# Mixed chimerism and tolerance induction

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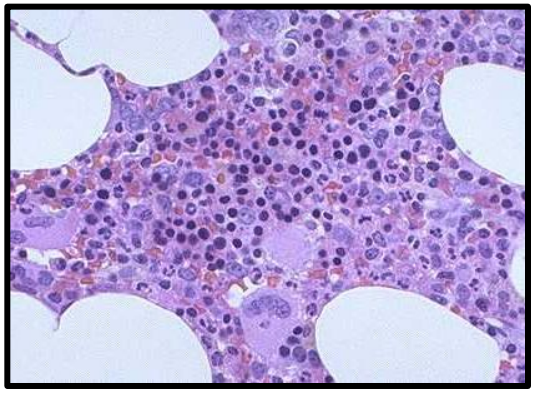
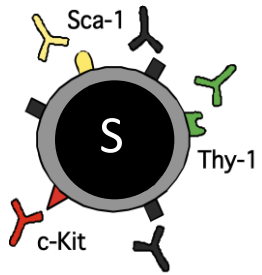
# Blood Chimerism

- 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






**STEM CELL**

CMP

CLP

MEP

GMP

Pro-B

Pro-T

R
R
Red blood cells

Mega
Platelets

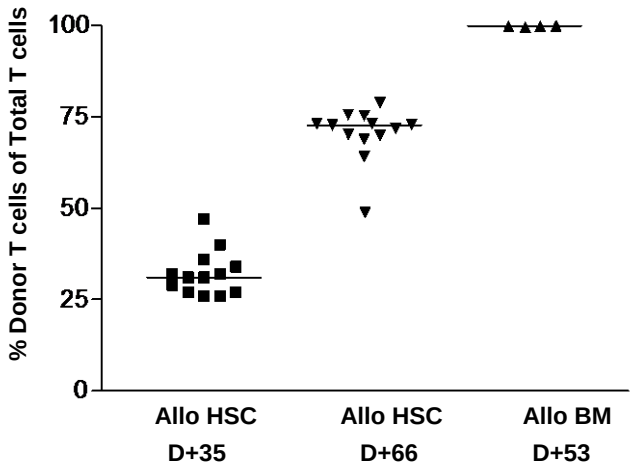
N
N
Granulocytes

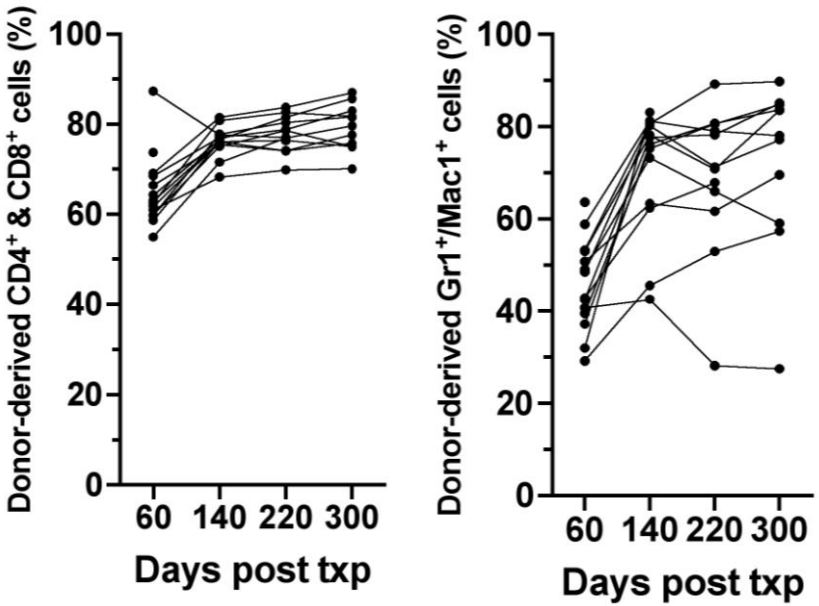
M
Monocytes

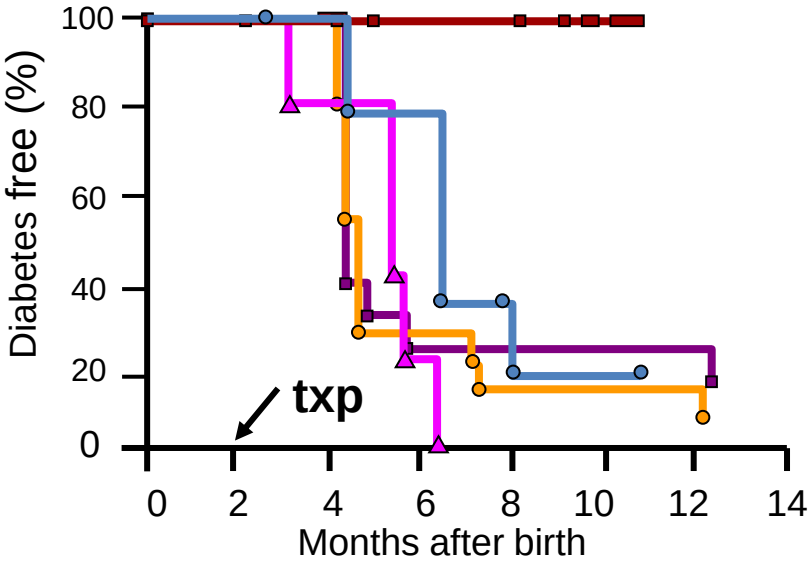
B
B lymphocytes

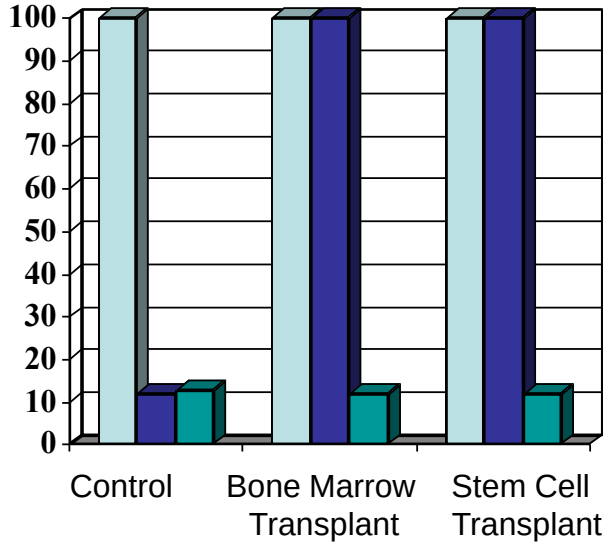
T
