



# **Mobilization of CD8+ Central Memory T-Cells with Enhanced Reconstitution Potential in Mice By a Combination of G-CSF and GMI-1271-Mediated E-Selectin Blockade**

Cell Collection and Processing

Program: Oral and Poster Abstracts

Type: Oral

Session: 711. Cell Collection and Processing: Comparative studies and Novel Agents

Monday, December 7, 2015: 7:15 AM

Tangerine 2 (WF2), Level 2 (Orange County Convention Center)

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T-cells. *Critical mediators of our immune defence*

## T-cell therapies

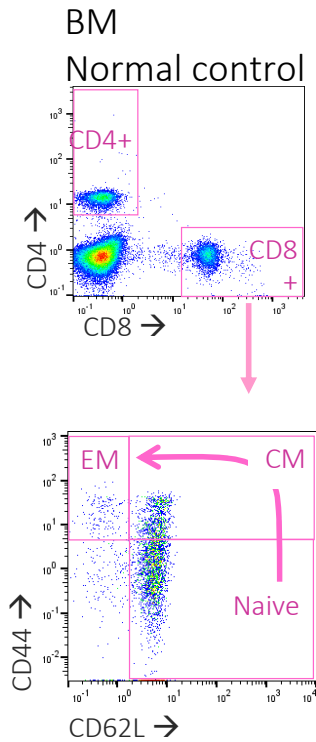
- Adoptive Tcell immunotherapy
- T-cell engineering approaches
- Innovative new strategies to treat cancer
- However, low survival after adoptive transfer

Aim. *Improved ways of harvesting CD8+ CM cells for clinical use*

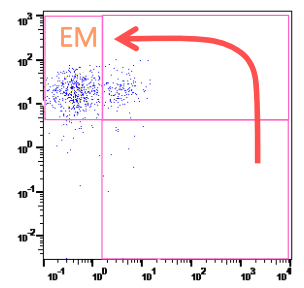


# CD8+ T-cell exhaustion during leukemia

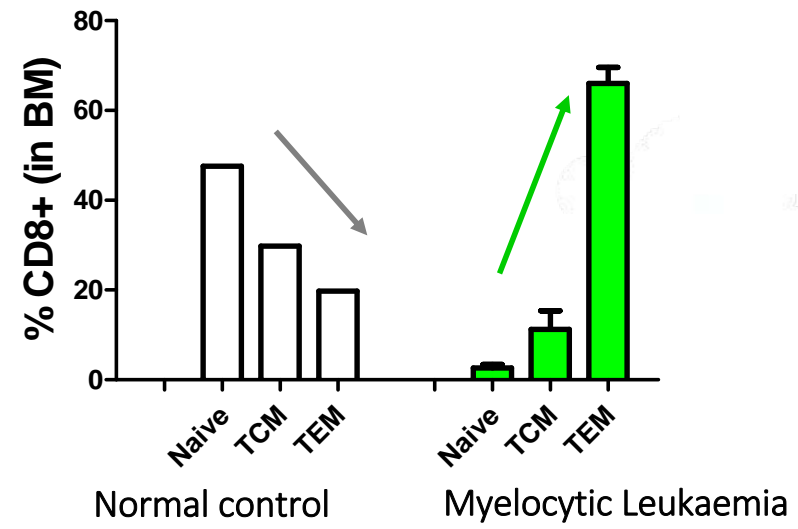
*... a problem for harvesting CD8+*



Myelocytic Leukaemia  
(MLL-AF9)

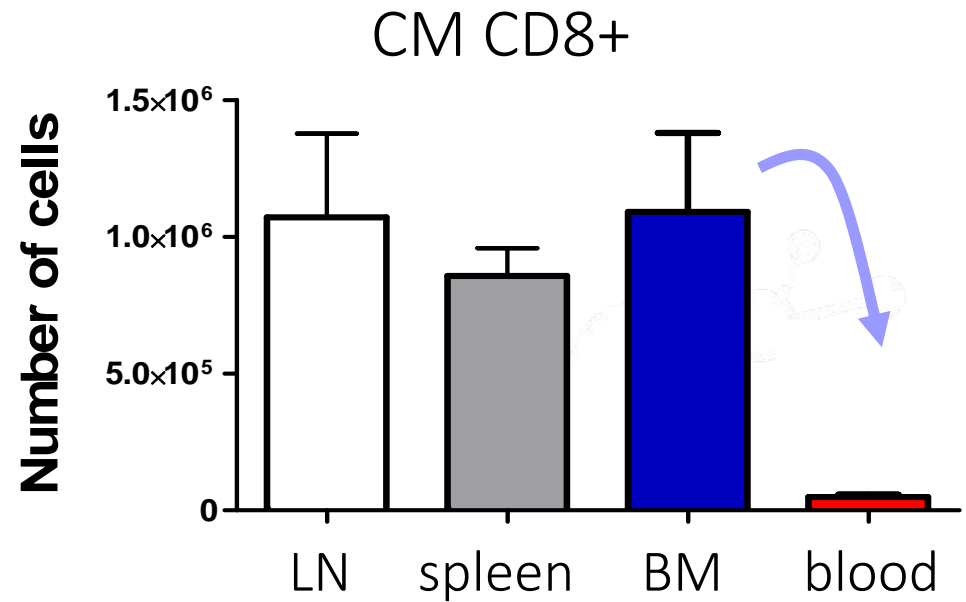


Skewing of CD8+ subsets





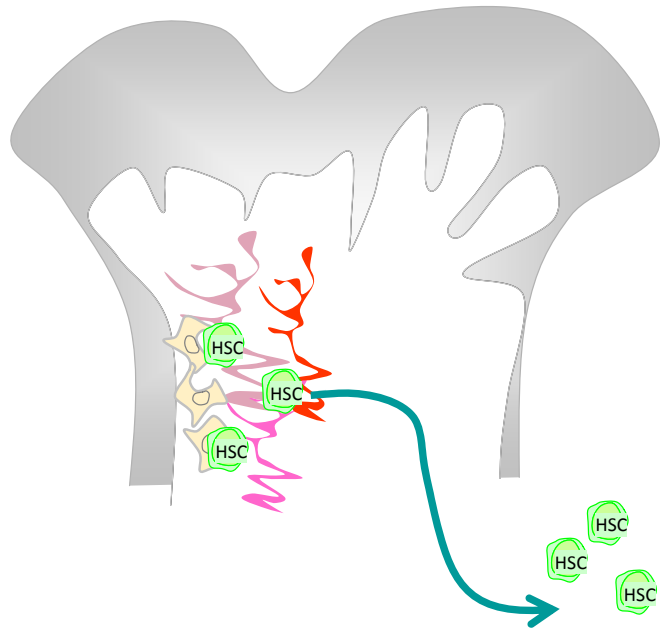
# CD8+ T-cell populations in normal mouse





