



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)

Ingrid G Winkler, PhD^{1*}, Valerie Barbier^{1*}, Kristen J Radford, Ph.D.^{1*}, Julie M Davies, Ph.D.^{1*}, Jean-Pierre Levesque, PhD¹, Theodore A.G. Smith, Ph.D.^{2*}, William E. Fogler, Ph.D.^{2*} and John L Magnani, Ph.D.²

1Mater Medical Research Institute, South Brisbane, Australia

2GlycoMimetics, Inc., Rockville, MD



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

T-cell therapies

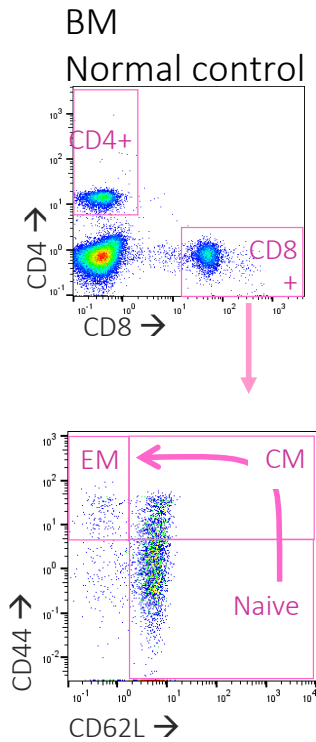
- Adoptive Tcell immunotherapy
- T-cell engineering approaches
- Innovative new strategies to treat cancer
- However, low survival after adoptive transfer

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

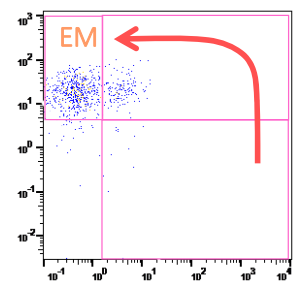


CD8+ T-cell exhaustion during leukemia

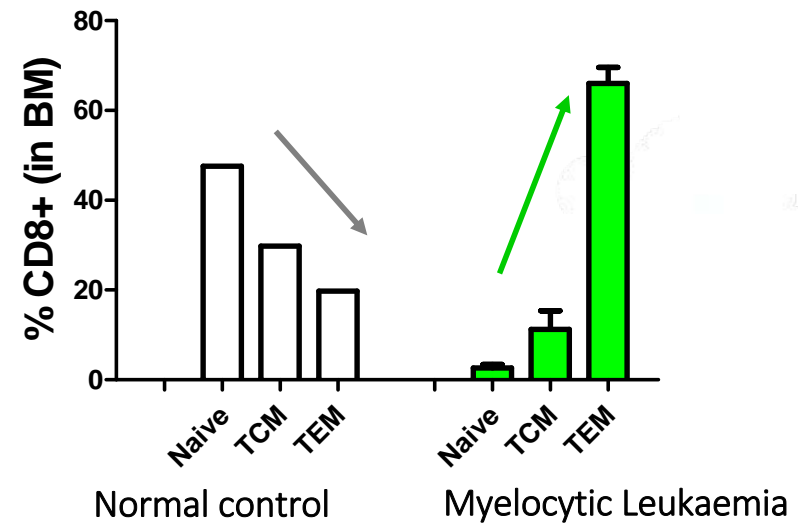
... a problem for harvesting CD8+



Myelocytic Leukaemia
(MLL-AF9)

