Accept or reject: are stem cell therapies being tolerated?

Richard Haworth
Head of UK Pathology
IATP/ESTP workshop
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Acknowledgements:
Bob Maronpot, Darlene Dixon and Kevin Keane (IATP),
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Michaela Sharpe
Julie Holder
• Immunogenicity and immunotoxicity of the cell products were considered risks in the light of clinical experience of transplantation.

• The relative immunogenicity of mesenchymal stem cell (MSC), embryonic stem cell (ESCs) and induced pluripotent stem cells (iPSCs) was a question being addressed through in vitro and syngeneic in vivo models.
The Plan

– Approved products and those in clinical trials

– Role of immune system in stem cell product longevity at desired site.

– Is an immune response to a cell product necessarily detrimental to efficacy/safety?

– Allogeneic versus autologous. Does it matter?

– How can we assess potential risk of immunogenicity in advance of dosing a stem cell product to patients?
Stem Cell Therapies in Clinical Trials: Progress and Challenges

Alan Trounson¹,* and Courtney McDonald¹

¹Hudson Institute for Medical Research, 27-31 Wright Street, Clayton, VIC 3168, Australia
*Correspondence: alan.trounson@hudson.org.au
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Clinical investigations using stem cell products in regenerative medicine are addressing a wide spectrum of conditions using a variety of stem cell types. To date, there have been few reports of safety issues arising from autologous or allogeneic transplants. Many cells administered show transient presence for a few days with trophic influences on immune or inflammatory responses. Limbal stem cells have been registered as a product for eye burns in Europe and mesenchymal stem cells have been approved for pediatric graft versus host disease in Canada and New Zealand. Many other applications are progressing in trials, some with early benefits to patients.
## Clinical studies assessing cell retention at desired site for cardiac repair

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Tracer</th>
<th>Imaging</th>
<th>Cells</th>
<th>Delivery</th>
<th>Early (&lt;2 h)</th>
<th>Late (&gt;12 h)</th>
<th>Remote organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hofmann et al.(^5)</td>
<td>STEMI (n = 9)</td>
<td>$^{18}$F-FDG</td>
<td>3D PET</td>
<td>BMNC (n = 3) BMNC (n = 3) Enriched CD34(^+) (n = 3)</td>
<td>IC IV + IC (sequential) IC</td>
<td>1.3–2.6 0 IV (1.8–5.3) 14–39</td>
<td>NA NA</td>
<td>85% Liver and spleen</td>
</tr>
<tr>
<td>Kang et al.(^7)</td>
<td>STEMI (n = 11)</td>
<td>$^{18}$F-FDG</td>
<td>PET/CT</td>
<td>G-CSF mobilized peripheral stem cells</td>
<td>IC (n = 8) IV (n = 3)</td>
<td>0.5–3.3 0</td>
<td>&lt;1.5* NA</td>
<td>24–45% Liver and spleen 19% Lung, 22% liver, and 15% spleen</td>
</tr>
<tr>
<td>Chronic MI (n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IC (n = 5)</td>
<td>0.2–2.4</td>
<td>NA</td>
<td>8% Liver, 15.7% spleen, 5.8% brain, and 6% bladder (n = 1)</td>
</tr>
<tr>
<td>Blocklet et al.(^6)</td>
<td>STEMI (n = 6)</td>
<td>$^{111}$In-oxine</td>
<td>3D PET</td>
<td>G-CSF mobilized CD34(^+)</td>
<td>IC</td>
<td>5.5 ± 2.3</td>
<td></td>
<td>48 ± 35% Liver, 29 ± 19% spleen</td>
</tr>
<tr>
<td>Penicka et al.(^9)</td>
<td>STEMI (n = 5) Chronic MI (n = 5)</td>
<td>$^{99m}$Tc-HMPAO</td>
<td>SPECT</td>
<td>BMNC</td>
<td>IC</td>
<td>1.3–5.1 1.3–3.0 1.1–1.3 0</td>
<td></td>
<td>No quantitative assessment, mostly liver, spleen and lungs, not in brain</td>
</tr>
<tr>
<td>Schots et al.(^8)</td>
<td>Chronic MI (n = 5)</td>
<td>$^{111}$In-oxine</td>
<td>SPECT</td>
<td>G-CSF mobilized CD133(^+)</td>
<td>IC</td>
<td>6.9–8.0 2.3–3.2</td>
<td></td>
<td>23–26% Liver, 24–28% spleen</td>
</tr>
<tr>
<td>Schachinger et al.(^10)</td>
<td>STEMI (n = 8) Intermediate (n = 4) Chronic MI (n = 5)</td>
<td>$^{111}$In-oxine</td>
<td>PET</td>
<td>Cultured EPC</td>
<td>IC</td>
<td>6.3 ± 2.9 ~1–5</td>
<td>4.5 ± 3.2 ~1–2 2.5 ± 1.6 ~0–2</td>
<td>~30% Liver, ~9% spleen, and ~8% lung (details, see Figure 2 in ref. 10)</td>
</tr>
</tbody>
</table>