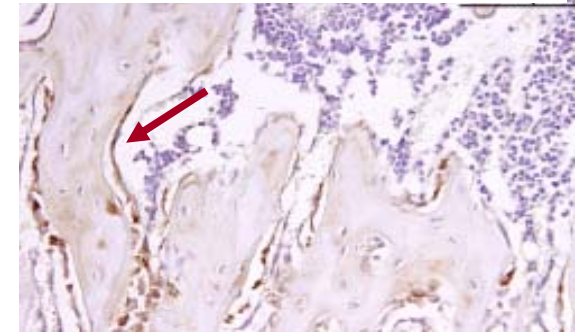
# G-CSF-induced mobilisation of cells from the BM ...

*G-CSF leads to HSC mobilization...by remodelling BM niches*



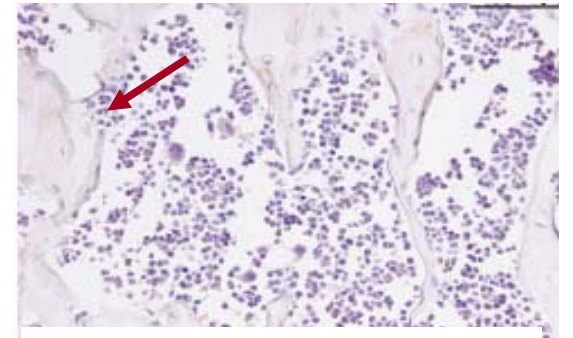
Osteocalcin  
Immunohistology

Saline treated



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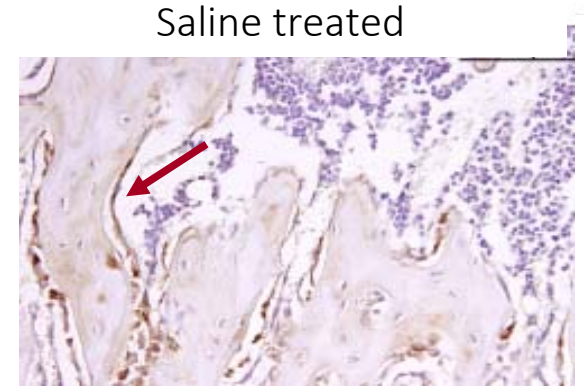
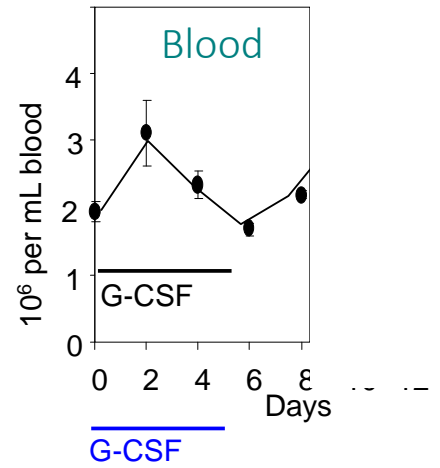
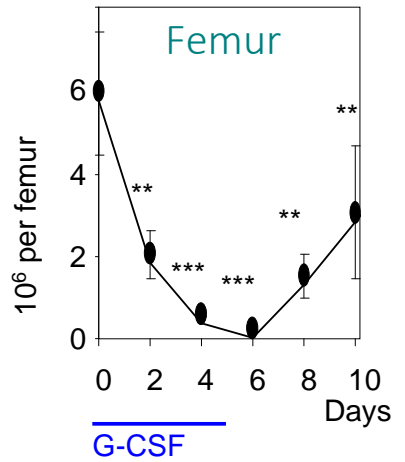
G-CSF treated (4 days)



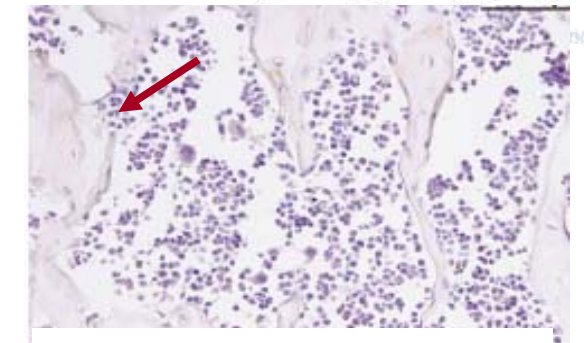
*Winkler et al., Blood 2010*  
*Winkler et al., Leukemia 2013*

# G-CSF-induced mobilisation of cells from the BM

... ablates B-lymphopoiesis



Saline treated



G-CSF treated (4 days)