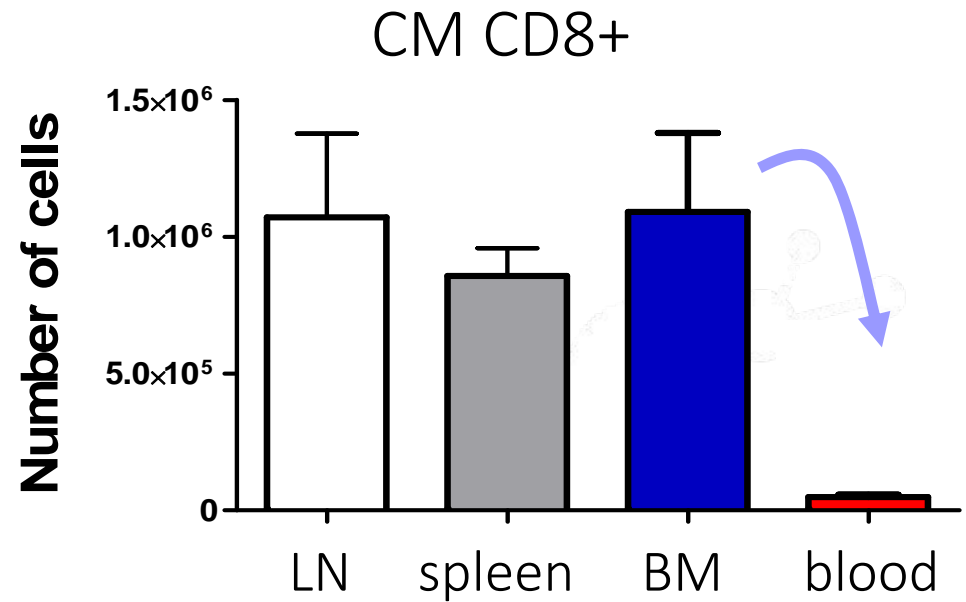


Skewing of CD8+ subsets





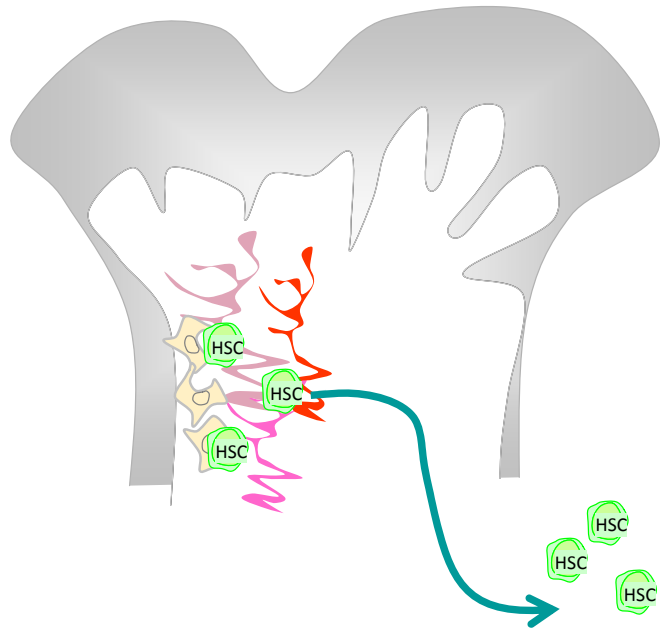
CD8+ T-cell populations in normal mouse





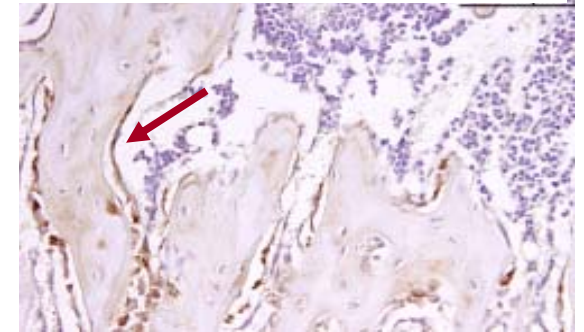
G-CSF-induced mobilisation of cells from the BM ...

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



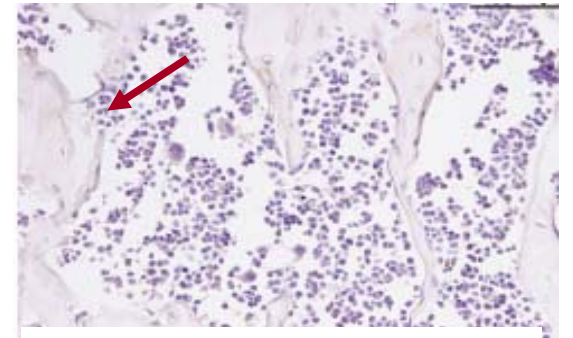
Osteocalcin
Immunohistology

Saline treated



research.mater.org.au

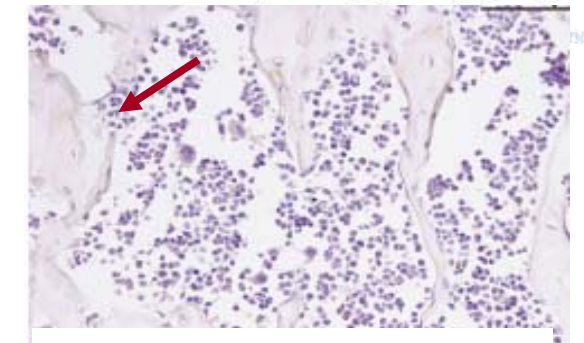
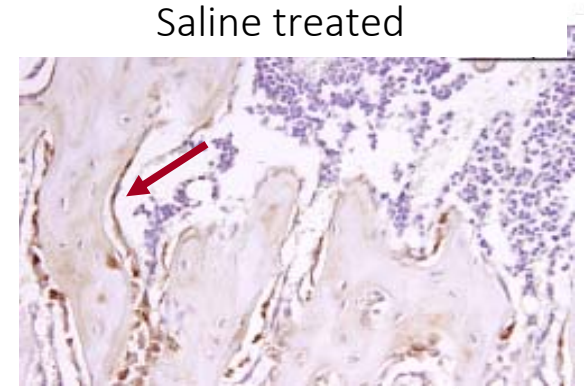
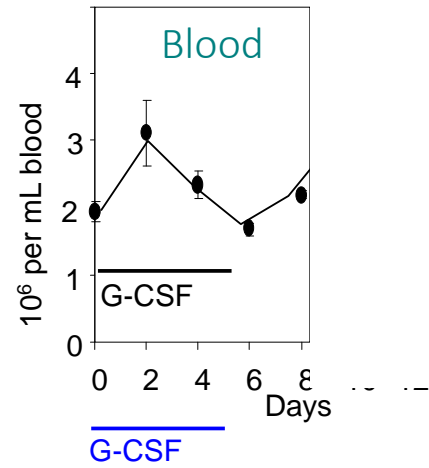
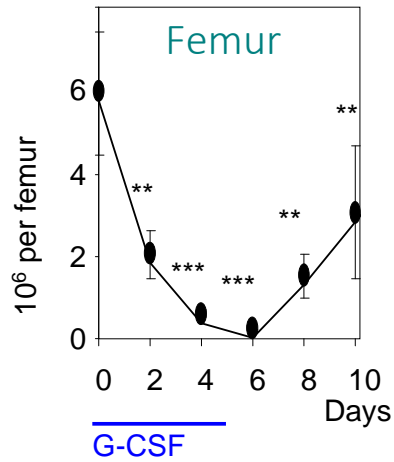
G-CSF treated (4 days)



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

G-CSF-induced mobilisation of cells from the BM

... ablates B-lymphopoiesis



G-CSF treated (4 days)

