation

Targeted tumor cytotoxicity

IL-12 secretion

Targeted tumor cytotoxicity

CAR-RES IL-12

IL-12 secretion

Enhanced CM phenotype, enhanced cytotoxicity, enhanced persistence

IL-12 secretion

Targeted tumor cytotoxicity

Reversal of anergy

.Generated T cells: a different paradigm
CAR-ires-IL12 T cell mediated tumor eradication: A proposed scenario

Infiltration of CAR-IRES-IL12 T cells into tumor

Killing of tumor by CAR-IRES-IL12 T cells

IL12 mediated recruitment of tumor targeted NK cells and reactivation of TILs

Tumor

CAR-IRES-IL12 tumor targeted T cells

Adoptive transfer of CAR-IRES-IL12 T cells

Complete tumor eradication

NK cell and TIL-mediated killing of tumor cells
Renier Brentjens
Yan Nikhamin
Raymond Yeh
Jae Park
Kevin Curran
Alena Checkmasova
Yelena Usachenko
Samith Sandadi

Michel Sadelain
Marco Davila
Michael Gong
Jean Baptiste Latouche

Richard O’ Reilly
Ekaterina Doubrovina

Clinical Research
Yvette Bernal
Maria Irwin

Biostatistics
Glenn Heller

Cell Therapy and Cell Engineering Facility
(Isabelle Riviere, Director)
R&D, Manufacturing
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