Winkler et al., Hematologica, 2013

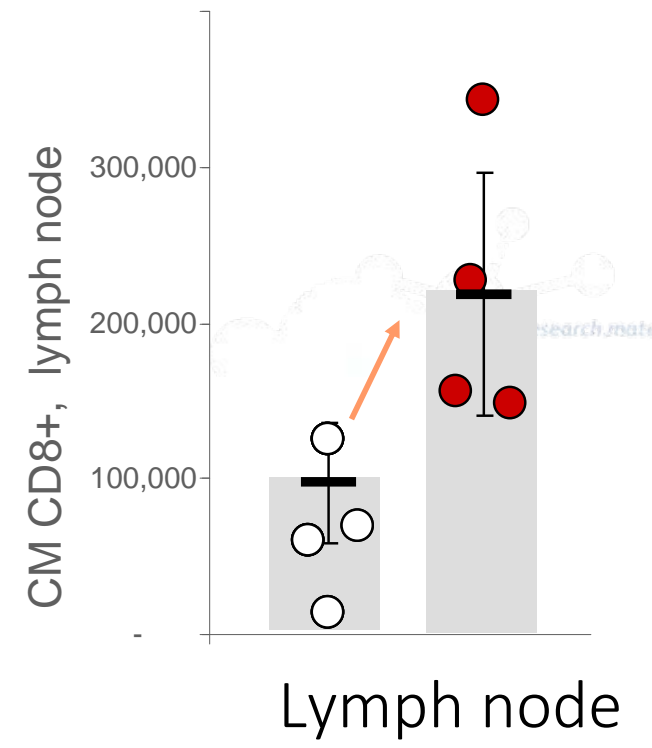
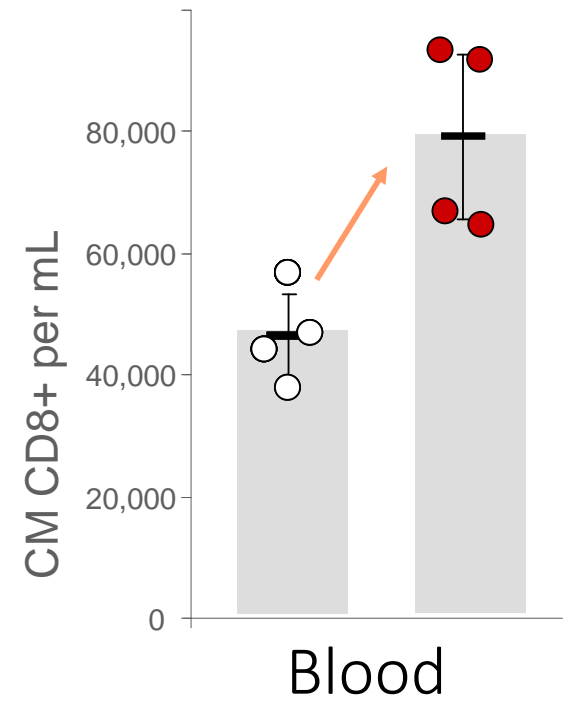
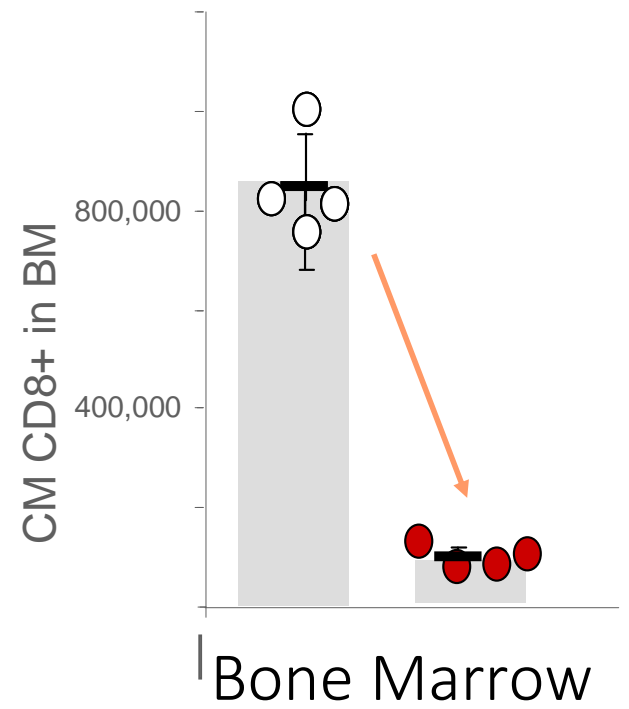
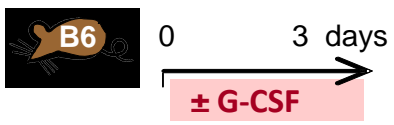
Winkler et al., Blood 2010

Winkler et al., Leukemia 2013



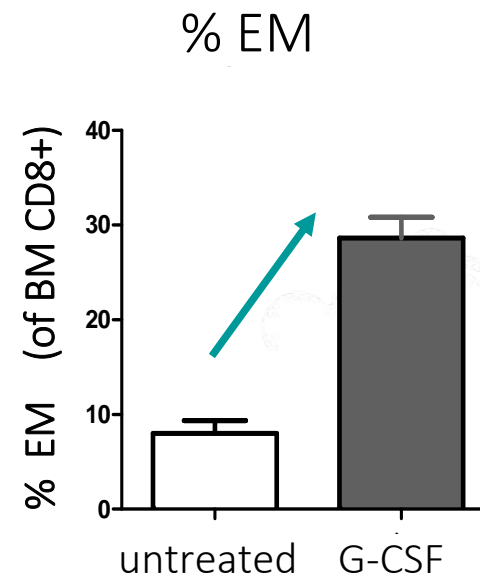
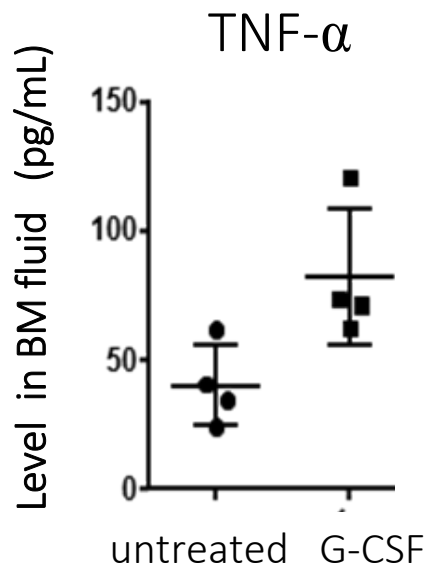
# G-CSF administration flushes CD8+ T-cells from BM into blood

.... lodgement in lymph nodes



# Mobilized BM is pro-inflammatory

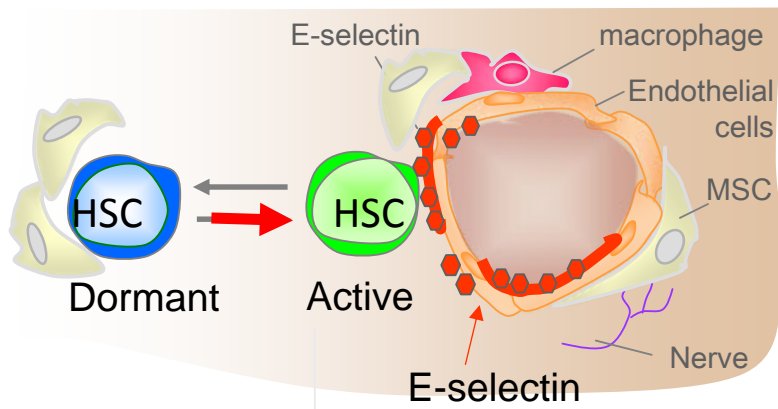
... *skews towards Effector Memory CD8+*