Winkler et al., Hematologica, 2013

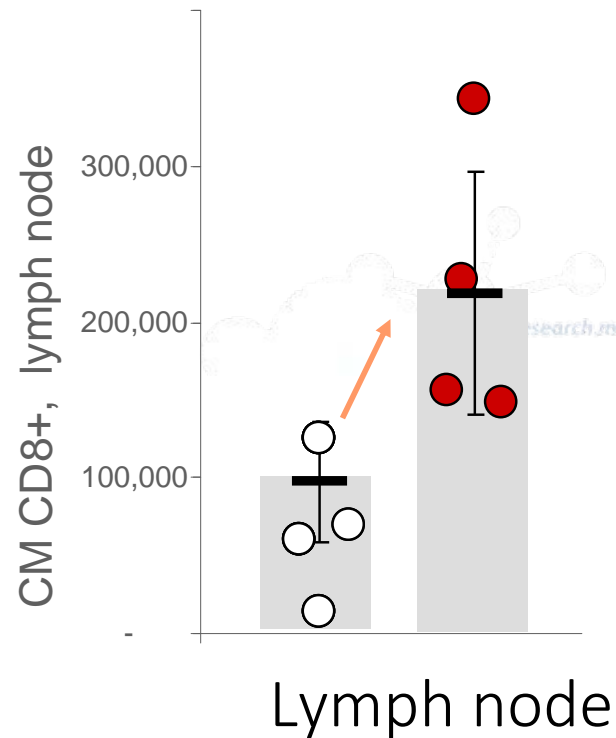
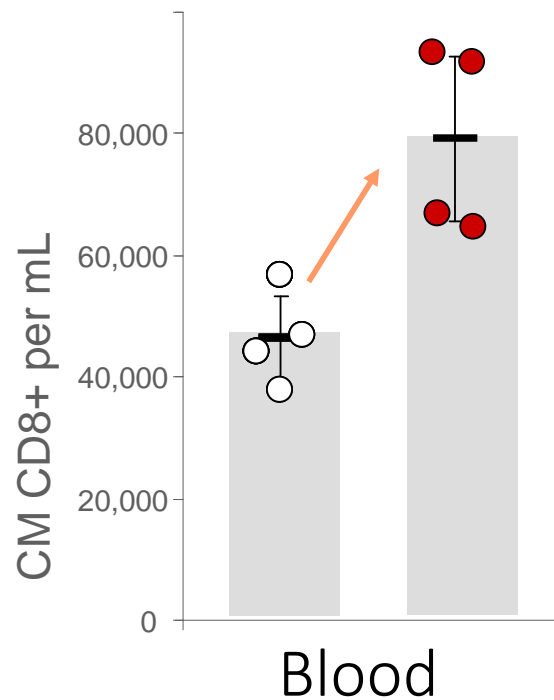
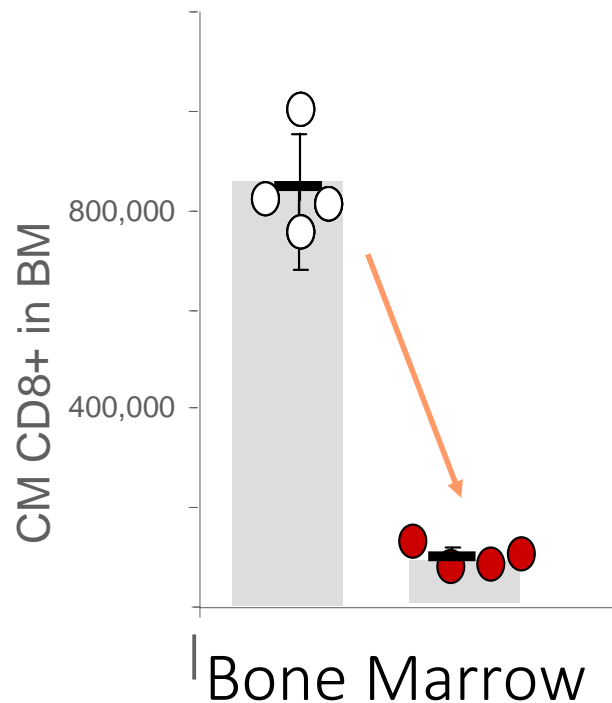
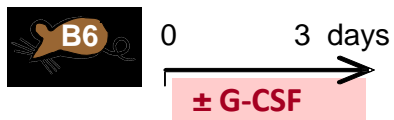
Winkler et al., Blood 2010

Winkler et al., Leukemia 2013



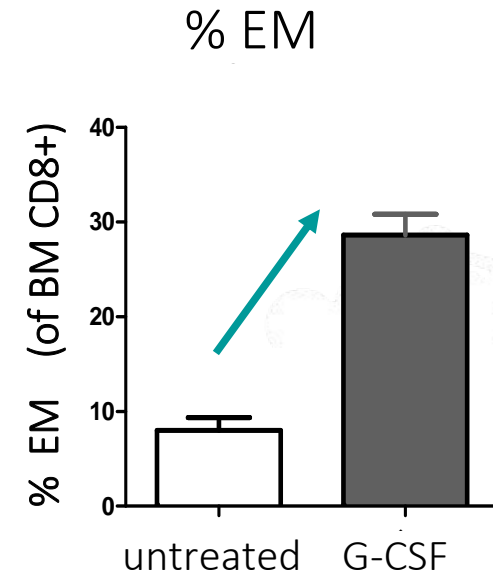
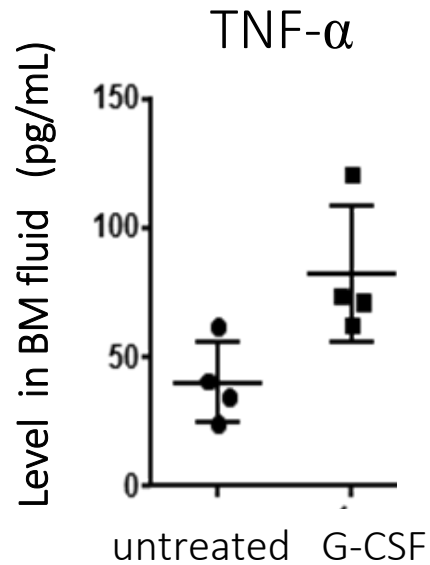
G-CSF administration flushes CD8+ T-cells from BM into blood

