Cell and Gene Therapy (comes of age)

Chiara Bonini

Valencia, April 4th, 2016
Why EBMT is interested in cell and gene therapy?

Why should we register patients undergoing cell and gene therapy?

How should we proceed?
Cell Therapy: n. of active studies (clinicaltrials.gov)
Example of Cell Therapy: MSC-based therapy: cell replacement versus cell 'empowerment'.

- Wang Nat. Immunol 2014
Mesenchymal stromal cells: n. of active studies (clinicaltrials.gov)
Gene transfer: is the process of transferring genetic material (DNA or RNA) into a cell to gain a missing function.

Cell Based Gene therapy: is the use of gene-modified cells or vectors for therapeutic purposes.
Gene Therapy

Direct Delivery

- Therapeutic gene
  - The therapeutic gene is packaged into a delivery vehicle such as a retrovirus
  - ...and injected into the patient

Target organ (e.g. liver)

Cell-based Delivery

- Genetically modified ES cells (can block immune rejection from patient)
  - OR
    - ES cell
    - HLA bank
  - OR
    - SCNT
- ES cells
- Adult stem cells
  - Are isolated and propagated in the laboratory.
- Adult stem cells
- Target organ (e.g. liver)
- The genetically modified cells are reintroduced into the patient.

- Therapeutic gene
  - The therapeutic gene is packaged into a delivery vehicle such as a retrovirus and introduced into the cells.
### Cell based gene therapy (excluding cancer)

<table>
<thead>
<tr>
<th>CELLS</th>
<th>DISEASE</th>
<th>GENE</th>
<th>VECTOR</th>
<th>Reference</th>
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<td>Burnett et al (2012)</td>
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<td>Lee et al (2013)</td>
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<td>Hepatocytes</td>
<td>HIV</td>
<td>ZFNs targeting Adenoviral</td>
<td>Grossman et al</td>
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<td>(1994)</td>
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<td>CCR5 (knock out)</td>
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<td>Keratinocytes</td>
<td>Familial</td>
<td>LDL receptor</td>
<td>Gammmaretroviral</td>
<td>Grossman et al</td>
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<td>bullosa</td>
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Hallmarks of cancer (and consequences for target selection)
Adoptive T-cell therapy for cancer

Allogeneic ACT

Donor

GVL

Patient

T cells given as donor lymphocyte infusion after HSCT

Antigen-specific T cells cultured from donor before infusion

GVHD

Toxicity

Autologous ACT

Excise tumour

Plate fragments

Culture with 6,000 IU/ml IL2

Assay for specific tumour recognition

Reinfuse post-lymphodepletion

Select and expand to 10^6 cells

Limited applicability

Adoptive T-cell therapy for cancer: The era of genetically engineered cells

Bonini and Mondino, Eur J Immunol. 2015 Sep;45(9)
Adoptive T-cell GENE therapy for cancer: Currently @ San Raffaele Scientific Institute

Viral-mediated gene transfer

Suicide gene therapy in allo-HSCT

CAR-T cells redirected to CD44v6 to treat hematological malignancies and solid tumors
(Casucci et al., Blood 2013)

TCR gene editing to treat hematological malignancies
(Provasi, Genovese et al., Nat. Med 2012; Mastaglio et al., in preparation)
HSV-TK cells approach

Haploidentical donor (from bone marrow or peripheral blood)

Sources: adapted from Bonini et al., Science 1997; Bonini et al., Nat. Med. 2003; Recchia et al., PNAS 2006; Ciceri et al., Blood 2007
TK cells show in vivo anti-tumor effect

Ciceri et al, Blood 2007

TK-DLI in 23 relapsed pts
TK cells clinical development in haploidentical SCT

- Haploidentical transplant is a lifesaving procedure for many patients with hematologic malignancies

  - *Ex vivo* T-cell depleted haplo grafts without any donor cell therapy
    - delayed immune recovery and increased non-relapse mortality
  
  - T-cell replete haplo grafts followed by *in vivo* T-cell depletion and immunosuppression
    - increased GvHD and relapse risks

Numbers of haploidentical transplants doubled since 2010 for all the indications*

*Passweg 2015*
**Phase I-II TK007**

Haplo-HSCT* plus TK cells

* T-depleted (T cells, 1x10^4/Kg)

Dose of TK cells (1x10^6/Kg - 1x10^7/Kg)
Up to 4 monthly doses up to IR (CD3+ cell count >/= 100/mcl)
Starting 21 to 49 days after HSCT in absence of IR and/or GvHD

Ciceri, Bonini et al, Lancet Oncol 2009

**Phase III TK008**

Haplo-HSCT* plus TK cells

R (3:1)

Haplo-HSCT**

* T-depleted (T cells, 1x10^4/Kg)

