Long term follow up in recipients of HSCs and Immune Effector Cells modified by Retroviral or Lentiviral Vectors

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Disclosures

• Founder Viracyte
• Founder Marker Therapeutics
• Research support Cell Medica and Tessa Therapeutics
• Advisory Boards: Gilead, Novartis and Cytosen
Initial Concerns

• Risk of RCR/RCL
  • Based on monkey experiments
  • Not observed so far
• Risk of insertional mutagenesis
  • Early retroviral vectors in HSC
  • Not observed so far in T cells
  • Not observed with newer retro/lentiviral vectors
Safety of Gene Therapy Using Lentiviral Vectors

Clinical trials using lentiviral vectors into HSC have been performed for:

1. X-Adrenoleukodystrophy
2. Metachromatic Leukodystrophy
3. Wiskott-Aldrich Syndrome
4. Chronic Granulomatous Disease
5. Adenosine Deaminase-Deficient SCID
6. X-linked SCID
7. Beta-Thalassemia
8. Sickle Cell Disease

No vector-related SAEs have been observed. No RCL has been reported in product or patients.

Integration site analyses do not show preferential integration near oncogenes, nor significant clonal expansion.
EFS-ADA  
Lentiviral Vector

MND-ADA  
Gammaretroviral Vector

A. Cooper, D Kohn,  
Blood, 2017 and Unpublished
Safety Record With Immune Effectors

- > 1000 patients in literature received immune effector cells modified with retro or lentiviral vectors
- No reported insertional mutagenesis
- No RCR
LTFU per 2006 Guidance

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### Long-Term Follow-Up Form

<table>
<thead>
<tr>
<th>Patient's Initials</th>
<th>DOB</th>
<th>MRN</th>
<th>Institution</th>
<th>CAGT ID</th>
</tr>
</thead>
</table>

#### Follow Up #:

<table>
<thead>
<tr>
<th>Type of Evaluations</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office Visit (TMH or TCH)</td>
<td><em><strong><strong>/</strong></strong></em></td>
</tr>
<tr>
<td>Office Visit at outside institution</td>
<td><em><strong><strong>/</strong></strong></em></td>
</tr>
<tr>
<td>Phone Interview by Research Nurse / Protocol MD</td>
<td><em><strong><strong>/</strong></strong></em></td>
</tr>
<tr>
<td>Blood Sample Collection</td>
<td><em><strong><strong>/</strong></strong></em></td>
</tr>
<tr>
<td>Other:</td>
<td><em><strong><strong>/</strong></strong></em></td>
</tr>
</tbody>
</table>

**RCR Sample Collected:** Yes / No / Not Applicable (circle one)

Reasons for not collecting RCR sample: ____________________________________________________________

**Patient Interview:**

Individual being interviewed and relationship to patient: _______

Date of Interview: ____________

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**CAGT ID:**

**Patient's Initials:**

- Have you developed any new medical problems?
  - [ ] No
  - [ ] Yes
  - Description: _______________________

- Do you have ongoing medical problems?
  - [ ] No
  - [ ] Yes
  - Description: _______________________

- Has your original malignancy recurrent? (if appropriate)
  - [ ] No
  - [ ] Yes
  - Date of recurrence: _____/_____  
  - Current status: _______________________

**Tissue Information:**

- Have you developed a new cancer?
  - [ ] No
  - [ ] Yes

**Type:** _______________________

**Site(s):** _______________________

**Pathology Report Requested and relevant discussion:** _______________________

**Received:** _____/_____  

**Tissue for testing requested and relevant discussion:** _______________________

**Received:** _____/_____
Successful LTFU Monitoring 1993-2011

- Protocol Number: 9303-038 NeoR Gene Marked EBV Specific Cytotoxic T Lymphocytes IND 5049
- 26 patient received marked CTLs
- 10 died during LTFU (6 relapse primary malignancy, 2 sepsis, 2 trauma)
- 16 completed 15 year follow up with no patients lost to follow-up
  - Pediatric bone marrow transplant patients at St Jude - culture of clinical trials and LTFU
  - St Jude paid for patients to come back for annual evaluation
Real World LTFU Monitoring