.... lodgement in lymph nodes



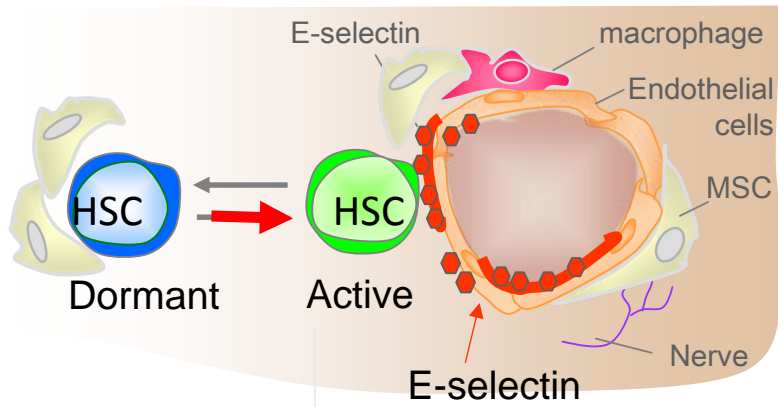
Mobilized BM is pro-inflammatory

... *skews towards Effector Memory CD8+*



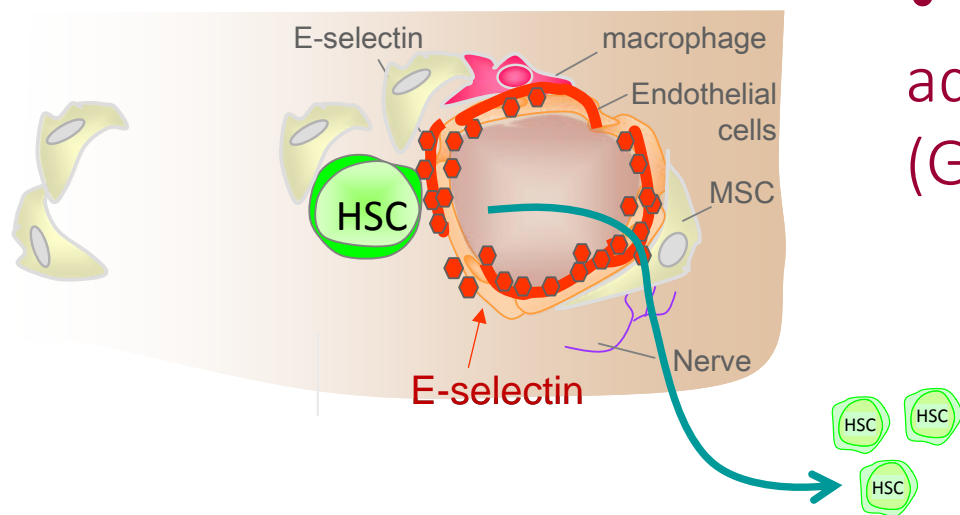
E-selectin

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



E-selectin

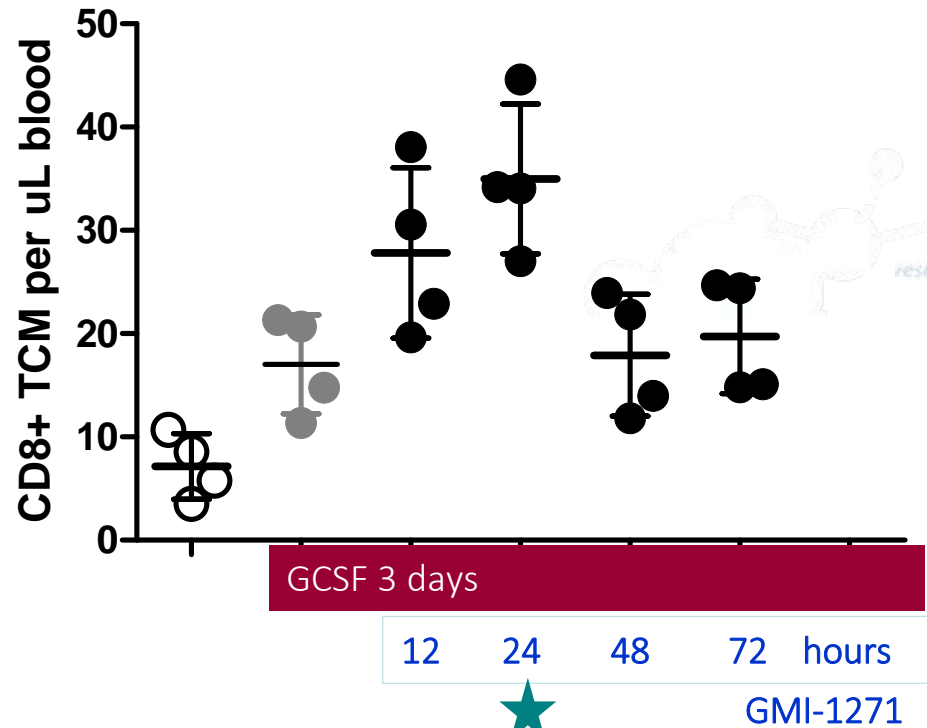
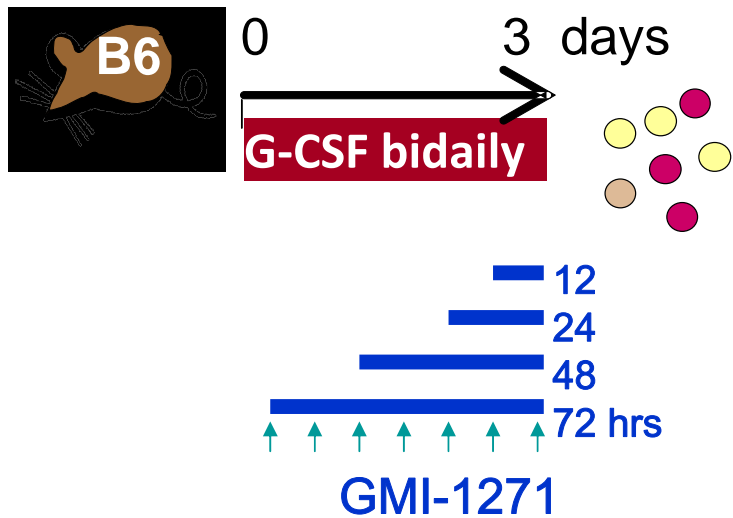
- Upregulated during G-CSF administration
- Activates transmigrating HSC



