Mixed chimerism and tolerance induction

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Blood Chimerism

• Old idea which has been shown over decades to be the most robust way to achieve donor specific immune tolerance

• Blood chimerism is achieved routinely as part of allogeneic bone marrow transplantation for malignancies but not for purposes of tolerance induction. Why?
  – upfront mortality of 10-20%
  – toxicities associated with getting cells to engraft
  – graft-vs-host disease
  – immune compromise
Most BMT recipients receive unmanipulated allografts
HSC transplantation for tolerance induction

**Graphs and Figures:**
- **Donor T cells of Total T cells (%)**
  - Allo HSC D+35
  - Allo HSC D+66
  - Allo BM D+53

- **Diabetes free (%)**
  - Months after birth
  - Control
  - BALB/c
  - BM Txp
  - HSC Txp
  - D+35
  - D+66
  - D+53

- **Survival (days)**
  - Control
  - BALB/c
  - BM Txp HSC Txp
  - D+35
  - D+66
  - D+53

- **Donor-derived CD4+ & CD8+ cells (%)**
  - Days post txp

- **Donor-derived Gr1+Mac1+ cells (%)**
  - Days post txp

- **Percentage (%)**
  - Control
  - Bone Marrow Transplant
  - Stem Cell Transplant
Challenge of engraftment: The immune barrier

High resistant strain AKR into B6

Days post-transplant
0 20 40 60 80 100
0
25
50
75
100
Survival (%)

Radiation control (n=6)
300 AKR HSC (n=10)
1000 AKR HSC (n=10)
3000 AKR HSC (n=10)
6000 AKR HSC (n=10)

Days post-transplant
0 25 50 75 100 125

Survival (%)

% donor Mac/GR1
0 25 50 75 100

6000 HSC n=5
3000 HSC n=4
1000 HSC n=4
200 HSC n=4
oxrt control n=2
Challenge of engraftment: The non-immune barrier
Kidney Transplant

rATG (1.5 mg/kg)

Donor CD34+ cell infusion
Inclusion of CD3+ cells (dose 1 x 10^6/kg)

Withdraw immunosuppression if:
- stable macrochimerism
- no evidence of rejection
- no GVHD

Day 0
TLI

Kidney Transplant
Prednisone x 10 days only
Cyclosporine wean month 3-6

Cyclosporine wean month 3
Prednisone x 10 days only
MMF d/c d+30

Withdraw immunosuppression if:
- stable macrochimerism
- no evidence of rejection
- no GVHD
Regenerative medicine

Embryonic stem cell line

Blood forming stem cells

Heart stem cells
Muscle stem cells
Pancreatic islet stem cells
Brain stem cells
Questions for the near future

• Are there concerns using pure HSC for clinical allogeneic transplant studies?

• What are acceptable methods for preparing patients with non-malignant disease to engraft with allogeneic HSC?

• Can we move directly to the use of an all monoclonal antibody regimen to permit engraftment of allogeneic HSC? (or does each monoclonal agent need to be tested separately in safety studies?)

• Is stable (life-long) mixed chimerism required for tolerance induction?
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