CT, computed tomography; EPC, endothelial progenitor cells; FDG, fluorodeoxyglucose; IC, intracoronary; IM, intramyocardial; PET, positron emission tomography; SPECT, single-photon emission CT; STEMI, ST elevation myocardial infarction; $^{99m}$Tc-HMPAO, $^{99m}$Tc-d,I-hexamethylpropylene amine oxime.
<table>
<thead>
<tr>
<th>Name</th>
<th>Developer</th>
<th>Indication</th>
<th>Approval date</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alofisel</td>
<td>TiGenix</td>
<td>Perianal fistulas in Crohn's disease</td>
<td>March 2018</td>
<td>Approved</td>
</tr>
<tr>
<td>Spherox</td>
<td>CO.DON</td>
<td>Cartilage defects in the knee</td>
<td>May 2017</td>
<td>Approved</td>
</tr>
<tr>
<td>Zalmoxis</td>
<td>MolMed</td>
<td>Stem cell transplantation in high-risk blood cancer</td>
<td>June 2016</td>
<td>Approved</td>
</tr>
<tr>
<td>Strimvelis</td>
<td>GSK</td>
<td>ADA-SCID</td>
<td>April 2016</td>
<td>Approved</td>
</tr>
<tr>
<td>Imlygic</td>
<td>Amgen</td>
<td>Melanoma</td>
<td>October 2015</td>
<td>Approved</td>
</tr>
<tr>
<td>Holoclar</td>
<td>Chiesi</td>
<td>Severe limbal stem cell deficiency in the eye</td>
<td>March 2015</td>
<td>Approved</td>
</tr>
<tr>
<td>Provenge</td>
<td>Dendreon</td>
<td>Metastatic prostate cancer</td>
<td>October 2013</td>
<td>Withdrawn in 2015</td>
</tr>
<tr>
<td>MACI</td>
<td>Vericel</td>
<td>Cartilage defects in the knee</td>
<td>July 2013</td>
<td>Withdrawn in 2014</td>
</tr>
<tr>
<td>Glybera</td>
<td>uniQure</td>
<td>Lipoprotein lipase deficiency (LPLD)</td>
<td>November 2012</td>
<td>Withdrawn in 2017</td>
</tr>
<tr>
<td>Chondrocelect</td>
<td>TiGenix</td>
<td>Cartilage defects</td>
<td>November 2009</td>
<td>Withdrawn in 2016</td>
</tr>
</tbody>
</table>

Source: European Medicines Agency
Alofisel (TiGenix NV / Takeda)

- treat complex perianal fistulas in adult patients with nonactive/mildly active luminal Crohn’s disease, when inadequate response to conventional or biologic therapy.
- allogeneic (donor-derived) expanded adipose-derived stem cells (eASCs), a form of MSCs
- intralesional injection which reduces proliferation of activated lymphocytes / release of pro-inflammatory cytokines at inflammation sites.

- In vitro interaction studies: cell viability/ immunomodulatory function of Alofisel is not affected by the presence of conventional therapies for Crohn’s disease (infliximab, methotrexate and azathioprine)
- **Immunogenicity**
  - ADMIRE-CD study, 36% of the eASC-treated patients showed anti-donor antibody production at Week 12. Of patients with donor-specific antibodies (DSA) at Week 12, 30% had cleared DSA by Week 52. Lack of de novo DSA generation was observed between Week 12 and Week 52.
  - Limited data exist but there does not appear to be a detrimental effect of DSA on efficacy and safety.
  - Concomitant use of stable doses of immunosuppressants (18% of patients) or anti-TNFs (33%) or both (28%) was allowed during the study.