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

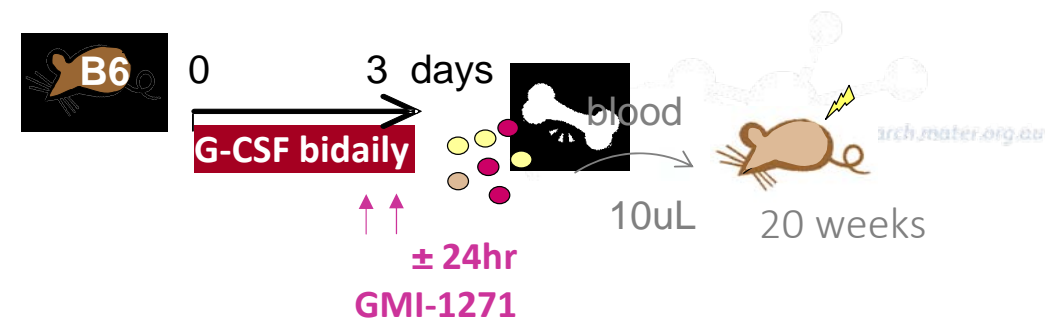
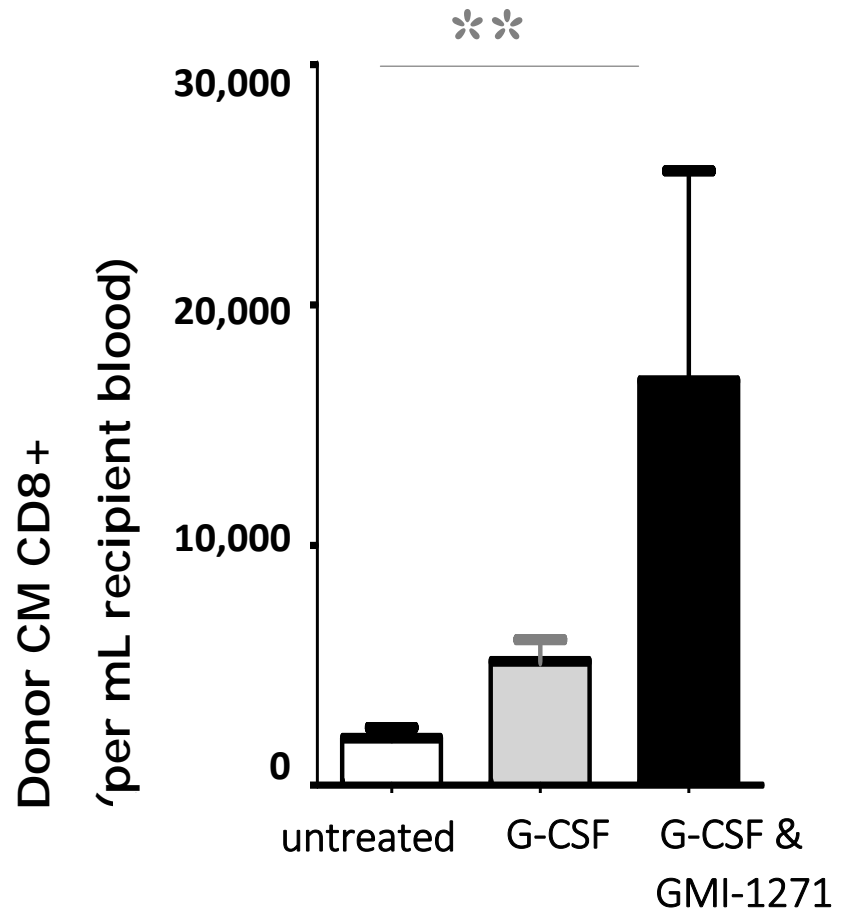


GMI-1271 synergises with G-CSF to boost CM CD8+ T-cells in blood





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 :

