T cell therapies
Helen Heslop
Disclosure

- Licensing agreement with Cell Medica for EBV-specific T cells
- Founder Viracyte - third party VSTs
- Founder Marker Therapeutics – tumor-antigen specific T cells
- Research support: Tessa Therapeutics
- Advisory Boards: Novartis, Cytosen
Benefits of T Cell Therapies

- Specific receptors give high targeting ability
- Recognize internal antigens (if processed)
- Good bio-distribution - traffic through multiple tissue planes
- Multiple effector mechanisms
- Self amplifying
Chimeric versus Native T-Cell Receptors

CAR T cells

Native T cells

Monoclonal antibody

Target cell

PBMCs

Antigenic peptide

Pepmixes

DC

CD3 complex

TCR

β2

MHC

αβ

β1β2

T cell

CH2

CH3

Monoclonal antibody

Spiller

TM

41BB

CD3z

CAR

CAR

Chimeric versus Native T-Cell Receptors

Monoclonal antibody

Spiller

TM

41BB

CD3z

CAR

CAR

Target cell

PBMCs

Antigenic peptide

Pepmixes

DC

CD3 complex

TCR

β2

MHC

αβ

β1β2

T cell

CH2

CH3

Monoclonal antibody

Spiller

TM

41BB

CD3z

CAR

CAR

Target cell

PBMCs

Antigenic peptide

Pepmixes

DC

CD3 complex

TCR

β2

MHC

αβ

β1β2

T cell

CH2

CH3

Monoclonal antibody

Spiller

TM

41BB

CD3z

CAR

CAR

Target cell

PBMCs

Antigenic peptide

Pepmixes

DC

CD3 complex

TCR

β2

MHC

αβ

β1β2

T cell
Recognition of intact molecule, including non-proteins

CAR T Cells

Native TCR T cells

Recognition of peptides processed through MHC
Viral Infections Post Transplant

- Major cause morbidity and mortality
- Pharmacologic therapy not available for all viruses and expensive
- Recurrences when therapy stopped
- Clearly related to lack of virus specific T cell response
Generating Virus Specific T Cells

- Repeated stimulation with viral antigens expressed on antigen presenting cells
- Expand viral antigen specific T cells
- T cells specific for other antigens will not survive
Donor-derived VSTs

AdV – Hexon, Penton
EBV – EBNA1, LMP2, BZLF1
CMV – IE1, pp65
BKV – LT, VP1
HHV6 – U11, U14, U90

mVSTs (multivirus VSTs)

Ulrike Gerdemann
Ann Leen

T cell stimulation/ expansion
10 days

+IL4/7
## 17 Patients – 40 infections

<table>
<thead>
<tr>
<th></th>
<th>CMV</th>
<th>EBV</th>
<th>Adv</th>
<th>BKV</th>
<th>HHV6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 viruses</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CMV</th>
<th>EBV</th>
<th>Adv</th>
<th>BKV</th>
<th>HHV6</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Activity in EBV-PTLD

EBV (copies/ug DNA)

Activity in EBV-PTLD

Pre mVST

Post mVST

EBV (copies/ul)

SFC/5x10^5

wk-2  wk-1  Infusion  wk1  wk2  wk3  wk4  wk5  wk6  wk12

Viral load

T cells

Pre mVST

Post mVST
Overall Response Rate 95%

<table>
<thead>
<tr>
<th></th>
<th>CMV</th>
<th>EBV</th>
<th>Adv</th>
<th>BKV</th>
<th>HHV6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 virus</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 viruses</td>
<td>PR</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3 viruses</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4 viruses</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

VST timeline

Epstein-Barr Virus

Cytomegalovirus
Adenovirus

BK virus
HHV6

Safety and efficacy maintained
3rd Party VST Therapy

Bank of VSTs

Cryopreservation

G-Rex 10

HLA - A

HLA - B

HLA - DR

Infected Patients

HLA - A

HLA - B

HLA - DR

HLA - A
Clinical Responses – EBV

Pre VSTs

1 month post VSTs
48 Infections in 42 Patients

<table>
<thead>
<tr>
<th>Viruses</th>
<th>CMV</th>
<th>EBV</th>
<th>Adv</th>
<th>BKV</th>
<th>HHV6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tzannou et al J Clin Oncol 2017
How Will Third Party VSTs Be Moved to More Widespread Use