- **Nonclinical studies:** After perianal and intrarectal injection of human eASC in athymic rats, cells were present in the rectum and jejunum and at the site of injection for at least 14 days and were undetectable after 3 months. eASC were not present in any of the tissues analysed after 3 months or 6 months.
Applications for mesenchymal stem cells (MSC)

Figure 1. Indications Being Addressed using MSCs in Clinical Trials
Data for 352 registered clinical trials.
### Table 1. ESC Trials

<table>
<thead>
<tr>
<th>Trial Sponsor (Location)</th>
<th>Disease Target</th>
<th>Cell Therapy</th>
<th>No. Patients</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chabiotech Co. Ltd. (S. Korea)</td>
<td>macular degeneration</td>
<td>human-ESC-derived RPE</td>
<td>12</td>
<td>phase I/II</td>
</tr>
<tr>
<td>Ocata Therapeutics (MA, USA)</td>
<td>Stargardt’s macular dystrophy</td>
<td>human-ESC-derived RPE</td>
<td>16</td>
<td>phase I/II</td>
</tr>
<tr>
<td></td>
<td>macular degeneration</td>
<td>human-ESC-derived RPE</td>
<td>16</td>
<td>phase I/II</td>
</tr>
<tr>
<td></td>
<td>myopic macular degeneration</td>
<td>human-ESC-derived RPE</td>
<td>unknown</td>
<td>phase I/II</td>
</tr>
<tr>
<td>Pfizer (UK)</td>
<td>macular degeneration</td>
<td>human-ESC-derived RPE</td>
<td>10</td>
<td>phase I</td>
</tr>
<tr>
<td>Cell Cure Neurosciences Ltd. (Israel)</td>
<td>macular degeneration</td>
<td>human-ESC-derived RPE</td>
<td>15</td>
<td>phase I/II</td>
</tr>
<tr>
<td>ViaCyte (CA, USA)</td>
<td>type I diabetes mellitus</td>
<td>human-ESC-derived pancreatic endoderm cell</td>
<td>40</td>
<td>phase I/II</td>
</tr>
<tr>
<td>Assistance Publique-Hopitaux de Paris (France)</td>
<td>heart failure</td>
<td>human-ESC-derived CD15+ Isl-1+ progenitors</td>
<td>6</td>
<td>phase I</td>
</tr>
<tr>
<td>International Stem Cell Corp. (Australia)</td>
<td>Parkinson’s disease</td>
<td>human parthenogenetic-derived neural stem cells</td>
<td>unknown</td>
<td>phase I/II</td>
</tr>
<tr>
<td>Asterias Biotherapeutics (CA, USA)</td>
<td>spinal cord injury</td>
<td>human-ESC-derived oligodendrocyte precursor cells</td>
<td>13</td>
<td>phase I/II</td>
</tr>
</tbody>
</table>
PEC-Encap: consists of ES cell-derived pancreatic progenitor cells (PEC-01) encapsulated in Encaptra® Cell Delivery System. Allogeneic.

2 year clinical study

- **Immunology Assessment:** The Encaptra Cell Delivery System appears to protect against allo- and auto-immune rejection and sensitization.

- Immune function tests showed no donor-specific antibodies, no increase in auto-antibody titers, no tolerance or sensitization to donor cells, and no increase in lymphocyte stimulation or antigen-specific CD8+ T cell frequency post-implantation.

- **Cell Differentiation and Survival:**

- Low levels of engraftment due to a foreign body giant cell response,

- Differentiation into endocrine islet cells was observed in both 12-week and two-year explants for both VC-01-250 and VC-01-20 units in regions where there was good host tissue integration and vascularization.