** T-depleted (T cells, 1x10^4/Kg)
or

** unmanipulated BMT/PB + HD CTX

Dose of TK cells (1x10^7/Kg)
Up to 4 monthly doses up to IR (CD3+ cell count >/= 100/mcl)
Starting 21 to 49 days after HSCT in absence of IR and/or GvHD

TK cells clinical trials
TK007 phase II trial: very low infectious mortality after TK-cells

- Non-relapse mortality
- Days after SCT

No IR
IR TK treated

60%
14%
GvHD-free survival:
TK008 experimental arm
TK008 & TK007 (pooled analysis): Impact on survival rates of TK-cell doses

DFS/PFS according to the dose of MM-TK cells (n=49)

- $\geq 3.0 \times 10^7$/Kg (n=8)
- 1.1 to $2.9 \times 10^7$/Kg (n=26)
- $\leq 1.0 \times 10^7$/Kg (n=15)

Percent survival vs. Time (years)

OS according to the dose of MM-TK cells (n=49)

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Percent survival vs. Time (years)
Fabio Ciceri, Arnon Nagler, Evangelia Yannaki, Maria Teresa Lupo Stanghellini, Attilio Bondanza, Giacomo Oliveira, Raffaella Greco, Eduardo Olavarria, Eva M Weissinger, Michael Stadler, Donald Bunjes, Dietger Niederwieser, Lutz Uharek, Wolfgang Bethge, John DiPersio, Michele Donato, Andrew Pecora, Antonio Lambiase, Claudio Bordignon
Adoptive T-cell GENE therapy for cancer: Currently @ San Raffaele Scientific Institute

**Suicide gene therapy in allo-HSCT**

**CAR-T cells redirected to CD44v6 to treat hematological malignancies and solid tumors**
(Casucci et al., Blood 2013)

**TCR gene editing to treat hematological malignancies**
(Provasi, Genovese et al., Nat. Med 2012; Mastaglio et al., in preparation)
T cells can be engineered to have retargeted specificity for tumours.
## Pros and cons of adoptive immunotherapeutic tools

<table>
<thead>
<tr>
<th></th>
<th>mAb</th>
<th>TCR</th>
<th>CAR</th>
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<tbody>
<tr>
<td>MHC restriction</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<td>Antigen processing</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Lipid/sugar antigens</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Biodistribution</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Persistance</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
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<tr>
<td>Safety factors</td>
<td>-</td>
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<tr>
<td>Intracellular antigens</td>
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<tr>
<td>Costimulation</td>
<td>/</td>
<td>+</td>
<td>+/-</td>
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</tbody>
</table>
94% CR rate for r/r ALL after CTL019

175 patients with CLL, ALL, NHL, MM have gotten CTL019

- 48 r/r pediatric ALL pts: 45 in CR at 1 mo (94%)
- 5 went to subsequent transplant
- 6-month DOR: 76%
- 18 patients out ≥1 year
- No relapses past 1 year
- 13 patients in remission ≥1 year, 10 without further therapy

6-month OS: 81% (95% CI: 70,94)
12-month OS: 78% (95% CI: 66,92)

Kindly provided by S. Grupp
## 2G CAR efficacy

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Target</th>
<th>Gene-Vector</th>
<th>Pts</th>
<th>Results</th>
<th>Reference</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>4-1BB (beads)</td>
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<td>OR rate 50%</td>
<td>Kalos ASH 2013</td>
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<td>4-1BB (beads)</td>
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<td>OR rate 64%</td>
<td>Kalos, ASH 2013</td>
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<td>MCL, CLL, DLBCL</td>
<td>CD19</td>
<td>2G CAR-RTV</td>
<td>10</td>
<td>2 PR, 6 SD</td>
<td>Kochenderfer, <em>Blood</em> 2013</td>
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<tr>
<td>DLBCL</td>
<td>CD19</td>
<td>2G CAR-RTV</td>
<td>15</td>
<td>8 CR, 4 PR</td>
<td>Kochenderfer, <em>JCO</em> 2014</td>
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<td>CD28 (OKT3)</td>
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<td>OR rate 80%</td>
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<td></td>
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<td>CD28 (beads)</td>
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<td>OR rate 88%</td>
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<td>ALL</td>
<td>CD19</td>
<td>2G CAR-LTV</td>
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<td>27 CR</td>
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<td>4-1BB (beads)</td>
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<td>CR rate 90%</td>
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updated from Bondanza et al, *ASGCT newsletter* 2012
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<td>CLL/B-ALL</td>
<td>CD19</td>
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<td>B-cell aplasia</td>
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<td>CD28 (beads)</td>
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<td>CRS</td>
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<td>CLL</td>
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<td>CRS</td>
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<td>Davila, Sci Transl Med 2014</td>
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<td>CRS</td>
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</table>
Combination therapies that help harness T cells and other immune cells in the cancer fight are a key area to watch.
CAR active trials (clinicaltrials.gov)
Baylor (2008)  
1G CD19-CAR on EBV CTLs

