# Inhibition of E-Selectin or E-selectin together with CXCR4 Re-sensitizes Multiple Myeloma to Treatment

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**AACR Annual Meeting 2017, Washington DC**
**Minisymposium – Microenvironmental Cues in Immune Escape and Therapy Resistance**
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# Disclosure Information

AACR Annual Meeting 2017, Washington DC

Minisymposium – Microenvironmental Cues in Immune Escape and Therapy Resistance

Presenter: Barbara Muz, Ph.D.

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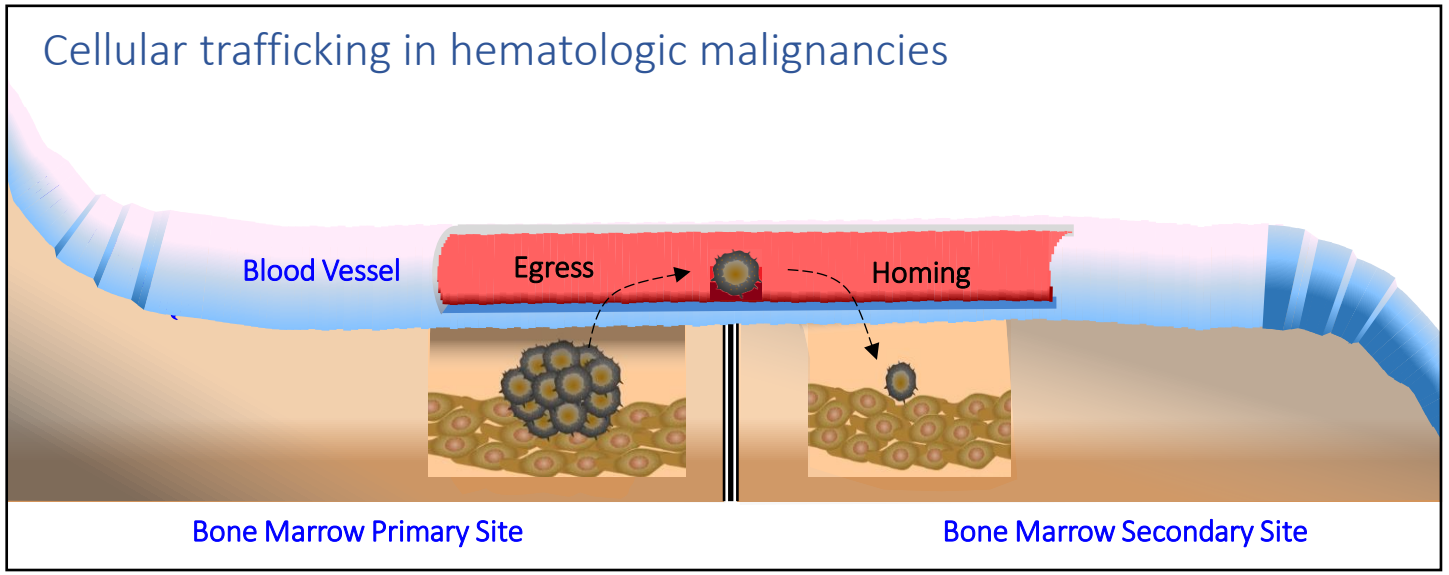
*- and -*

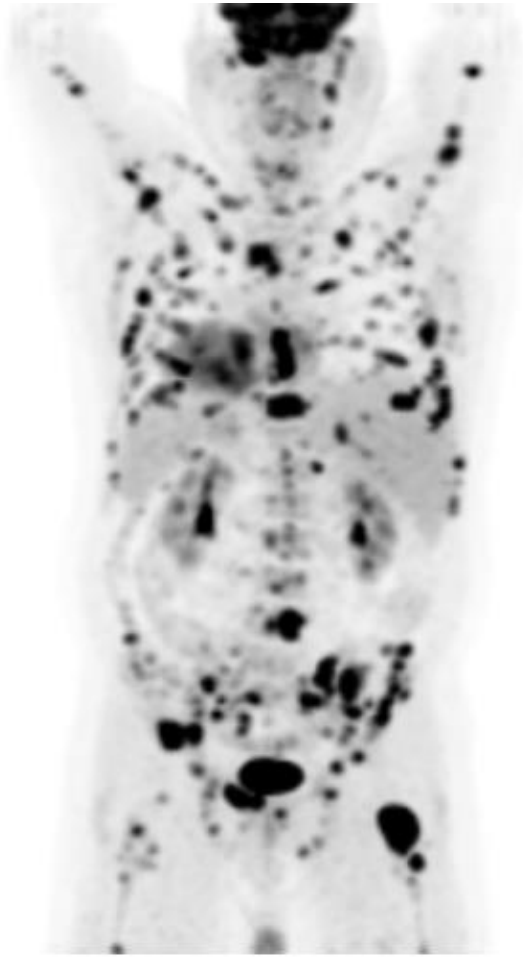
I will not discuss off label use and/or investigational use in my presentation.

