New developments in Cancer Immunotherapy

Denis Claude Roy, MD, FRCPC
Director of Research, East of Montreal Hôpital Maisonneuve-Rosemont
CEO, CellCAN
Prof. Medicine, Université de Montréal

Lymphoma Canada, Montreal
September 16, 2017
Drug therapy for cancer
CELL therapy for cancer
STEM CELL TRANSPLANTATION

PATIENT WITH CANCER

CHEMOTHERAPY

RADIATION THERAPY

CELL TRANSPLANT

COMPATIBLE DONOR
- Familial
- Unrelated
- Umbilical Cord Blood
- Haploidentical family donor

PATIENT IS DONOR
(Frozen stem cells)
Allogeneic Hematopoietic Cell Transplantation (AHCT)

• One of the most important medical breakthrough of the last 50 years
• Can cure ~50% of refractory HCs
• By far the most effective form of cancer immunotherapy
• Cure by AHCT (the GVTE effect) is mediated by donor T cells that react against minor histocompatibility antigens (MiHAs) present on cancer cells – GVTE strength is sub-optimal
Challenge in Haploidentical Donor Transplantation
ATIR: Selective removal of GVHD-causing T-cells while retaining key innate and adaptive components of immune system

ATIR characteristics
- Selective removal of GVHD-causing T-cells
- Key immune cells are retained to protect against infections
- T-cells directed against leukaemic cells are retained

Potential clinical benefits
- Improved donor availability
- Minimal risk of life-threatening GVHD
- No prophylactic immune suppression needed
- Less cancer relapse
- Reduced TRM; improved OS

1. Immune cells collected and mixed ex vivo
2. Activation of donor T-cells
3. TH9402 addition
4. Exposure to light
5. ATIR infusion

Day 1 - 4
- non-activated GVHD-causing donor T-cells
- Irradiated patient cells
- Activated GVHD-causing donor T-cells
- Graft-vs-Leukaemia T-Cells

Day 5
- Activated GVHD-causing donor T-cells with TH9402 retained
- Other immune cells (e.g. virus specific memory and effector cells, naïve cells, NK cells)
Haploidentical HSCT + ATIR: high-risk hematologic malignancies

Conditioning regimen | Haplo HSCT | ATIR Infusion
--- | --- | ---
-11d | -9d | -8 to -7d
-6d | -2d | 0d
+28 to 42 days

CD3/kg Pts
I - 1x10^4/kg | 1
II - 5x10^4/kg | 3
III - 3x10^5/kg | 3
IV - 3.2x10^5/kg | 3
V - 7.9x10^5/kg | 3
VI - 2.0x10^6/kg | 3
VII - 5.0x10^6/kg | 3

G-CSF mobilization
CD34+ selection
ClinMACS

Donor

Donor

Apheresis

MLR

ATIR Selective Depletion of host-reactive donor cells

Cryopreservation

ATIR Selective

Methylprednisone

CD34+/kg cell graft

DLI

TBI

Thiotepa

ATG

Fludarabine
Phase I clinical trial:
Defining ATIR cell dose

- Cohort 1-3: 0.1-1.3x10^5 CD3
- Cohort 4-6: 0.3-2.0x10^6 CD3
- Cohort 7: 5.0x10^6 CD3
- no ATIR

Percent survival vs Months post-transplantation
Phase II international clinical trial: 23 patients

Acute GVHD
- No grade III/IV GVHD after ATIR101 infusion
- Only 3 cases of grade II GVHD after ATIR infusion (late-onset)
- In 2 patients GVHD occurred before ATIR infusion (1 grade I, 1 grade II), delaying infusion until resolution

Chronic GVHD
- Only 1 case of chronic GVHD (severe) has been reported
• Comparison with control data from an observational cohort study\textsuperscript{1}

\textbf{Overall survival}

ATIR101 significantly reduces TRM and improves OS compared to CD34+ haplo-transplants
Erik (patient) and his father (donor)
From AHCT to MiHA-targeted Rx

• Despite its success, conventional AHCT is a rudimentary and toxic form of Tx based on injection of unselected T cells

• Selected→Can we select cells that will react toward cancer cells in a selective fashion?
Immune cells react against MiHA non-self peptides (protein fragments) on the surface of cancer cells.

Donor cells of the immune system able to recognize non-self (leukemia)

Target: MiHA

Patient cancer cells harboring peptide (MiHA)
What is a Minor Histocompatibility Antigen (MiHA)?
Graft-vs-Tumor Effect is mediated by donor immune cells that recognize MiHAs on leukemic cells
Cancer Immunotherapy with H7a-specific T cells

- Leukemia (Nat Med 2001; 7:789-794)
Using Proteogenomics For MiHA Discovery

Personalized translated transcriptome

Candidate selection
- Novel MiHA
- Binding motifs
- Allelic frequency (SNPs)
- Immunogenicity
  Expression of MiHA coding genes in leukemic cell

Number of peptides selected
~15,000 MiHA Candidates
467 MiHA Candidates expressed at high frequency
98 neo-MiHAs appropriate for immunotherapy
Manufacturing Anti-Cancer Cells