UPenn (2011)  
2G CD19-CAR (4-1BB)

Juno Therapeutics (2013)  
MSKCC-Hutch  
2G CD19-CAR (CD28)

Kite Pharma (2013)  
NIH

Bluebird (2013)  
Celgene  
NIH (1995)  
1G FR-CAR
Beijing (2012)
4G CD19-, CD30, CD33-CAR

Cellular Biomedicine Group
(2015)
Palo Alto, CA

Melbourne (2013)
2G Lewis-Y CAR
• Why EBMT is interested in cell and gene therapy?
• Why should we register patients undergoing cell and gene therapy?
• How should we proceed?
CTIWP: Mission and implementation

To improve EBMT Registry, with a dedicated registry for cellular products, and clinical trials of cell and cell-based gene therapy.

To promote retrospective and prospective trials of cell/gene therapy under the EBMT shelter

To map GMP facilities spread in Europe

To implement an EBMT Cellular Repository for Cell/gene therapy clinical trials

To promote partnerships with the International and European Societies of Cell/Gene Therapy and with major investors in the field.

#EBMT2015
• An effort to upgrade the **EBMT registry** forms and improve the EBMT ability to collect additional and high-quality clinical and biological information from patients receiving **innovative cellular therapy and cell-based gene therapy**. (Joined effort with STWP, ADWP, IEWP)

• An upgrade of **the EBMT Annual activity Survey** to include Cellular therapy and Gene therapy (Baldomero & Passweg)

• A survey on currently used practices for **minimally-manipulated cell products**, with a view to harmonized recommendations (Chabannon)

• A survey of high resolution typing in the EBMT database regarding the use **unrelated donors** (Rocha & Fleischhauer)

• A survey on **mesenchymal stem cell manufacture harmonization**. (Dazzi, Bernardo)
Table 2: Cellular therapies using manipulated or selected cells

<table>
<thead>
<tr>
<th>Non HSCT Cellular Therapy</th>
<th>Indication for treatment (Number of patients)</th>
<th>MSC</th>
<th>Selected T cells (non DLI)</th>
<th>Regulatory T cells (TREGS)</th>
<th>NK cells</th>
<th>Expanded CD34</th>
<th>Genetically modified T cells (CAR/TCR)</th>
<th>Genetically modified T cells (suicide gene)</th>
<th>Genetically modified CD34</th>
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<tr>
<td></td>
<td>GvHD after HSCT</td>
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Allo: Allogeneic; Auto: Autologous.
CTIWP: A dedicated registry

To improve EBMT Registry, with a dedicated registry for cellular products, and clinical trials of cell and cell-based gene therapy.

Joined effort with ADWP, STWP, IEWP of EBMT
Possible partnership with ESGCT, AGORA, ISCT, other Scientific Societies

→ A Cellular Therapy Registry Committee
PROPOSAL for a Cellular Therapy Registry Committee (CTIWP-ADWP-STWP-IEWP)

• Chiara Bonini (CTIWP)
• Christian Chabannon (CTIWP)
• Carmen Ruiz (EBMT Registry)
• Steffie van der Werf, EBMT
• Fabio Ciceri (CTIWP)
• Alessandro Aiuti (IEWP, ESGCT)
• Maria Pia Cicaelese (IEWP)
• Maria Ester Bernardo (CTIWP)
• Marina Cavazzana Calvo (IEWP, ESGCT)
• Alessandra Magnani (IEWP)
• Elisa Magrin (IEWP)
• Fabien Touzot (IEWP)
• Attilio Bondanza (CTIWP)
• Eliane Gluckman (CTIWP, Eurocord)

• Dominique Farge-Bancel (ADWP)
• John Snowden (ADWP)
• Francesco Lanza (STWP)
• Paolo Pedrazzoli (STWP)
• Patrizia Comoli (STWP)
• Francesco Dazzi, (CTIWP)
• Martin Bonhauser (CTIWP)
• Hans-Jochem Kolb (CTIWP)
• Jakob Passweg (CTIWP)
• Helen Baldomero (CTIWP)
• Andrea Velardi (CTIWP)
• Loredana Ruggeri (CTIWP)
• Katarina LeBlanc (ADWP, CTIWP)
Cell Therapy
-MED – A Registration to day 100
-MED – A Annual Follow-up
- Manual
Registry for Cellular Therapy: Roadmap

- The **new MED/A + manual are ready**, and shall be presented during the CTIWP business meeting.
- Registration shall be **implemented** in the **summer**,
- **validated** by the Cellular Therapy Registry Committee Members in the **fall**,
- **ready for all the Centers by the end of 2016**.
Coming soon

Registry for Cellular Therapy

In order to collect pertinent and good quality clinical data, please register all your cellular therapies in this registry in a timely manner via the Cell Therapy Registry MED A form.

More Information ➔ contact CTIWPebmt@lumc.nl