# Multiple myeloma (MM)

- Plasma cell malignancy localized mainly in the bone marrow
- Characterized by metastasis of MM cells across the skeletal system
- The progression of MM involves a continuous **egress (re-circulation)** of the tumor cells in the peripheral blood and **homing (re-entrance)** into the bone marrow




Areas of active myeloma (PET scan)



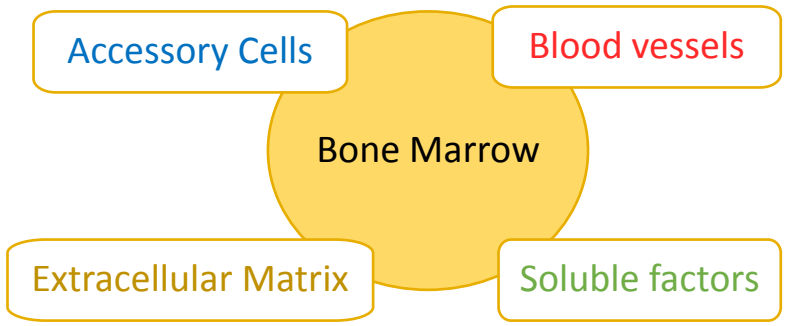
Lu et al 2012

# The supportive role of the bone marrow microenvironment in MM

- The interactions of tumor cells with their bone marrow microenvironment facilitate **tumor progression, metastasis** and **drug resistance**