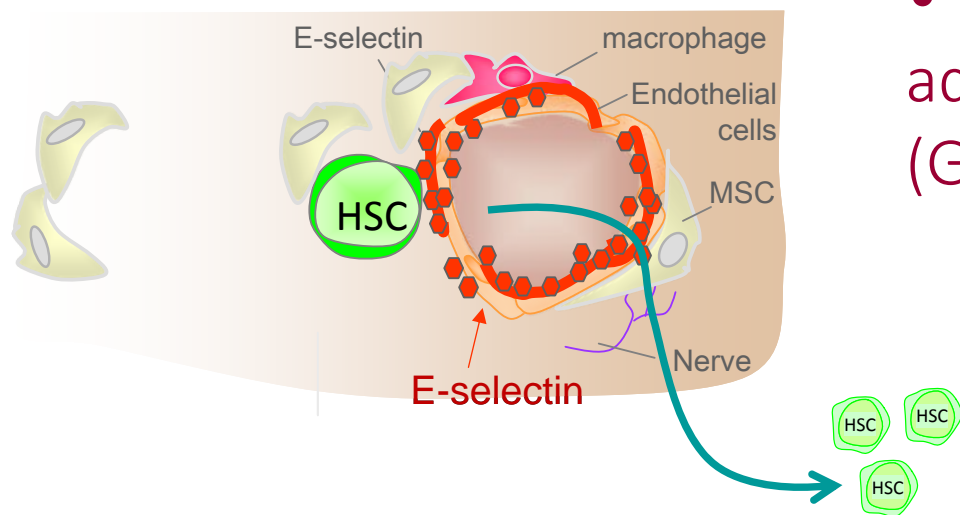
# E-selectin

- Vascular adhesion molecule
  - upregulated during stress
- Roles
  - leukocyte homing
  - Prime leukocytes for action



# E-selectin

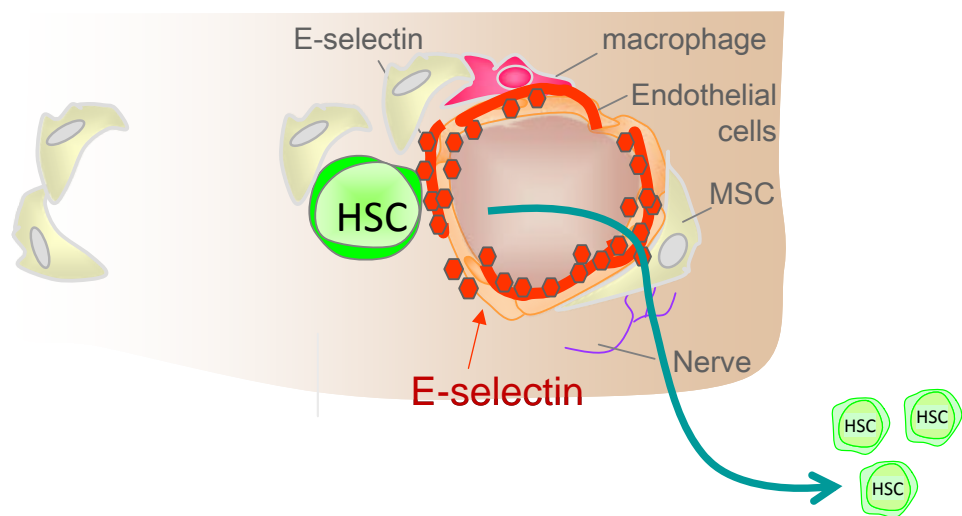
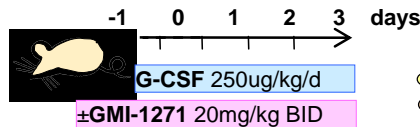
- Upregulated during G-CSF administration
- Activates transmigrating HSC



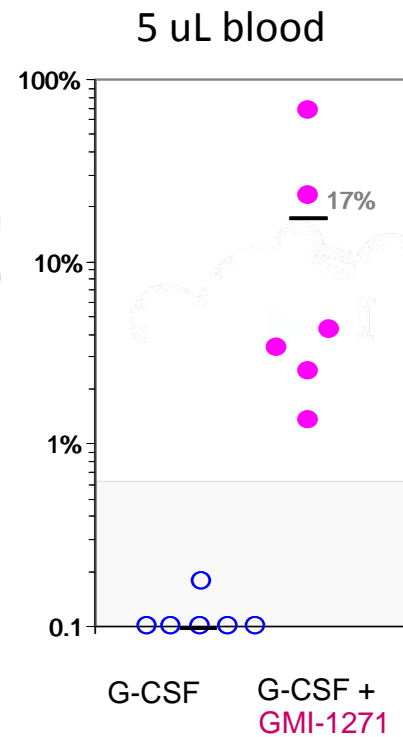
- Therapeutically block E-selectin by administration of antagonist GMI-1271 (GlycoMimetics)