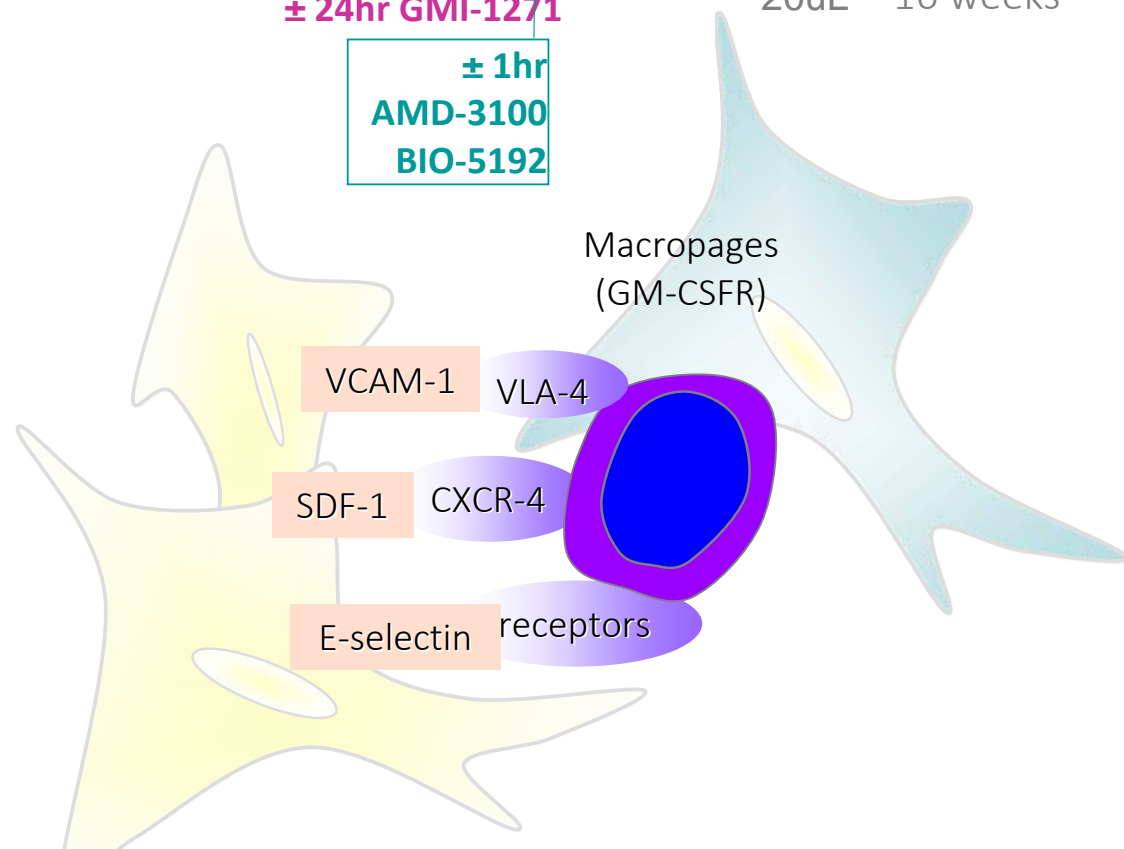
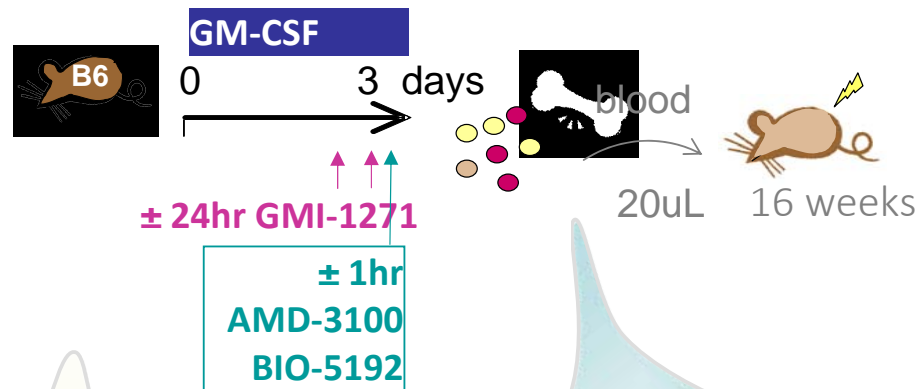
anti-CXCR4 (AMD-3100, 1mg/kg iv last 1hr)

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 :

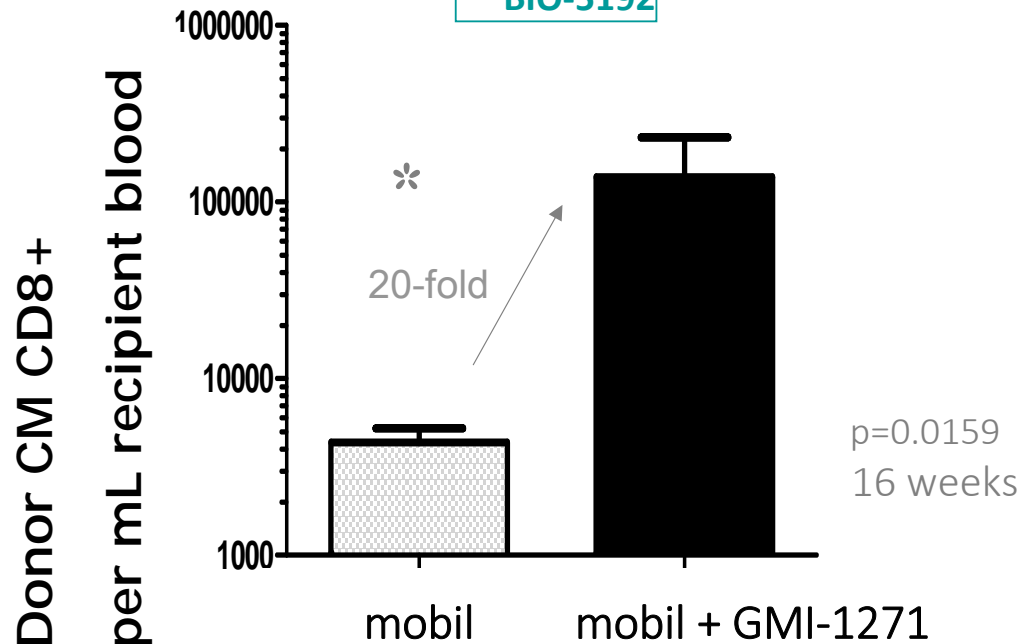
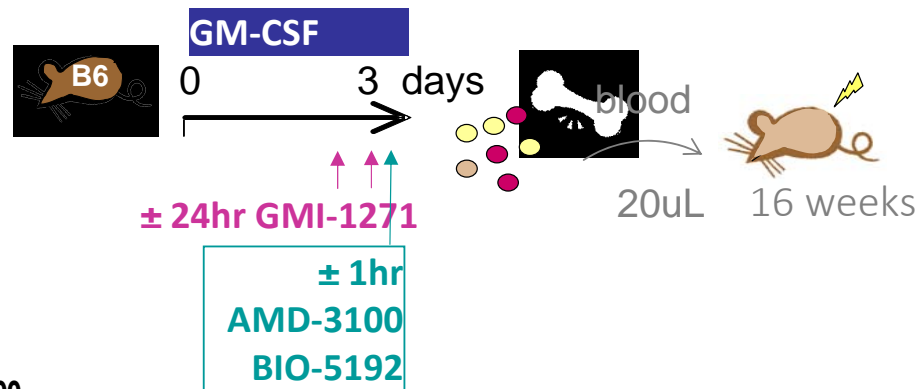
anti-CXCR4 (AMD-3100, 1mg/kg iv last 1hr)