T lymphocytes

# HSC transplantation for tolerance induction

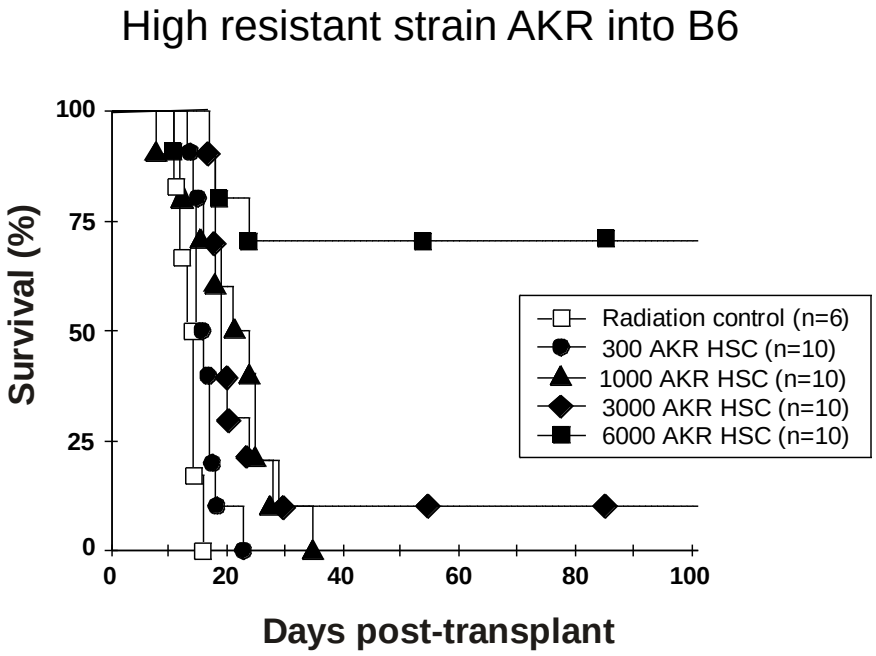


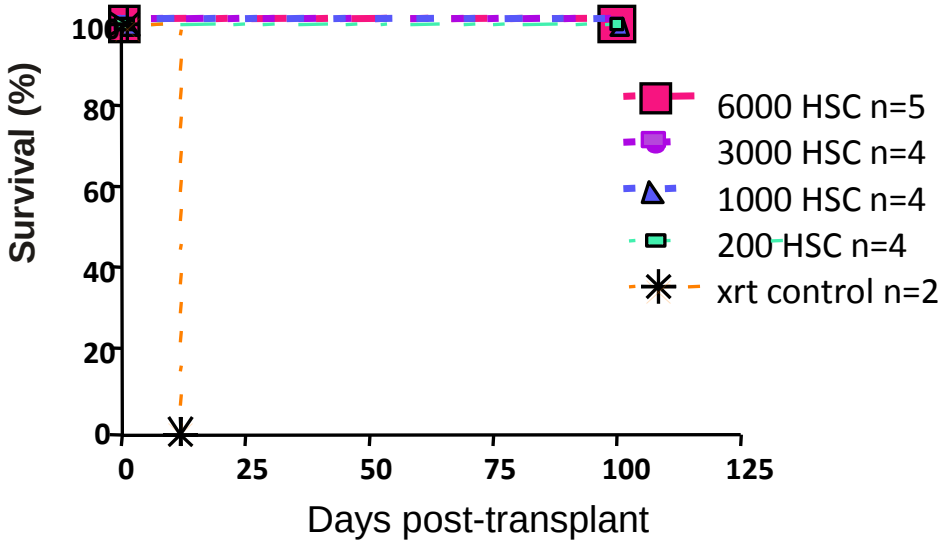



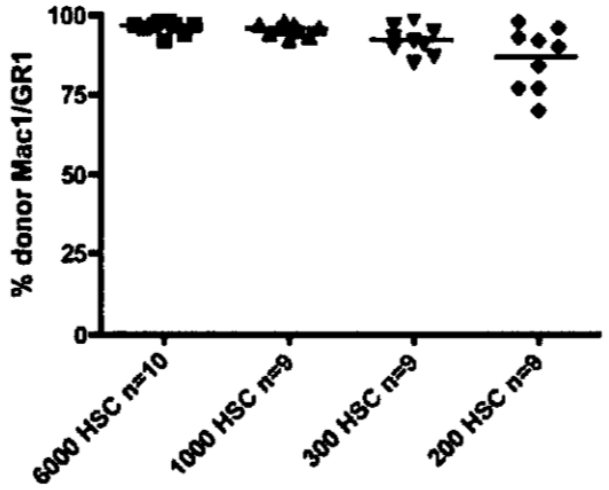



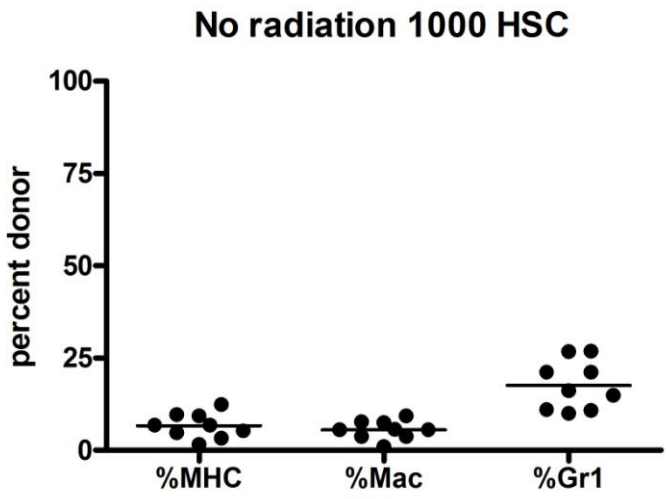
# Challenge of engraftment: The immune barrier