• Individual centers have banks
• Centralized bank
  – Scottish Blood Transfusion Center
• Commercialization
  – MSKCC EBV specific T cells (Atara)
  – Baylor Third party VSTs (Viracyte)
EBV-associated Malignancies

Latent Malignancy

Type 3
Post transplant lymphoma
HIV-associated lymphoma

Type 2
Hodgkin’s lymphoma
NHL

Type 1
Burkitt’s lymphoma

Latent Gene Expression

EBNA1
LMP1
LMP2
EBNAs 2, 3a, 3b, 3c
LP

Immunogenicity

EBNA1
LMP1
LMP2
Manufacture of LMP-Specific T cells

Ad5f35-ΔLMP1-LMP2

GM-CSF, IL-4, IL-1β, IL-6, TNF-α, PGE-2

mDC

PBMC

LCL

LMP-specific T cells

Bollard et al, JIT 2004
Gottschalk et al, Blood 2004 and Leen et al, JIT 2007
Clinical Responses post LMP-CTL

Relapsed Disease Arm (n=21)
- No toxicity
- 11 CR
- 2 PR
- 8 progressive disease (2-8 weeks)

Adjuvant Therapy (n=29)
- Post SCT (14) or chemo (15)
- 1 relapsed 8 weeks post CTL

Bollard et al JCO 2014
Conclusions-LMP1/2 Study

- No significant attributable toxicity
- Anti-tumor effects seen
- Sufficiently scalable and robust for pivotal studies?
- Currently evaluating peptide-induced T cells
Targeting HPV+ve Cancers

- HPV-16/18 E6/E7-Specific T Lymphocytes transduced with dominant negative TGFB
- Lymphodepletion with Flu/Cy and PD1 inhibition added when shown to be safe

Carlos Ramos and Clio Rooney
MultiTAA T Cell Therapy

Heterogeneous tumor

PRAME
MAGEA4
SSX2
Survivin
NYESO1

MultiTAA T cells
Clinical Response – Myeloma

- **Diagnosis**
- **Pre 1st ASCT**
- **ASCT +6m**
- **ASCT +22m**
- **Pre 2nd ASCT**
- **Post-T cells (day+61)**
- **Post-T cells (day+113)**
- **Month 6**

20% Clonal plasma cells

Free lambda mg/L

1st line

1st ASCT

2nd line

2nd ASCT

3rd line

MultiTAA T cells

1st line

2nd line

3rd line
Clinical Response – Myeloma

- 20% Clonal plasma cells
- Cyclin D1 neg
- <1% Clonal plasma cells

- Diagnosis
- Pre 1st ASCT
- 1st ASCT
- ASCT +6m
- 2nd line
- ASCT +22m
- 3rd line
- Pre 2nd ASCT
- Pre 2nd ASCT +27m
- MultiTAA T cells
- Post-T cells (day+113)
- Post-T cells (day+61)
- Month 6

Free lambda mg/L
Clinical Response – Myeloma

**PBMC**

Targeted antigens

- Survivin
- NYESO-1
- MAGE A4
- SSX2
- PRAME

**Marrow**

- Survivin
- NYESO-1
- MAGE A4
- SSX2
- PRAME

<table>
<thead>
<tr>
<th>Pre</th>
<th>Wk4</th>
<th>Wk6</th>
<th>Mo3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFC/5x10^5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8 Wk Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFC/5x10^5</td>
</tr>
</tbody>
</table>
Clinical Response – Myeloma

MAGE-A4

- Pre-infusion
- 8wk post T cells

- 1+
- 3+

Marrow

- Survivin
- NYESO-1
- MAGE A4
- SSX2
- PRAME

SFC/5x10^5

8 Wk Post
T cell therapy for cancer

Broadening The Scope

WT1
PRAME
Survivin
NYESO1

AML/MDS
Clinical PI: Premal Lulla

ALL
Clinical PI: Swati Naik
Relapse of AML

Disease relapse

Resolution

WT1
MultiTAA T Cells - Summary

- Safe to date
- Feasible adjuvant and treatment
- In vivo expansion of tumor-specific T cells
- Antigen spreading
- Potential to extend to neoantigens
- Clinical benefit in lymphoma, myeloma and acute leukemia
Chimeric Antigen Receptors