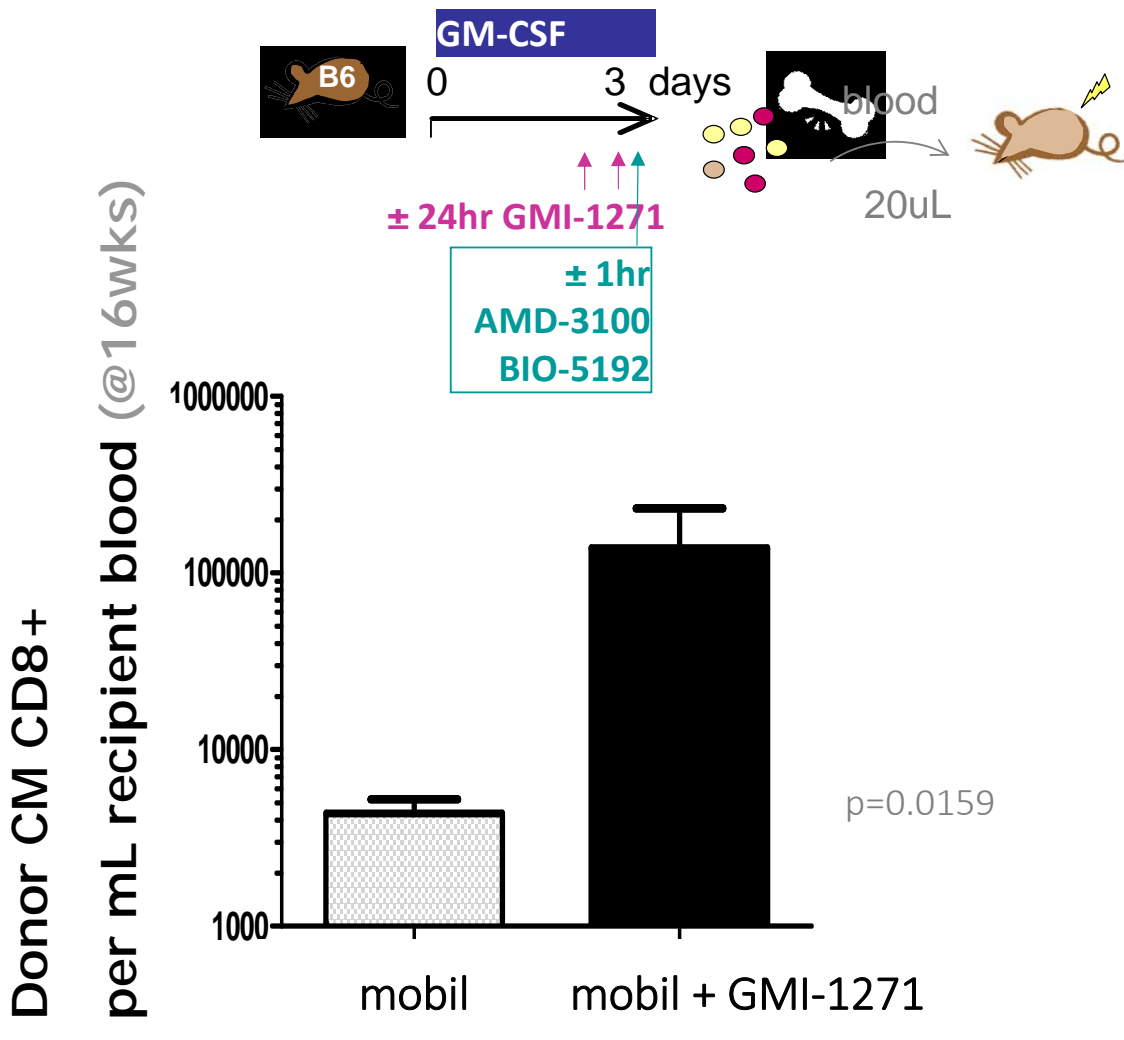
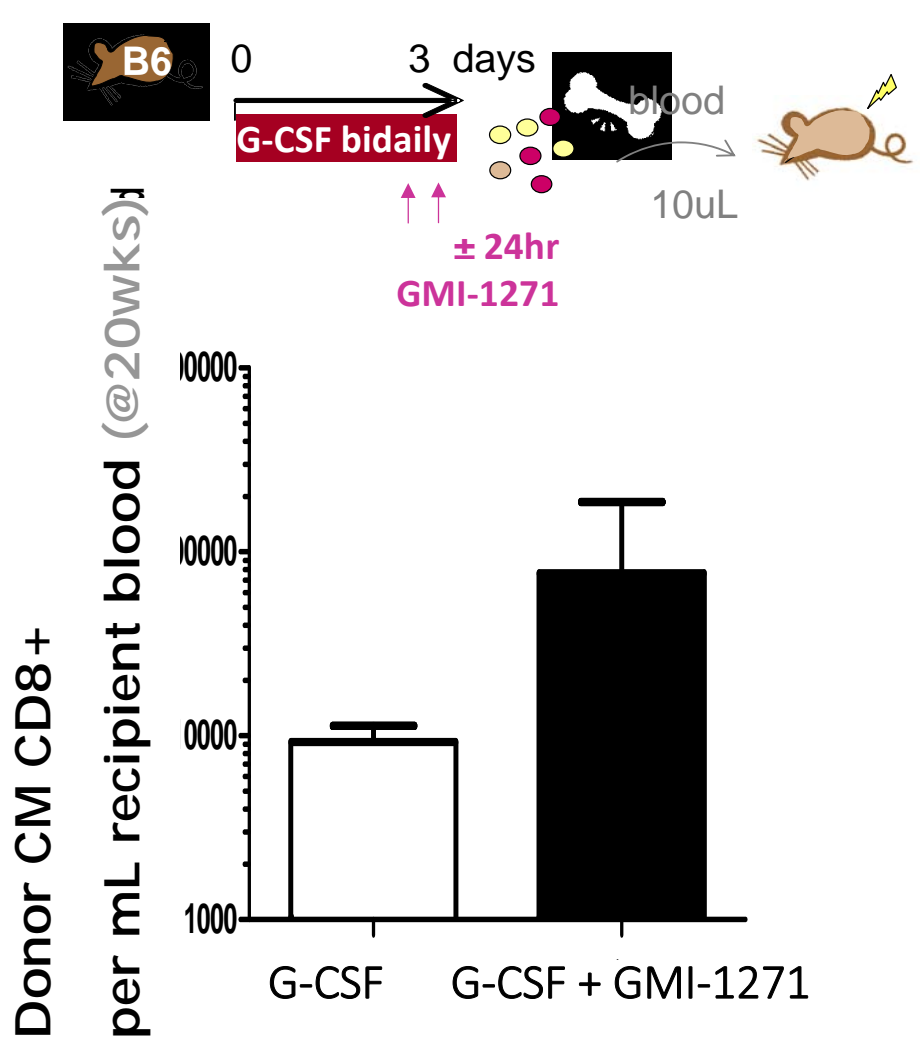
anti-VLA-4 (BIO-5192, 1mg/kg iv last 1hr)