- Several two-year VC-01-250 explants had regions containing insulin-producing beta cells and glucagon-producing alpha cells, indicating that when engraftment occurs, cells can persist for long durations without the need for immunosuppression.

immunogenicity of stem cells may have been underestimated

only if the cell implanted is absolutely identical to the recipient in every respect, including epigenetically, will it evade immune recognition
### Factors influencing the host immune response to stem cell graft

<table>
<thead>
<tr>
<th>Age</th>
<th>Immunosenescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue location</td>
<td>Immune privileged sites</td>
</tr>
<tr>
<td>Immune status</td>
<td>Absence of self tolerance to functional gene introduced in to autologous iPSC could trigger immune response</td>
</tr>
<tr>
<td></td>
<td>Some disease settings more likely to trigger an immune response</td>
</tr>
<tr>
<td></td>
<td>Immunodeficient</td>
</tr>
</tbody>
</table>
Immune privileged sites – a reality or immunologists wishful thinking?

- evolutionary adaptation to locally regulate the immune system to protect non-renewable cells from the damaging effects of an inflammatory immune response
- tolerate the introduction of antigens without eliciting an inflammatory immune response.
- tissue grafts can survive for extended periods of time without rejection.
- all these tissues are privileged, but some are more privileged than others.

<table>
<thead>
<tr>
<th>eyes</th>
<th>testicles</th>
<th>articular cartilage</th>
<th>brain (certain sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>placenta</td>
<td>fetus</td>
<td>hair follicles</td>
<td>liver</td>
</tr>
</tbody>
</table>
Immune privileged sites

Factors (active and passive) that contribute to the maintenance of immune privilege include:

- Selective entry of immune cells
- Low expression of classical MHC class I molecules
- Increased expression of surface molecules that inhibit complement activation
- Local production of immunosuppressive cytokines such as TGF-β and presence of neuropeptides
- Constitutive expression of Fas ligand that controls the entry of Fas-expressing lymphoid cells
- Reduced lymphoid drainage

However, surgical implantation of cells can breach the blood: organ barrier and induce inflammation which can increase risk of immune rejection. A loss of privilege…. 
Why has the eye been a leading organ for treatment?

- Small numbers of cells required
- Accessible for surgery and monitoring of effects
- Immune privilege
- One eye remains untreated as control
- Ability to differentiate pluripotent cells for use in eye
The immune response of stem cells in subretinal transplantation

- The subretinal space (SRS) maintained as an immune privileged site by the retinal pigment epithelium (RPE) layer

- Immunosuppressive drugs not necessary if the blood-retinal barrier is not breached during surgery. However, in recent Pfizer trial for their ES cell derived therapy for macular degeneration, slow release steroids surgically implanted in eye.

- Despite low rates of graft rejection in animal models, survival rates for ESCs, MSCs, and iPSCs in retina are generally poor, possibly due to resident microglia activated by cell transplantation.

- The mechanisms conferring immune privilege include
  - (1) suppression of T-cell activation by release of cytokines from the RPE, such as e.g. TGF-beta,
  - (2) production of other immunosuppressive factors by RPE cells that suppress innate immune activity, including pigment epithelium-derived factor and somatostatin;
  - (3) surface expression of program death-1 (PD-L1) and Fas ligand by RPE cells;
  - (4) conversion of CD8+ and CD4+ T cells into regulatory T cells; and
  - (5) the intact physical barrier of the RPE layer.
Stem Cell therapy factors influencing the immune response

Cell Origin
- Human ESCs can express new antigens after differentiation, e.g. ABO blood group
- Genomic wide sequencing / transcriptome analysis to compare effect of cell source

Cell differentiation protocol
- Will undifferentiated cells in iPSC mix be more immunogenic? Can they be removed?
- Culture conditions can influence epigenetic changes, e.g. TLR4 expression

Dosing schedule, frequency, encapsulation
- Will encapsulation prevent leakage of stem cell proteins which could lead to humoral immune response
- Repeat intralesional dosing stimulates innate immune response through danger signals
Induced Pluripotent stem cells (iPSC) | Embryonic stem cells (ESC) | Adult stem cell lines
---|---|---
- iPSCs with strong immunogenicity reported by Zhao et al. were retrovirus derived. Results have been challenged.
- Retroviral vectors can integrate at transcriptional sites and produce immunogenic proteins.
- Immunogenicity of mouse iPSCs decreases the closer surface antigen expression comes to the parent somatic cell – very low for skin, bone marrow, hepatocytes and neuronal cells.
- Non human primate (NHP) Parkinson model- autologous iPSC derived dopamine neurons functioned for 2 years in brain without IS.