1

15X10⁶ PBMCs

MiHA peptide

Irradiated and pulsed 2h 37°C 1.5X10⁶ DCs

PBMCs

DCs 9 days

D0

D7

D10

D14

D18

D21

Cytokine-based cell-expansion protocol

REP D0 (D21)
REP D4 (D25)
REP D8 (D29)
REP D12 (D33)

Further expansion protocol

Testing

2

IFNγ capture assay

T cell purification protocol

Rapid expansion protocol

Rapid expansion protocol

Cytokine-based cell-expansion protocol
MiHA anti-leukemia therapy (GLIDE) (Genome Québec/Génome Canada/Amorchem/BioCanRx)
Antigen-specific T cells against refractory Epstein-Barr Virus infection and lymphoma

EBV-TCL-01
(NCT02580539 - JS Delisle)

2 weeks post infusion

3.5 months post infusion

ELISPOT – persistence of response (EBNA1 et LMP2)
Can Cellular Therapy be Industrialized?

- **Manual**: ✓ Translation ✗ Regulatory ✗ Scalable ✗ Economical
- **Robotic Duplication**: ✗ Translation ✓ Regulatory ✓ Scalable ✓ Economical
- **Automated Bioreactors**: ✓ Translation ✓ Regulatory ✓ Scalable ✓ Economical

Real time – quality monitoring
Chimeric Antigen Receptor (CAR) Technology

Brower V, The Scientist, April 1, 2015
On July 1, 2014, the FDA granted “breakthrough therapy” designation to CTL019, the anti-CD19 CAR T-cell therapy developed at the University of Pennsylvania (UPenn).

Gene transfer technology using a lentiviral vector is used to transduce T cells to CTL019 cells.

The CTL019 CAR consists of T-cell activation domains coupled to an anti-CD19 single-chain variable fragment\(^1-3\)

1. **Antigen-binding domain**
   - Recognizes CD19 antigen on B cells
2. **4-1BB costimulatory domain**
   - Increases T-cell activation and enhances cytolytic function of T cells
3. **CD3-zeta chain signaling domain**
   - Induces T-cell activation

CD19 is an Ideal Tumor Target in B-Cell Malignancies

CD19 expression is generally restricted to B cells and B cell precursors\(^1\)

- CD19 is not expressed on hematopoietic stem cells\(^1\)

CD19 is expressed by most B-cell malignancies

- CLL, B-ALL, DLBLC, FL, MCL\(^1\)

Antibodies against CD19 inhibit tumor cell growth


CTL019 in ALL: Efficacy

### Response

<table>
<thead>
<tr>
<th>Response</th>
<th>n/n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>27/30</td>
<td>90</td>
</tr>
<tr>
<td>Negative minimal residual disease</td>
<td>22/30</td>
<td>73</td>
</tr>
<tr>
<td>Duration of response (7 mo median follow-up)</td>
<td>19/27(^a)</td>
<td>70</td>
</tr>
</tbody>
</table>

\(^a\) 15 patients received no further therapy, and 4 patients withdrew from the study to receive other therapy.

- 7 patients who had achieved a CR subsequently relapsed (time to relapse ranged from 6 weeks to 8.5 months)
  - 3 patients with CD19\(^-\) ALL experienced relapses
  - 3 relapses developed after early loss of CTL019-modified T cells at 2 weeks to 3 months and were CD19\(^+\)
- CTL019-modified T cells were detected in the CSF of 17 of 19 patients with evaluable specimens, which may have implications for successful disease surveillance in that compartment
  - The 2 patients with CSF blasts at infusion had no detectable CNS leukemia with a follow-up of 6 months, and no CNS relapses were observed

• CTL019-modified T cells were detectable in the blood by flow cytometry for up to 11 months (left)
• The probability of 6-month CTL019 persistence was 68% (95% CI, 50%-92%; right)
• CTL019 cells were observed to traffic to the CNS in pediatric patients with ALL

CTL019 in ALL: Updated Results (Pediatric)

- Data reported from 48 pediatric pts with r/r ALL, as presented at ASPHO 2015\(^1\)
- 45 of 48 pts (94%) in complete remission
- The 6-month overall survival was 81% (95% CI, 70,94; figure)

A Variety of Neoplasms Arise at Different Stages of B-cell Differentiation

- CD19 expression is generally restricted to B cells and B cell precursors and, importantly, is expressed by most B-cell malignancies and is therefore an ideal target\(^1,2\).
- Accordingly, a number of trials are planned investigating the use of CTL019 in a range of B-cell malignancies.