• Trials run by 3 longstanding research coordinators who know all the patients
• 140 patients on 16 studies
• 22 declined or lost to follow up at some stage
  • Some will provide follow up information but not send blood
Challenges with Monitoring

- Continues after funding ends for research studies
- Mobility of patients and investigators
- Other life events

Detection DNTGFB transgene by PCR

In prison
Challenges with Monitoring

- Reconsent at age 18
- Challenges obtaining tissue samples from subsequent malignancies
  - Biopsies at different sites
  - HIPPA
- LTFU in original protocol/IND or in separate LTFU study?
  - If multiple studies easier to consolidate LTFU in one study
Commercial CARs

• No funding for LTFU
• Need clarity on degree reporting for expected side effects
• Grade 2 CRS resolved with Tociluzumab
  • Provide details on concurrent medications including batch number and expiry date
  • Provide all medications within last 6 months
  • Provide dates and results with normal ranges of all lab tests performed
Challenges with 2018 Guidance

• “Assure that investigators maintain, in the case history, a detailed record of exposures to mutagenic agents and other medicinal products”
  • Oncology patient may receive many subsequent therapies
• “Such a plan needs to facilitate reporting of delayed adverse events, including unexpected illness and hospitalization by study subjects and HCPs”
  • Many adverse events potentially related to subsequent therapies
  • ? Evaluate in real time

9 year old with ALL 1st Relapse March 2017
COG study AALL1331
VP-CTX x 2
Blinatumomab x 28 days
TAT AALL1131
Axicabtagene Ciloleucel on Clinical Trial
Capizzi MTX
Kymriah commercial product
CFZ008
Carfilzomib+VXLD
Carfilzomib+consolidation
Capizzi AraC, with MRD decreasing further to 0.01%.
VCR/Cytox
Hydroxyurea
TACL study.
Detection of Adverse Events and Coordination of Data Collection

• “Recommend LTFU protocol identify suitable HCPs ...not otherwise associated with the clinical trial...such individuals notified to provide prompt reports of AE to the investigators”
  • Challenges in HCPs not associated with study prioritizing LTFU with other clinical duties
  • Electronic EMRs some help
Detection of Adverse Events and Coordination of Data Collection

• “You should submit information including, a summary of all IND safety reports submitted during the past year, and a tabular summary showing the most frequent and most serious adverse experiences by body system”
  • Implies collect all AEs – may be numerous in patient proceeding to other therapies
  • Most investigators not resourced to do this
Could Registry Reporting Provide LTFU Data?

- Many current studies target HSCs and Immune Effectors and patients treated on transplant units.
- HPC transplant programs have experience with registry reporting and LTFU for hemopoietic stem cell transplant recipients.
Basic Model for Collection of all Cellular Therapies

1. **Unique ID Assignment and Indication**
   - F2804/2814

2. **Pre-CTED**
   - F4000
   - Information prior to Cellular therapy

3. **Disease Classification**
   - F2402
   - Indications for CT
   - Disease characteristics, prior treatment and condition prior to CT. For example: acute leukemia and NHL.

4. **Product**
   - F4003
   - Product information and details on manufacturing

5. **Post CTED**
   - F4100
   - Outcomes form
   - 3, 6 and 12 months then yearly

6. **Subsequent Neoplasm**
   - F3500
   - Event-driven forms

7. **Pregnancy**
   - F3501

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Advancing knowledge, awareness, and education of gene and cell therapy
Model for the Cellular Therapy Registry
CT Model for Long Term Follow up

- **Center 1**
  - Sponsor
  - Cellular Product 1
  - Patient
  - Single CRID

- **Center 2**
  - Sponsor
  - Cellular Product 2

- **eDBTC**
- **FDA**

- **eDBCT** = Enhanced Data
  - Back to Centers

**Advancing knowledge, awareness, and education of gene and cell therapy**
Inclusion in the CIBMTR registry should be an acceptable alternative for LTFU

- Harmonize reporting for IND studies and commercial products with standardized database
- Feasible option for centers with experience in reporting
- Cost recovery for centers
- Promote innovative approaches for patient tracking and follow up
  - Patient reported outcomes
- Availability data for research
Advancing knowledge, awareness, and education of gene and cell therapy