| | ESCs and derivatives escaped host immune attack and survived for long periods in animal models. |
| | Theoretical risk of mitochondrial antigens from donor oocyte in nuclear transfer ESC |
| | At least three reasons for this low immunogenicity. |

1. human ESCs express low (HLA) class I molecules and do not express HLA class II molecules in either resting/ differentiated state
2. ESCs lack co-stimulatory molecules, such as CD80 and CD86
3. ESCs suppress naive and dendritic cell-mediated T-cell proliferation in allogeneic settings

MSCs: negligible immunogenicity and the capacity for immune suppression.

- MHC mismatched MSCs did persist longer than MHC mismatched fibroblasts, supporting that they are immunomodulatory in vivo
- MSCs express low MHC I and lack MHC class II and the co-stimulatory molecules CD80, CD86, and CD40.
- MSCs inhibit dendritic cells, T cells, B cells, natural killer cells, and macrophages

Little difference between autologous and allogeneic MSCs in their actions or clinical effects, suggesting that they deliver a payload of cytokines and other influences on endogenous tissue regeneration.
In-vivo immune responses to MHC-mismatched MSCs and corresponding in vitro assays
Strategies to reduce stem cell immunogenicity

- Creation of human ESC cell bank with diversity of HLA antigens to provide match for patients
- Knock down MHC expression of stem cells, but may leave cells vulnerable to NK cell killing
- Some stem cells produce immunomodulatory molecules, e.g. iPSC mesoangioblasts
- Immunosuppression by drugs. However long term use increases risk of cancer and infection and organ toxicity e.g. kidney. Risk / benefit different from organ transplantation. Will short term use allow host immune regulation mechanism to enable graft survival?
- Use of non-depleting antibodies to block co-stimulatory molecules, e.g. CTLA-4, CD40L or receptors, e.g. CD4.
- Ex vivo expansion of induced, autologous regulatory T cells to control CD8+ T cells or macrophage responses.
- Use of mechanism which induces and maintains central and peripheral tolerance to induce tolerance to donor alloantigens. Used in transplant medicine; could be applied to stem cell therapy. This could include mixed or full chimerism (donor and recipient hematopoietic cells) in HLA mismatched recipient. However requires significant conditioning.
- Use of same stem cells to differentiate into both source of cells to induce tolerance (e.g. immature dendritic cells) and fully differentiated tissue for therapy.
Conclusions

- Consider potential immunogenicity of both your stem cell product and the recipient factors which may influence cell survival
- You need to know what your product contains…
- Evidence of little difference between autologous and allogeneic MSCs in their actions or clinical effects
- Insufficient clinical data to answer many postulated immunological risks
- Host immune response more likely to lead to reduced cell efficacy than toxicity
- Limited ability to assess immunogenicity risks preclinically
References

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  Therapeutic Applications. Trends Immunol, 37(1), 5-16.
Thank You

Any questions?
<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency and ease of use</td>
<td>Limited to using rodents</td>
<td>Allow use of large animal species</td>
<td>Difficult to achieve consistent immunosuppression (IS)</td>
</tr>
<tr>
<td>Allows certain disease/injury modeling</td>
<td>Does not predict immunoreactivity to transplanted cells</td>
<td>Wider array of disease models</td>
<td>IS agent might affect transplanted cells</td>
</tr>
<tr>
<td>Defined degree of immunodeficiency</td>
<td>Susceptible to disease</td>
<td></td>
<td>Need to discriminate IS toxicity from cell product toxicity</td>
</tr>
<tr>
<td></td>
<td>Limited pathology database</td>
<td></td>
<td>Uncertain translation of immunogenicity from animal (xenoreactivity) to patient (alloreactivity)</td>
</tr>
</tbody>
</table>
Advanced Therapy Medicinal Products (ATMP) : FDA

- somatic cell therapy medicinal product: treating, preventing or diagnosing a disease