# E-selectin

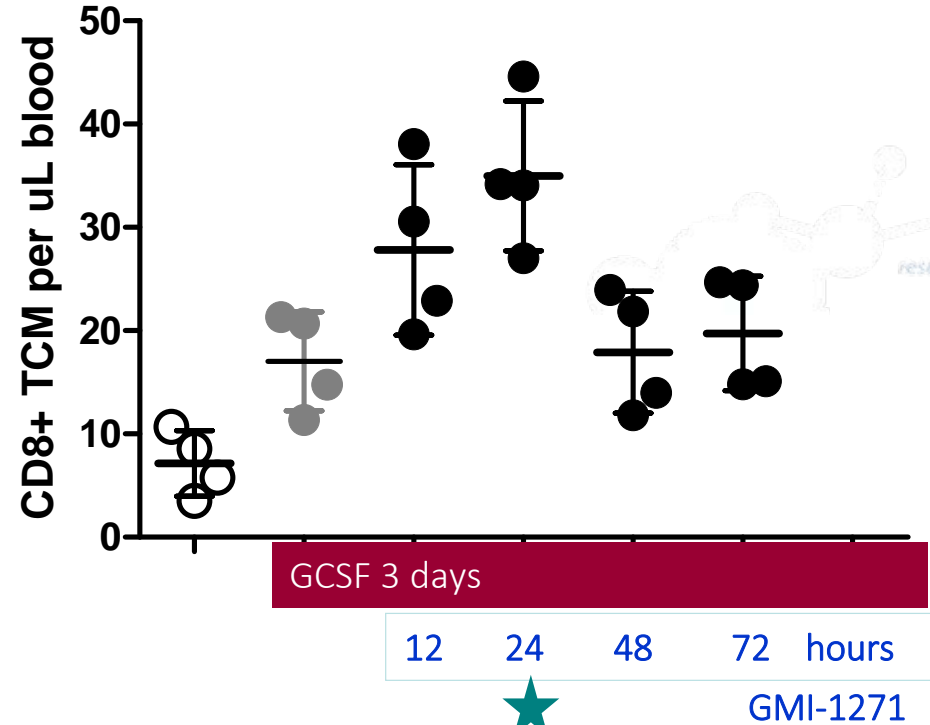
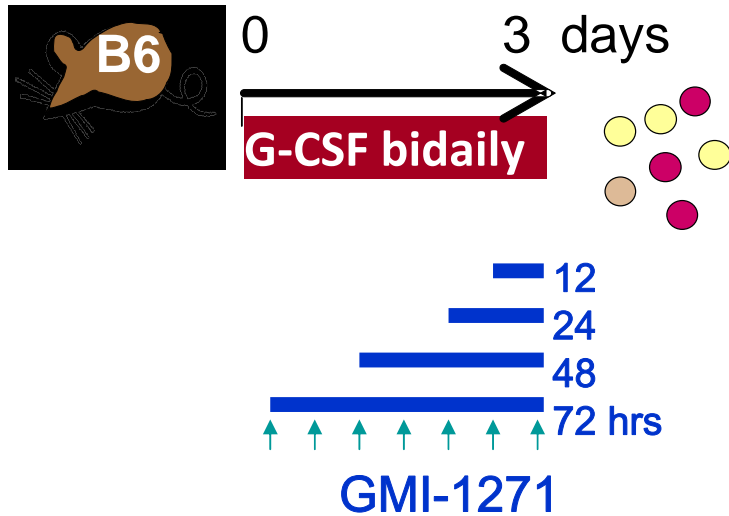


Long-term reconstitution (16 wks)



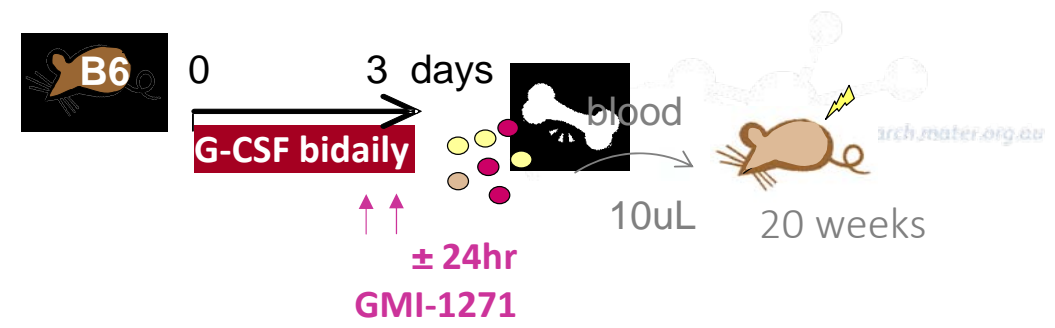
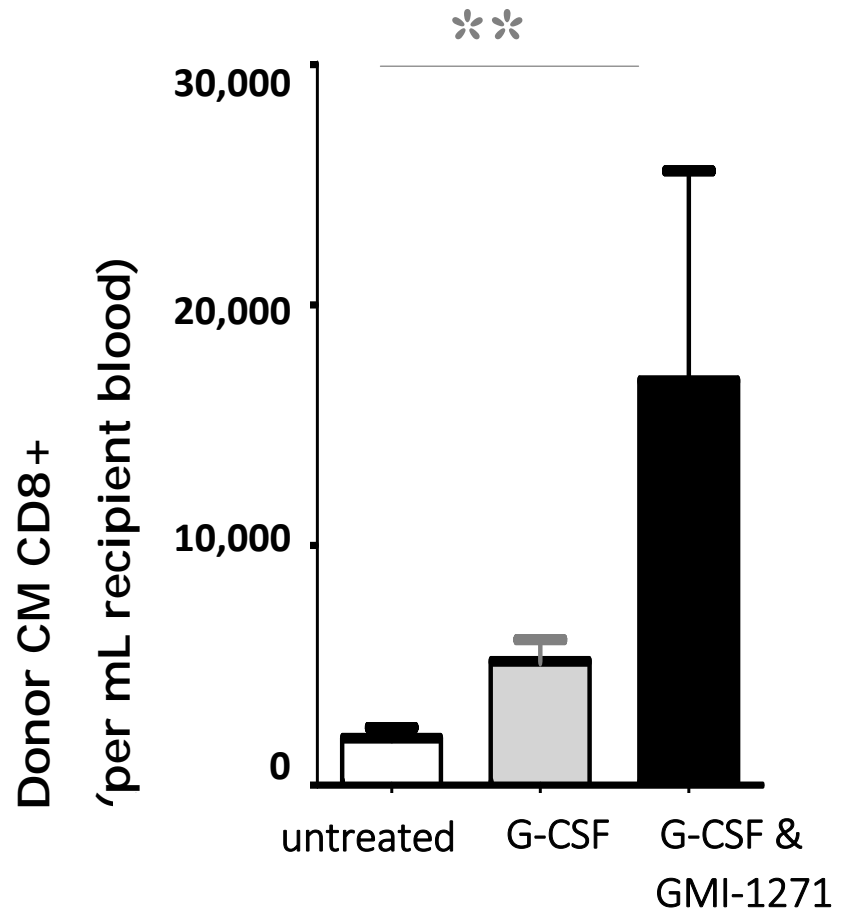


