Adoptive Cellular Therapy to Treat Cancer

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Timeline for Cancer Treatment

- **1882**: Development of Radical Mastectomy
- **1903**: First Use of Radiation Therapy to treat Skin Cancer
- **1947**: First Use of Antimetabolites with Use of Aminopterin to Treat Leukemia
- **1958**: Frei, Freireich and Holland Demonstrate Efficacy Combination Chemotherapy
- **2001**: Development of Imatinib, Targeted Therapy for CML
Last 10 Years Focus on Immunotherapy

Emma Whitehead article in NYT featured 6 year old cured of ALL with CD19.CAR T cells at U Penn

<table>
<thead>
<tr>
<th>Approval First</th>
<th>Approval First</th>
<th>Approval First anti-PD-1 Inhibitor</th>
<th>CAR T cell Therapy Approved for ALL</th>
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<tr>
<td>Cancer Vaccine</td>
<td>Checkpoint Inhibitor</td>
<td>Pembrolizumab</td>
<td>for ALL</td>
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<td>2010</td>
<td>2011</td>
<td>2014</td>
<td>2017</td>
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Chimeric Antigen Receptor T cells

T cell
- Viral DNA Insertion
- Expression of CAR

Tumor cell
- CAR enables T cell to recognize tumor cell antigen
- CAR T cells multiply and release cytokines
- Tumor cell apoptosis

Antigen
CAR-T Cell manufacturing

1. Collect blood
   Blood is collected from the study participant.

2. Activate T cells
   The T cells are isolated from the blood and activated using anti-CD3 and CD28 antibodies.

3. Express CAR
   A virus is used to transfer DNA information into the T cells that instructs the T cells to produce a chimeric antigen receptor (CAR) on its surface. The result is a CAR-T cell that is designed to recognize and attack cancer cells.

4. Expand T cells
   Researchers use growth factors to spur the CAR-T cells to multiply by the tens of thousands.

5. Testing and freezing
   Once there is a sufficient number of CAR-T cells, they are tested for functionality, confirmed to be sterile and frozen until needed.

6. Infusion
   The CAR-T cells are thawed and administered to the study participant via an IV infusion. Monitoring for safety and response is performed at specific intervals.
Future Directions and UNC Trials
UNC and Baylor Develop CAR T cell Therapy Effective Against Hodgkin Lymphoma

CD30 CAR-T Cell Trials

Anti-CD30 CAR-T Cell Therapy in Relapsed and Refractory Hodgkin Lymphoma

Carlos A. Ramos, MD; Natalie S. Girwer, MD; Anne W. Brown, MD; Premal D. Lulla, MD; Meng-Fen Wu, MS; Anastasia Ivanova, PhD; Tao Wang, PhD; Thomas C. Shea, MD; Clara M. Rooney, PhD; Christopher Ditto, DO; Steven L. Park, MD; Adam P. Gee, PhD; Paul E. Elledge, PhD; Kathryn L. McKay, MS; Biju Mehta, MS; Catherine J. Cheng, MS; Faith B. Buchanan, PA; Bambi J. Gille, RPh; Matthew Morrison, MD; Malcolm K. Bremner, MD, PhD; Jonathan S. Serody, MD; Gianpietro Dotti, MD; Helen E. Herlop, MD; and Barbara Sankoff, MD, PhD

July 2020
CD30.CAR-T Cells

- Phase 1/2 trials run in parallel at BCM and UNC
- CD30+ lymphomas
  - Progressed after 2 lines of tx
  - Any level of CD30 expression
- Primary objective: safety
- Secondary: response per Lugano
  - Initial assessment at week 6

**Lymphodepletion**

- Cell Procurement
- Bridging therapy
- CAR T cell Infusion
- d1, d3-6, 6 wks
- Initial assessment

**Bridging Therapy**

- Bendamustine (90 mg/m²/day) x 2 days
- Bendamustine (70 mg/m²/day) x 3 days
- Fludarabine (30 mg/m²/day) x 3 days

**Cell Procurement**

- Cyclophosphamide (500 mg/m²/day) x 3 days
- Fludarabine (30 mg/m²/day) x 3 days

**NCT02690545**
Feb 2016

**NCT02917083**
Sept 2016
Clinical Responses

Benda (n=5)
- PD 80%
- SD 20%

Benda/Flu (n=15)
- PD 13%
- CR 73%
- PR 7%
- SD 7%

Cy/Flu (n=17)
- PD 23%
- CR 47%
- PR 18%
- SD 12%

Patients with active disease at time of treatment
Clinical Responses

Patients had active disease and complete response
N=19, Median PFS: 444 days, 95% CI: 260 - NA
FDA granted RMAT designation to CAR T-cell therapy for HL
Can we be effective without causing toxicities?
CARs with a Safety Switch

• CAR-T cells with inducible caspase 9 safety switch

Chemical inducer of dimerisation (CID): AP1903 or AP20187

CAR T cells eliminated

Active caspase 9 dimer

Inducible caspase 9 homodimer (iCasp9)

Drug-binding domain

Activates proapoptotic molecules

Apoptosis
CD19.CAR-T with iC9 Safety Switch

- 26 yo F with refractory B-ALL received CD19 CAR-T cells with iC9 safety switch
- Developed severe neurotoxicity (ICANS) with non-convulsive status epilepticus with stupor persisting for 72 hours despite standard of care steroids
Neurotoxicity Resolved with Rimiducid (Dimerizing Agent)

TO THE EDITOR:
Utility of a safety switch to abrogate CD19.CAR T-cell-associated neurotoxicity

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0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Days Post CAR-T Cell Infusion
0 200 400 600 800 1000 1200 1400
pg/ml
IL-6
IL1Ra
PCR
methylprednisolone
tocilizumab and
dexamethasone
0 20000 40000 60000 80000 100000 120000 140000
Copies/ug DNA
= grade 1 ICANS
= grade 3-4 ICANS

- Neurotoxicity Resolved with Rimiducid (Dimerizing Agent)
One of the first approaches demonstrating the activity of CAR T cells to treat relapsed/refractory breast cancer

For the first time using this model we cured over 70% of the mice permanently

Now testing this approach in head and neck cancer

From: STING agonist promotes CAR T cell trafficking and persistence in breast cancer
Other Open CAR-T Trials

• CD30 CAR with CCR4 – Hodgkin Lymphoma and Cutaneous T cell Lymphoma
• C30 CAR- T cell Lymphoma
• CD138.CAR – Multiple myeloma*
• Kappa.CAR – Lymphoma
• GD2.CAR- neuroblastoma and osteosarcoma* (pediatric trial)
• B7H3 CAR – ovarian cancer
• HER2 CAR Macrophage – Solid Tumors

*: Studies supported by philanthropy
Philanthropy also critical to support manufacturing of all CAR products