Monoclonal Antibody

TCR complex

Intracytoplasmic

CAR

scFv

T cell

Tumor

Tumor Antigen
First Versus Later Generation CARs

- **Ectodomain**
- **Transmembrane**
- **Endodomain**

**First Generation CARs**
-  scFv
-  Spacer
-  Linker
-  ζ (zeta)

**Second Generation CARs**
-  CD28
-  ζ

**Third Generation CARs**
-  CD28
-  4-1BB
-  ζ
CD19 as a Target

• Present on B lineage cells from the pro-B cell stage to mature B cells
• High expression most B lineage lymphoma
• **NOT** expressed on hematopoietic stem cells (or other tissues)
  • Should not be myelosuppressive effects
  • Should not be other organ toxicities
• Will cause depletion normal B cells
CD28-ζ versus 41BB-CD28-ζ
CD19CAR in NHL

Pre

- 64 yo F, extranodal marginal zone lymphoma, s/p R-CVP × 6, with CR
- Transformation 3 years later, s/p R-CHOP → HDT/ASCT, with CR;
- Relapsed transformed disease, biopsy proven
- Lymphodepletion, then 2\textsuperscript{nd}+3\textsuperscript{rd} gen CARTs
CAR-T Cells In Hematologic Malignancies

- Encouraging response rates with CD19 CARs in ALL and NHL in studies by many groups
- Two approvals in 2017
  - Tisagenlecleucel (Kymriah) for relapsed/refractory pediatric ALL
  - axicabtagene ciloleucel (Yescarta) for relapsed DLBCL
Trials that Produced Approvals

ELIANA: Novartis Pediatric ALL Study with Kymriah
- CR rate of 83%
- 75% ongoing responses at 6 months
- 64% in CR at 12 months

ZUMA-1: Kite B-NHL Study with Yescarta
- ORR of 82% with 49% CRs
- 41% ongoing responses at 3 months
- 36% in CR at 6 months
Safety concerns blight promising cancer therapy

As the first T-cell treatments for tumours near US approval, researchers race to engineer less-toxic versions.

BY HEIDI LEDFORD

A groundbreaking treatment that arms immune cells called T cells to battle cancer is barrelling towards regulators, fuelled by unprecedented clinical success and investor exuberance.

But progress of the therapy, called CAR-T, has been marred by its toxicity; several deaths have been reported in clinical trials. Even as the company readies its application to the US Food and Drug Administration (FDA) — expected by the end of the year — researchers are hard at work to make the supercharged T cells safer.

Doing so is crucial to expanding the use of the therapy to more people, says Anthony Walker, a managing partner at Alacrita, a consulting firm in London. “Right now it is heroic medicine,” he says — a gruelling treatment deployed only in people for whom all else has failed. “Patients are taken sometimes to within an inch of their lives.”

Most CAR-T procedures begin by harvesting a patient’s white blood cells and sifting out the T cells. Those T cells are engineered to recognize cancer cells, and then infused into the patient, ready to do battle. The approach has shown remarkable success against leukaemias and lymphomas: in one

Adverse Events with CD19 CARs

- Cytokine Release Syndrome (CRS)/ Macrophage Activation Syndrome
- CNS toxicity
- Prolonged B cell aplasia
- Failures due to antigen escape - evaluation of CD19 and CD22 CARs
CD19 CAR-T Cells as Approved Product

- Where will it be available
  - FACT Immune Effector Standards

- What will the reimbursement model be?