# GMI-1271 synergises with G-CSF to boost CM CD8+ T-cells in blood





# GMI-1271 E-selectin blockade synergises with G-CSF to boost adoptive transfer



# GMI-1271 E-selectin blockade synergises with other mobilizing combinations .....

Non-GCSF mobilisation :

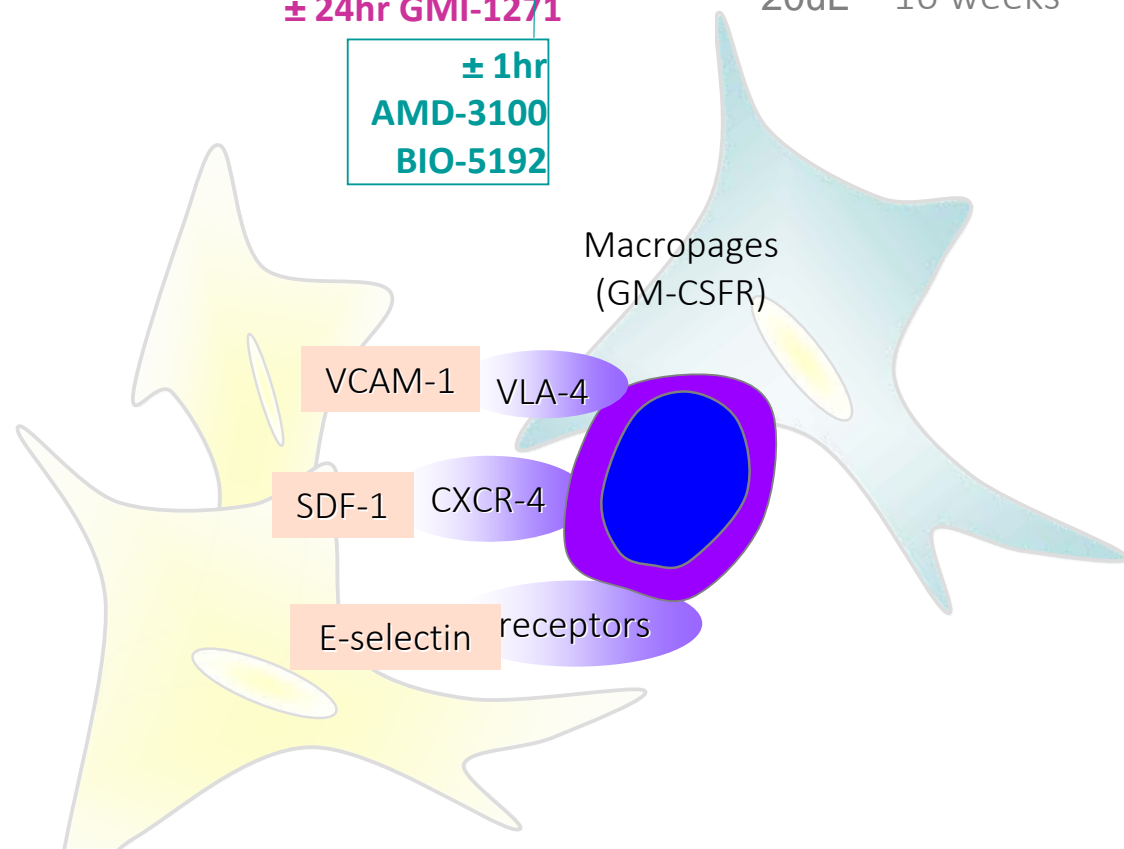
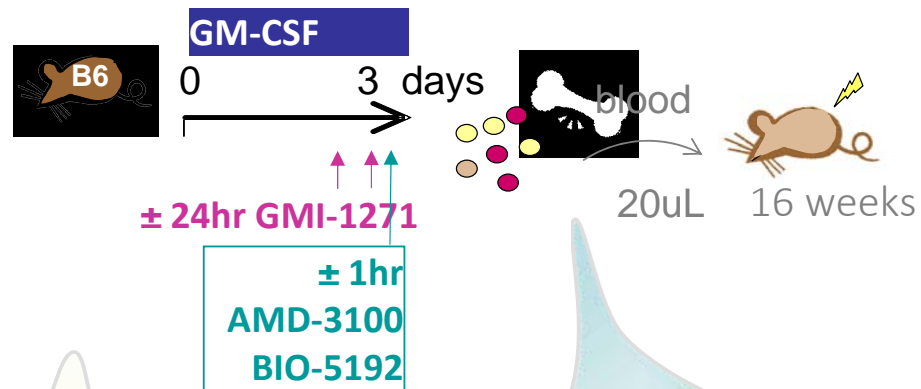
anti-CXCR4 (AMD-3100, 1mg/kg iv last 1hr)

anti-VLA-4 (BIO-5192, 1mg/kg iv last 1hr)

GM-CSF (50mg/kg/day ip for 3 days)

± E-sel blockade

(GMI-1271 20mg/kg BID ip last 24hrs)



# GMI-1271 E-selectin blockade synergises with other mobilizing combinations .....

Non-GCSF mobilisation :