- tissue engineered product: regenerating, repairing or replacing a human tissue (+combination products)
  active substance: cells or tissues, substantial manipulated so that characteristics, functions or structural properties have been altered or that are not intended to be used for the same essential function(s) in the recipient and the donor (“not homologous use”)

- gene therapy medicinal product: regulating, repairing, replacing, adding or deleting a genetic sequence
  active substance: recombinant nucleic acid

Useful information at http://www.aub.edu.lb/irb/Documents/FDA.pdf
Pathophysiology of acute GVHD

Preparative chemo or radiotherapy

Know your product

- In vitro and in vivo
- Cell source- donor infection status
- Maturation status – changes upon delivery
- Partially or fully differentiated
- Population purity- heterogenous, residual undifferentiated cells
- Stability/ genetic drift
- Absence of micro-organisms- TSE prions
- Karyotype and epigenomic status (hESC lines every 10-15 passages (on feeders) or population doublings (feeder-free conditions).
Immunogenicity- in vitro assessment

- the MHC haplotype of donors,
- recipients, stimulators, and responders should be determined
- to understand if donor or stimulator MSCs are full
- or partial mismatches to recipients or responder cells

- Preformed T-cell responses measured using ELISPOTs accurately predict graft rejection in
- organ transplantation cases [47] and may be able to predict
- the in-vivo cell-mediated immunogenicity of donor
- MSCs.
- Cytotoxicity assays can be used to measure direct lysis of
- MSCs by MHC-specific cytotoxic T lymphocytes (CTLs).
- microcytotoxicity assays
  - use eosin or fluorescent dye to detect antibody-mediated
  - complement-dependent cytotoxicity (CDC) following incubation
  - of sera from animals injected with MHC-matched or
  - MHC-mismatched MSCs with donor PBLs or MSCs and
  - rabbit complement
Immunogenicity- in vivo assessment

- Species specific homologue possible but practical issues (not clinical product.)

- If use clinical product, may lead to xenogeneic response which is not clinically relevant.

- Long term assessment required.

- Secondary pharmacology from cell transplant: off target effects resulting from secretion of bioactive compounds from the graft.

- Humanised mouse models (e.g. NOD/SCID/gamma null (NSG)) reconstituted with a human immune system from same donor (fetal liver) can evaluate different cells differentiated from iPSC, e.g. RPE and smooth muscle. Zhao, Cell Stem Cell 17, 353–359, September 3, 2015
## Types of immune response

<table>
<thead>
<tr>
<th>Products</th>
<th>Acute</th>
<th>Chronic</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Graft versus host disease</strong>&lt;br&gt;Reaction of donor immune cells against host tissues</td>
<td>Acute (weeks)-donor / recipient HLS mismatch. Targets: skin (rash), liver (jaundice), eyes, or gastrointestinal tract (nausea, vomiting, diarrhea). 30-50% incidence for haematopoietic stem cells.</td>
<td>Chronic-weeks-years. donor / recipient HLS mismatch. Targets: skin, liver, eyes, mouth, lungs, gastrointestinal tract, neuromuscular system, or genitourinary tract. For cancer treatment-patients who develop GvHD haver lower relapse rates (graft versus tumor effect).</td>
<td>Immunosuppression, prednisolone.</td>
</tr>
<tr>
<td>Allogeneic donor marrow or stem cells</td>
<td>Higher risk with: multiparous female donor, older donor, higher proportion of CD34+ cells. Lower risk with cord blood stem cells.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Direct antigen presentation by stem cells

- If MHC mismatch, donor stem cells could present directly to patient’s T cells if they also expressed co-stimulatory molecules (e.g. CD86, CD80, CD11c)

- However, expression levels are low on human ESC and iPSC. Therefore direct allo stimulation probably of limited significance.

- However for stimulation of memory T cells, then lower levels of co-stimulation are required. This is a risk if stem cells express molecules recognised by host memory cells.

Could this be a risk for re-administration of stem cells to a patient?

The formation of memory immune cells in recipients of MHC-mismatched MSCs is important since immunologic memory can lead to accelerated rejection of allogeneic cells upon reinjection.

Pre-existing antibodies crossreactive for donor MHC molecules or alloantibodies produced following activation of B cells by cognate alloantigens can also contribute to rejection of allogeneic cells.