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

± E-sel blockade

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



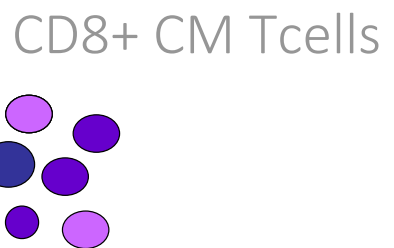
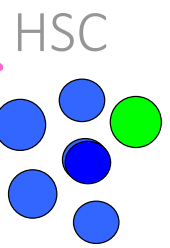
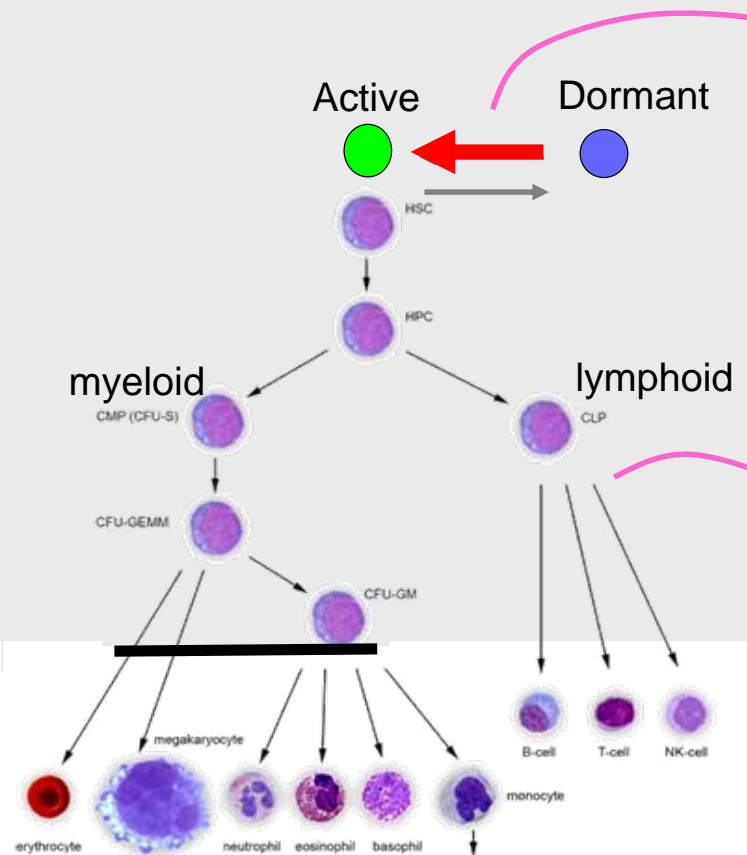




BM

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

[Mucosal Immunology](#) - Mater Research –TRI

Mike McGuckin

Sumaira Husnain

[Leukaemia](#) -- PACE

Tom Gonda

Diwakar Pattabiraman

[Haematologists](#) - PAH, Mater-UQ

Andrew Perkins

Paula Marlton

Devinder Gill

Tony Mills

[GlycoMimetics](#) - USA

John Magnani – Glycobiologist

Heather Nutt
Jessica Lowe

Financial support

NHMRC project grants

NHMRC fellowships

Cancer Council of Queensland.

Smart Futures, Qld Govt

Flack Trust

GlycoMimetics