---

Checkpoint blockade

PD-L1/PD-1 binding inhibits T cell killing of tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell

Antigen

T cell receptor

T cell

© 2015 Terese Winslow LLC
U.S. Govt. has certain rights
Myeloma

Activating receptors
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory receptors
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Agonistic Abs

Blocking Abs

T cell stimulation
Checkpoint inhibition: a game changer

Metastatic melanoma

Advanced lung cancer


Small molecule down-regulation of PD-1 reduces B16 metastatic melanoma

The upstream pathway regulating PD-1 expression is not clear. Rudd and colleagues show that inhibition of the serine/threonine kinase GSK-3 upregulates T-bet expression, which decreases PD-1 expression and enhances CTL function. They demonstrate that the use of GSK-3 inhibitors in vivo inhibits PD-1 and enhances T cell clearance of viral infections.
Centré d’excellence en thérapie cellulaire (CETC)
Centre of Excellence in Cellular Therapy
Hopital Maisonneuve-Rosemont
L'Assomption
CETC building
Accelerating market access of breakthrough innovations to fight cancer
Vision & Mission

- Vision: C3i will be Canada’s catalyst for cancer immunotherapy business development

- Mission: Accelerate the discovery, commercialization and access to cancer immunotherapy
C3i’s One-Stop-Shop Model

C3i Structure in 4 Business Units with Unique Combination of Key Assets

Biomarker & Diagnostic Unit
- Focussing on Immunomonitoring and Precision Medicine

cGMP Manufacturing Unit
- Only GMP cell production facility in Canada

Clinical Research Unit
- Strong focus on Cancer Immunotherapy

Innovation & Commercialisation Unit
- Investing in Innovative Cancer Immunotherapies, asset development & commercialization.

Features:
- Translation from bench to clinic
- Large Network of Investigators
- Regulatory Expertise
- In-house development of biomarkers
- On Site cGMP facility
- Efficient Clinical Trial Implementation
- Business Oriented Team
- Venture Capital Investment
MOBILIZING KNOWLEDGE
and promoting advances in regenerative medicine and cell therapy

STATE-OF-THE-ART FACILITIES
State-of-the-art cleanrooms to accommodate clinical grade production of human cell products.

WORLD-RENOWNED EXPERTISE
Key Canadian investigators and highly specialized personnel come together in the field of stem cell therapy to assist you with your research needs.

EXPLORE OUR SERVICES
- THERAPEUTIC AREAS
- TISSUE TYPES
- CELL TYPES
Dans le cas du cancer du sein, la recherche sur les cellules souches cancerueuses, « mères » des cellules tumorales, est une voie particulièrement originale et innovante, portée de grands espoirs pour l'avenir.
Customized tools for knowledge dissemination – Information booklets

- From research to cell therapy
  All you need to know

- Medical tourism
  The potential dangers

- From microscope to stethoscope

For general practitioners & health care professionnels
Customized tools for knowledge dissemination – Mobile App

Hi, my name is Reggie! Let’s discover the potential of stem cells.

Stem Cells
Interactive Body
Search by Illness
About

BLOOD DISORDERS

What are scientists hoping stem cells can do?

Because hematopoietic stem cells normally make all the red and white blood cells that populate the bone marrow and blood, they are the perfect tool for restoring blood components in patients who have blood deficiencies. For example, scientists have learned that transplanting hematopoietic stem cells into a patient who has undergone chemotherapy or radiation can supply new, healthy red and white blood cells. Scientists are also hoping that basic research on cancer stem cells will shed light on cancer initiation and relapse, and that this knowledge will lead to the development of future therapies targeting blood-related cancers.

Are there stem cell treatments for blood disorders?

Yes. Hematopoietic stem cell transplants from bone marrow, umbilical cord and peripheral blood are approved by Health Canada and the FDA to help treat a variety of different blood-based cancers including multiple myeloma, leukemia and lymphoma, and other blood disorders, including anemia, thalassemia and severe combined immune deficiency or SCD.

Are clinical trials currently underway?

Many clinical trials have already proven that hematopoietic stem cell transplants can play an important role for helping to treat blood disorders. Today, there are literally thousands of new clinical trials underway to explore how to improve...
• Remerciements

• Clinical transplant teams
  - S Lachance, J Roy, S Cohen, I Ahmad, T Kiss
  - C Perreault, JS Delisle, G Sauvageau, L Bernard, N Bambace (HMR Montreal)
  - I Walker, R Foley (Hamilton, Canada)
  - J Maartens (Leuven, Belgium)
  - P Lewalle (Brussels, Belgium)
  - D Selleslag (Brugges, Belgium)
  - E Olavarria (London, England)
  - S Mielke (Wuerzburg, Germany)
  - M Levings, K Schultz (Vancouver, Canada)
  - D Kim, H Messner, D Wall (Toronto, Canada)
  - D Allan, C Bredeson, D Stewart (Ottawa, Canada)
  - D Wall, D Szwajcer (Winnipeg, Canada)
  - L West, S Maiers (Edmonton, Canada)
  - H Ly (ICM, Montreal, Canada)

• Cell manufacturing teams
  - M Giroux, M Corriveau, J Darwiche (HMR, Montreal)
  - H Bonig (Frankfurt, Germany)

DC Roy laboratory
  - V Dave, S Thiant, D Yared, R Sidi Boumedine, J Trottier
  - JP Bastien, MP Giard, F Larochelle, C Leboeuf, S Blaise
  - N Zeidan, C Tebid, E Cournoyer, S Lepine, MP Lachambre