- Can CAR-T cell therapy replace transplant?
# BCMA CAR Studies

<table>
<thead>
<tr>
<th>NCI</th>
<th>bluebird bio/ Celgene</th>
<th>Penn/ Novartis</th>
<th>Nanjing Legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retro ζ-CD28</td>
<td>Lenti ζ-41BB</td>
<td>Lenti ζ-41BB</td>
<td>Lenti ζ-41BB</td>
</tr>
<tr>
<td>16</td>
<td>18</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td>1 CR 7 PRs</td>
<td>4CRs 12PRs</td>
<td>1CR 3PRs</td>
<td>15CRs 13PRs</td>
</tr>
</tbody>
</table>

ASCO 2017
Extending CAR Strategies to T and Myeloid Cells

All targets also expressed on normal myeloid or T cells
Potential Mitigation Strategies

- CAR T cells as a bridge to transplant
- Incorporate suicide genes
- Activation switches
- Render normal cells resistant to CAR by gene editing with CRISPR/Cas9

Silva…Mamonkin Blood 2017
Second Chapter

T cell therapy has successfully targeted blood cancers. A bigger challenge is to make it work on solid tumors

By Jennifer Cousin-Frankel

Last month, Roisin O’Cearbhaill, an Irish oncologist who looks younger than her 37 years, slipped on gloves and a protective gown and stepped through the doorway of a room in her hospital’s intensive care unit. Patient No. 3 awaited her.

All other treatments had failed this woman, who is in her early 70s and has ovarian cancer. Now, she was about to be infused with her own T cells, the workhorses of the immune system, which had been removed and genetically engineered to fight her disease.

Like all first-in-human trials, O’Cearbhaill’s is small and narrowly focused: She hopes to enroll just 15 women at her home base, Memorial Sloan Kettering Cancer Center in New York City, over the next 18 months, and she’s testing mainly whether the treatment is safe. But it’s hard not to fantasize about something more dramatic. Genetically engineered T cells have proven almost miraculously effective in some patients with blood cancers, including certain leukemias and lymphomas. Dozens of adults and children near death have been helped, and some remain healthy 4 or 5 years after treatment.

As researchers try to take T cell therapy in blood cancers from proof-of-principle to practical treatment, trials like O’Cearbhaill’s present another looming test for the approach: Can engineered T cells also save people with solid tumors spreading through the breasts, lungs, brain, and ovaries? Solid tumors are far more common than blood cancers and, if they metastasize, can be very difficult to halt. Immunotherapy drugs called checkpoint inhibitors are approved or in testing for a number of solid tumors—but even there, the fraction that responds is often modest and response doesn’t always last. O’Cearbhaill and colleagues at Sloan Kettering, around the country and beyond hope this first wave of clinical trials will help chart a path toward success for a strategy that could upend cancer treatment as we know it.
## Published Clinical CART Studies in Solid Tumors

<table>
<thead>
<tr>
<th>Target</th>
<th>Disease</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>FR</td>
<td>Ovarian Cancer</td>
<td>No activity (Clin Can Res, 2006)</td>
</tr>
<tr>
<td>CAIX</td>
<td>Renal Cancer</td>
<td>On target/Off cancer tox (JCO, 2006)</td>
</tr>
<tr>
<td>CD171</td>
<td>Neuroblastoma</td>
<td>1/6 PR (Mol Ther, 2007)</td>
</tr>
<tr>
<td>HER2</td>
<td>Colon Ca</td>
<td>1 Death (Mol Ther, 2010)</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>Mesothelioma, Pancreas Ca</td>
<td>2/14 with tumor shrinkage (Cancer Imm Res 2014)</td>
</tr>
<tr>
<td>HER2</td>
<td>Sarcoma</td>
<td>4/17 SD (JCO, 2015)</td>
</tr>
<tr>
<td>IL13Ra2</td>
<td>GBM</td>
<td>2/3 transient response (Clin Can Res, 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 impressive regression (NEJM, 2016)</td>
</tr>
<tr>
<td>HER2</td>
<td>GBM</td>
<td>1/17 PR &amp; 7/17 SD (JAMA Onc, 2017)</td>
</tr>
<tr>
<td>EGFRvIII</td>
<td>GBM</td>
<td>1/10 SD (STM 2017)</td>
</tr>
</tbody>
</table>
CARs in Solid Tumors: Responses