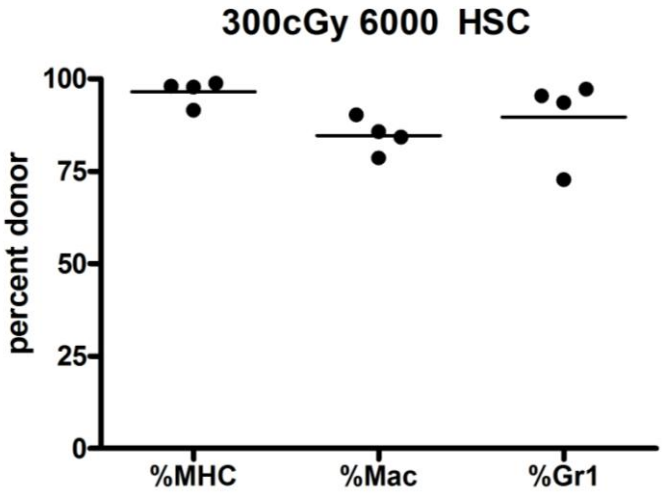


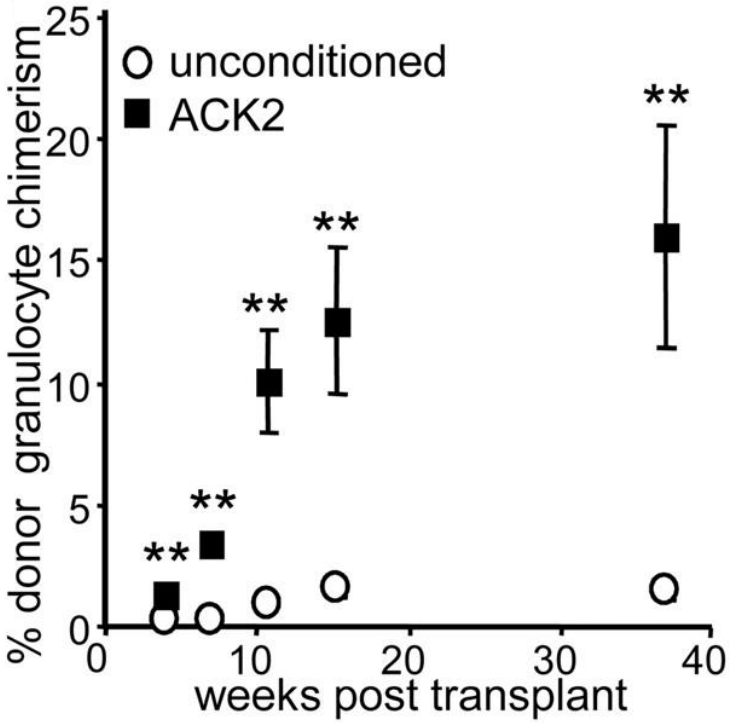



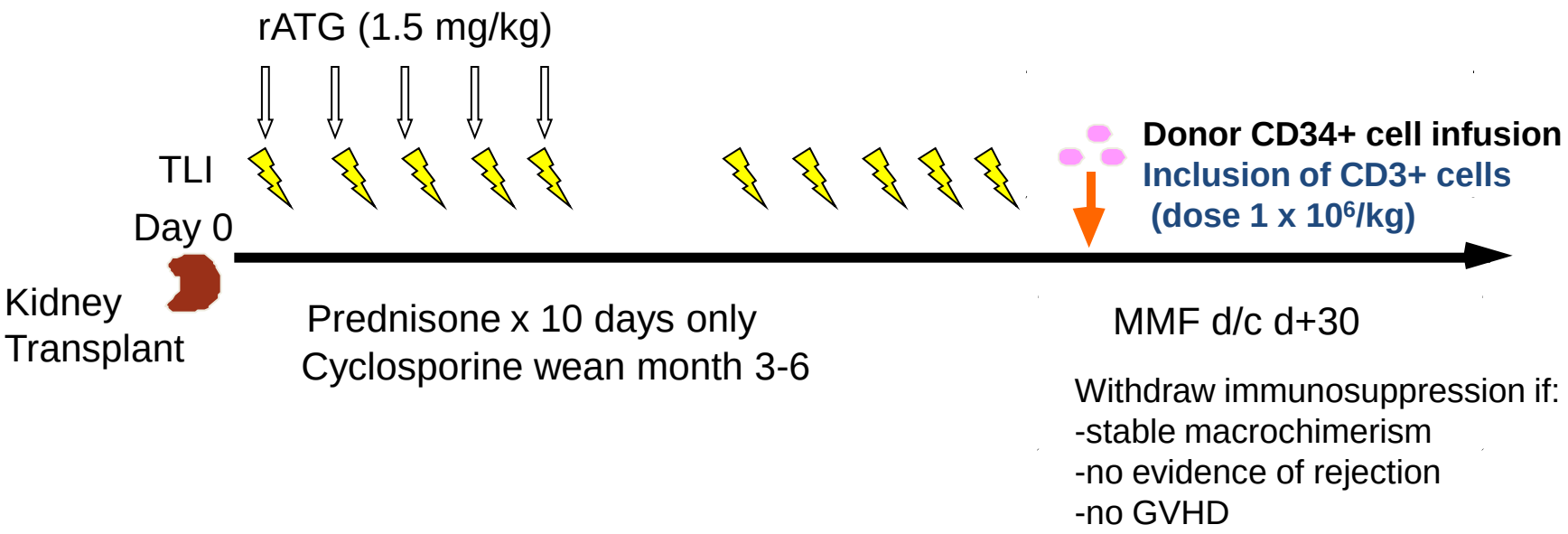
# Challenge of engraftment: The non-immune barrier



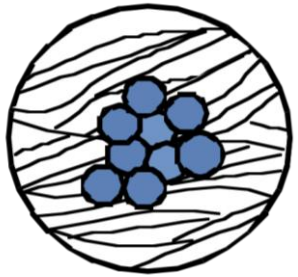



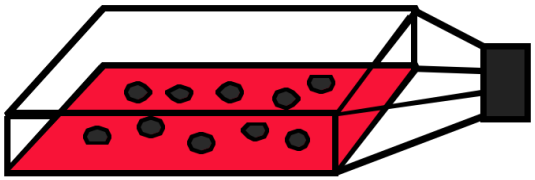
# Clinical Protocol and Chimerism

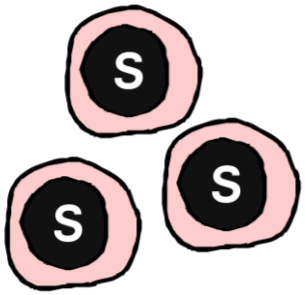


# Regenerative medicine



Embryonic stem cell line





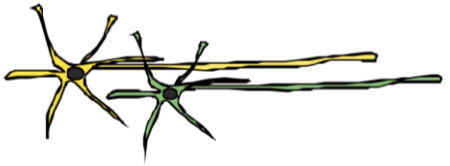

Blood forming stem cells

+

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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