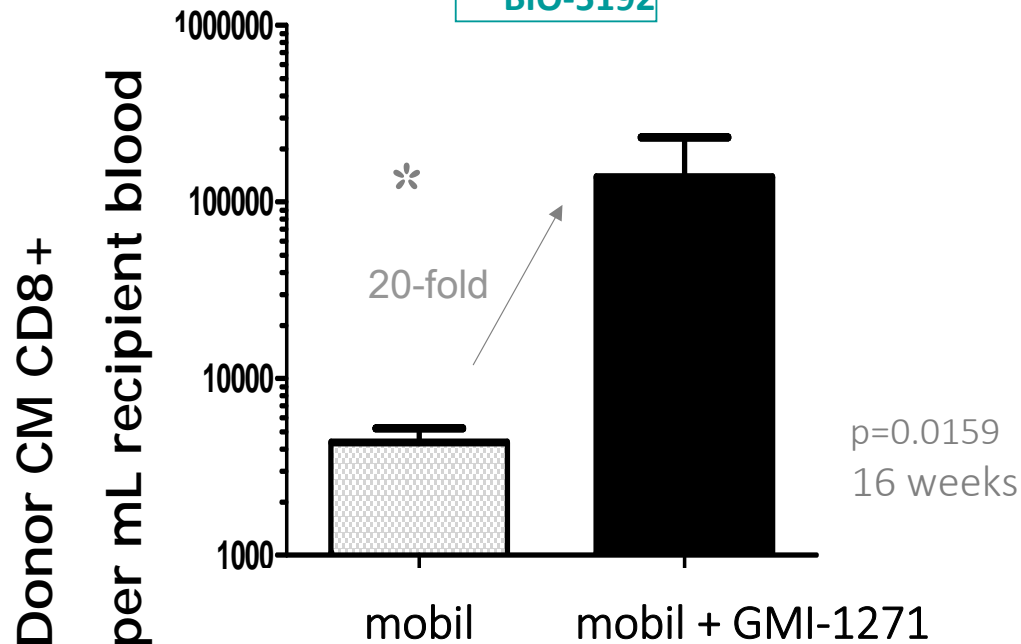
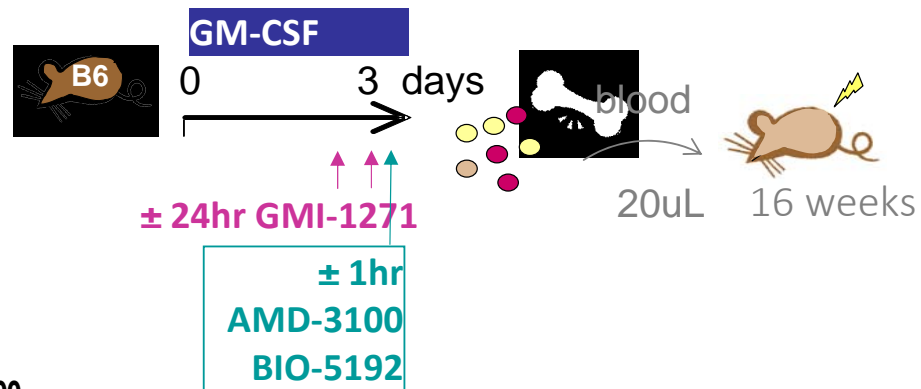
anti-CXCR4 (AMD-3100, 1mg/kg iv last 1hr)