GD2 CARTs in neuroblastoma

Her2Neu CARTs in glioblastoma

Recurrent/refractory Rhabdomyosarcoma: CR post HER2-CART

Malcolm Brenner, Stephen Gottschalk, Nabil Ahmed
CAR-T Therapy for Solid Tumors

- Need broad response that evolves with tumor and tumor microenvironment
- Need to convert “cold” tumor to “hot” tumor
- Overcome tumor evasion strategies
Tumor Evasion Strategies

- **Tumor stroma**
  - IL4
  - TGFB
  - IL13
  - IL10

- **Inhibitory cytokines**
  - Tregs
  - MDSCs
  - Immune cell
  - Tumor cell
  - Stromal cell

- **Inhibitory molecules**
  - FASL
  - FAS
  - PDL1
  - PD1

**Suppressor cells**
Genetic Modification To Enhance CART Function

- Enhance migration
  - Chemokine gradient
  - CCR4
  - Enhance T cell migration
- Increase Safety
  - IC9
  - Suicide gene
  - Thymidine kinase
- Resistance to environment
  - Reduced response to FasL
  - Neutralize an inhibitory cytokine
- Engineered T cell
  - IL2 cytokine
  - IL7 cytokine
  - IL7Rα
  - Restore the response to growth factor
  - Production of growth factors by T cells
- Improve T-cell persistence
  - Bcl-2/Bcl-xL
- Decrease apoptosis
  - IL-2
  - IL-15

(adapted from Vera et al. Lancet Onc; 2013)
Combination Therapies

- Combinations
  - Other Immune modulators
  - Oncolytic viruses
Recurrent metastatic squamous cell carcinoma post 6 lines of therapy
Received Nivolumab
TAA-specific T cells (targeting survivin, PRAME, SSX, MAGE A3, Ny-ESO)
Combining Checkpoint Inhibition and T Cell Therapies
Gene Editing of CAR-T Cells

• Off the shelf CARs by knocking out endogenous TCR and HLA
  – Off the shelf product immediately available
  – Lower cost of goods

• Enhance CAR function
  – Control integration site for optimized function
  – Knock out checkpoint molecules
Conclusions

• 2nd generation CD19 CARTs can have remarkable activity against B-cell malignancies
• CARs can successfully travel beyond CD19
  – CD22 and BCMA
• Extension to Myeloid and T cell disease requires strategy to mitigate effects on normal progenitors
• Extension to solid tumors requires combination strategies to increase immunogenicity and overcome tumor evasion
Future Directions

• Combination CAR-T cells and
  – checkpoint inhibitors
  – other immunomodulatory agents
  – oncolytic viruses

• Genetic strategies to enhance function and overcome tumor evasion mechanisms

• Targeting multiple antigens
Future Directions: Improve accessibility

• Faster manufacturing
• “Off the shelf” Third party cell
  – Gene edited T cell
  – Multivirus specific T cell
  – NK-T or NK cells
• Comparative effectiveness/QOL
Acknowledgements

TRL Lab PIs
Cliona Rooney
Malcolm Brenner
Ann Leen
Nabil Ahmed
Juan Vera
Carlos Ramos
Leonid Metelitsa
Valentina Hoyos

Transplant Service
Bob Krance
Kathy Leung
Caridad Martinez
George Carrum
Ram Kamble
Premal Lulla
Swati Naik

TRL Laboratory
Lisa Rollins
Olga Dakhova

Clinical Research
Bambi Grilley
Bridget Medina
Elicia Casteneda
Kristal Black
Munu Bilgi
Vicky Torrano
Amy Reyna

GMP Laboratory
Adrian Gee
Natasha Lapteva
Debbie Lyon
Zhuyong Mei

TRL Junior Faculty/
Postdocs/PhD students
Bilal Omer
Robin Parihar
Rayne Rouce
Meena Hegde
Andras Hegde
Chris Derenzo
Max Mamonkin
Serena Perna
Ulrike Gerdemann
Anastasia Papadopolou
Ifigeneia Tzannou
Sandhya Sharma
Minhtran Ngo

Alumni
Cath Bollard
Barbara Savoldo
Gianpietro Dotti
Stephen Gottschalk
Caroline Arber

T cell Laboratory
Huimin Zhang
Tamara Tripic
Pallavi Mohpatra
Birju Mehta
Silva Perconti
Mary Ge