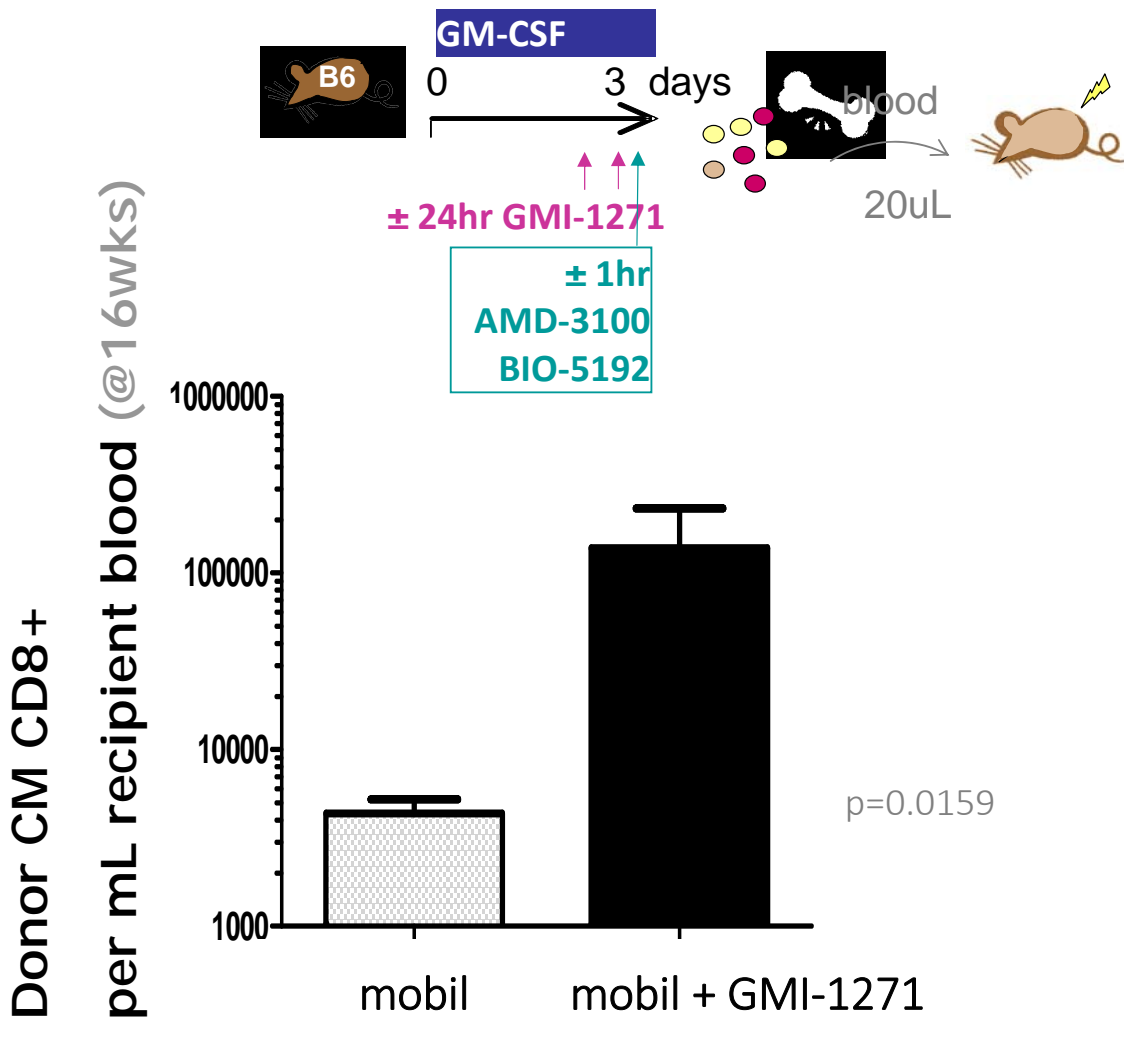
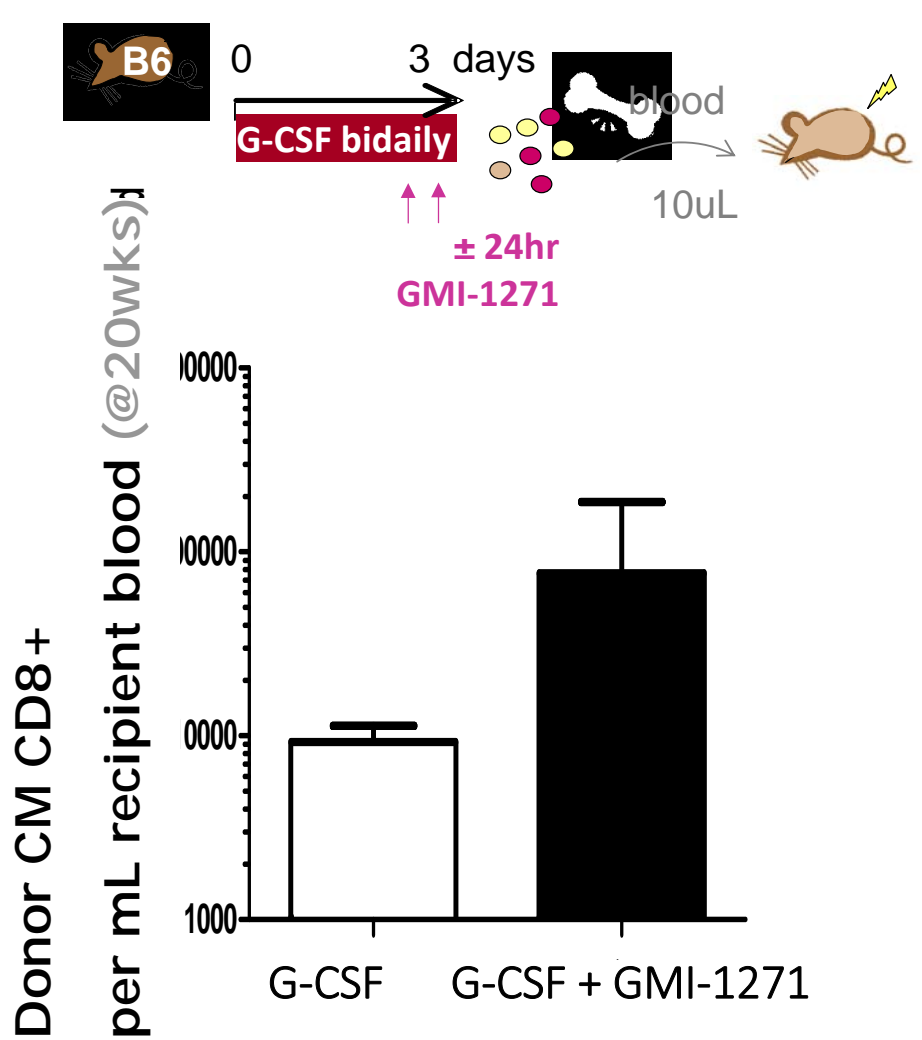
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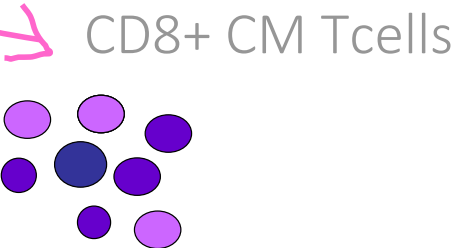
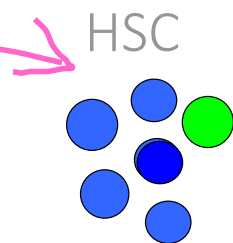
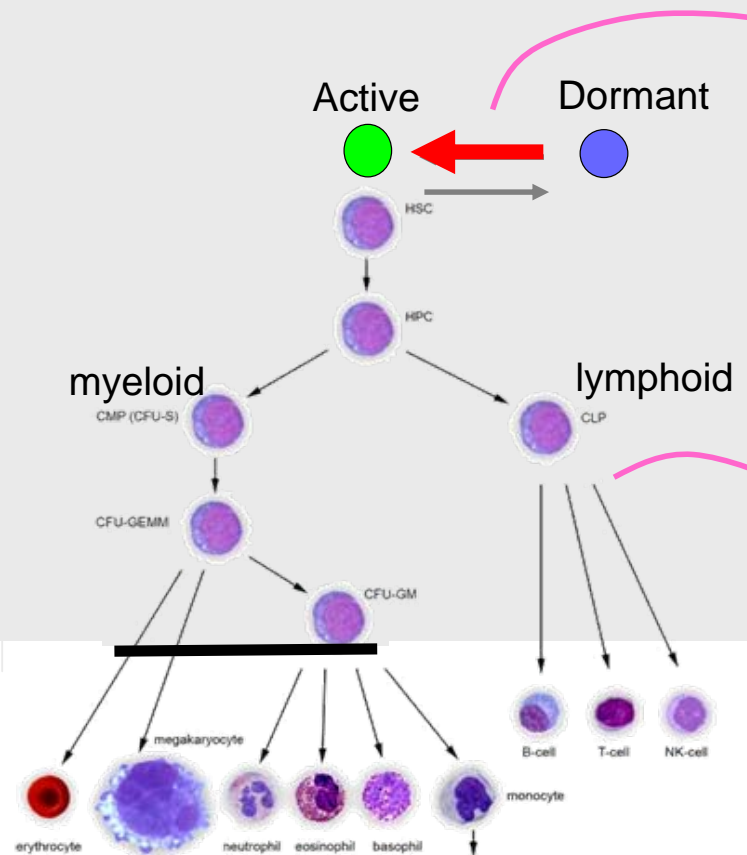




BM

blood

# Summary



GMI-1271 blockade of E-selectin during mobilisation:

- increases number harvested in blood, and
- boosts potential post adoptive transfer.

# Thankyou



HSC biology team

Stem Cells & Cancer team

## Collaborators

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**GlycoMimetics**