**Cellular compartment:**

**Non-cellular compartment:**

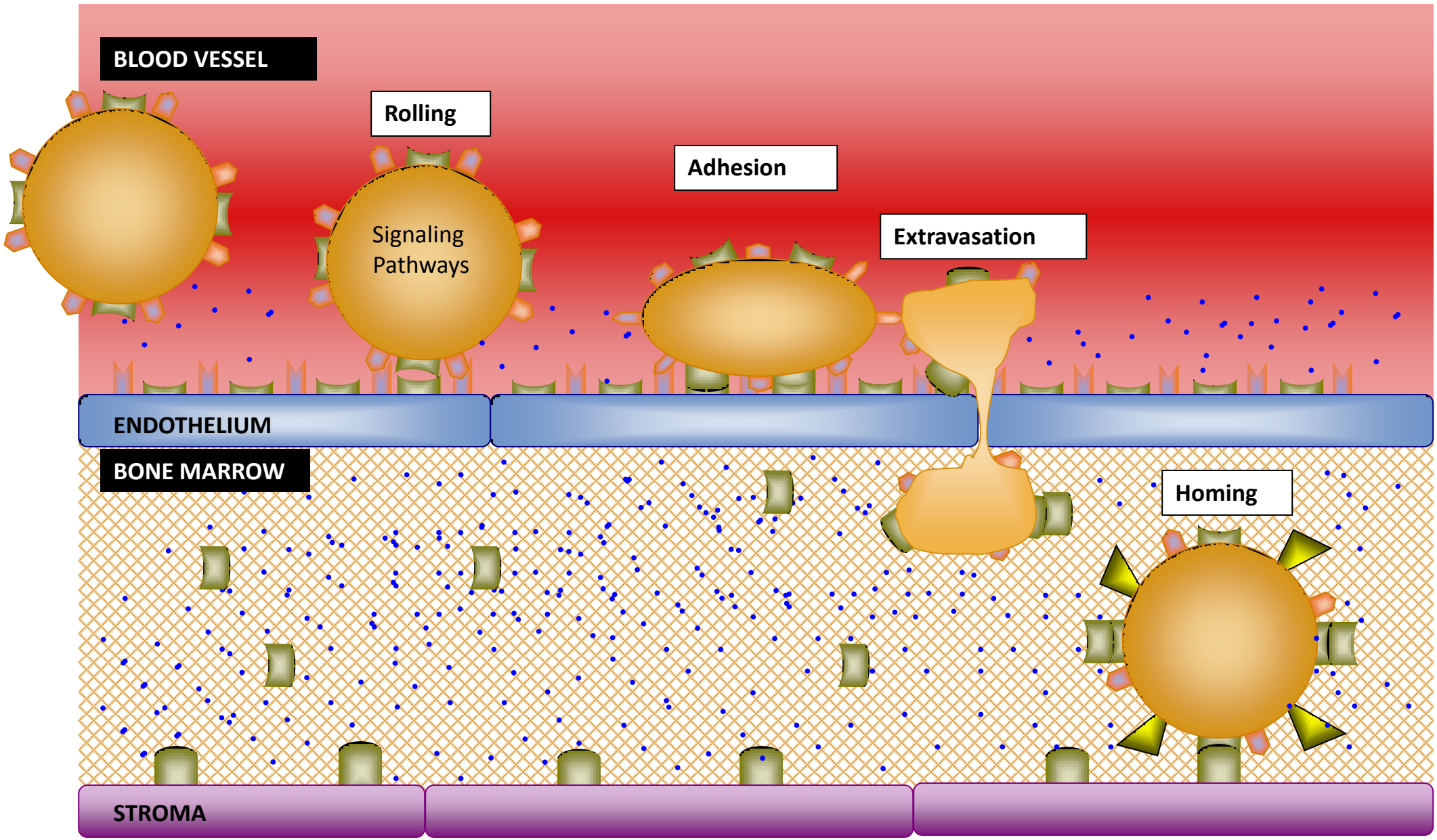




Azab AK et al. **Blood** 2012;119:1468-1478 (Selectins and endothelial cells)
Azab AK et al. **Blood** 2009;113:4341-4351 (Chemokines an stroma)
Azab AK et al. **Blood** 2009;114:619-29 (ECM and stroma)
De la Puente P et al. **Haematologica** 2016 Jul;101(7):e307-11 (MSP-1)
De la Puente P et al. **Biomaterials** 2015 (3DTEBM)

Muz B et al. **BioMed Res Int** 2015; 2015:417586 (P-selectin and PSGL-1)
Muz B et al. **Mol. Cancer Res** 2015 (Cell trafficking)
Muz B et al. **Blood Cancer J** 2015 (Hypoxia)
McMillin DW et al. **Nat Med** 2010;16:483-9 (Stroma)
Fulciniti M et al. **Clin Cancer Res** 2009;15:7144-52 (IL-6)

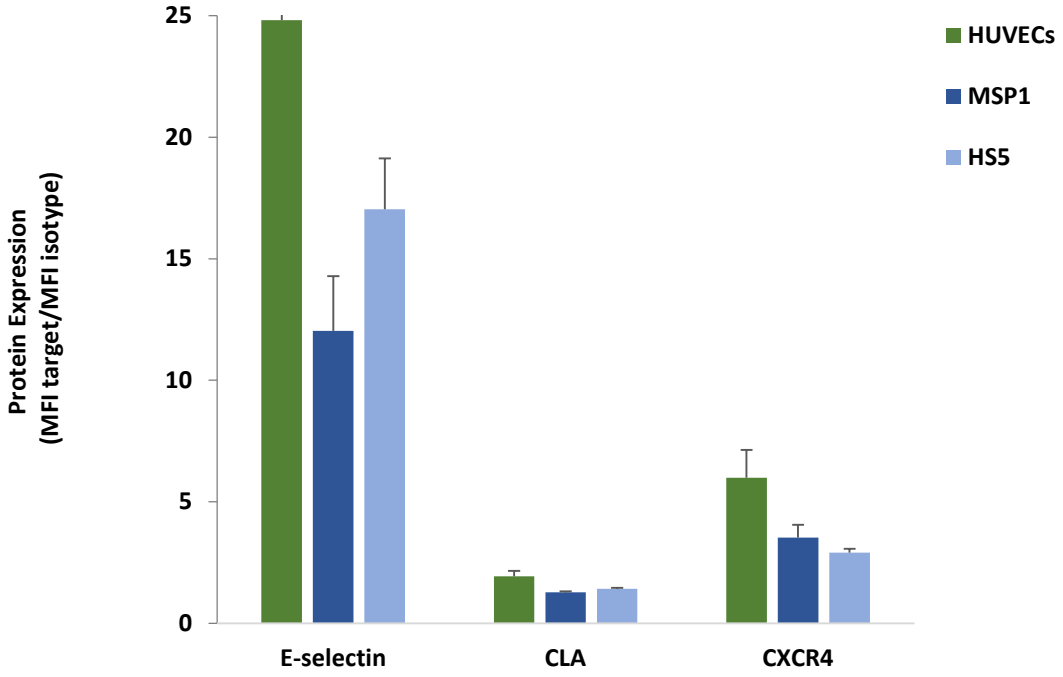
# Targeting cell trafficking as a strategy to sensitize MM cells

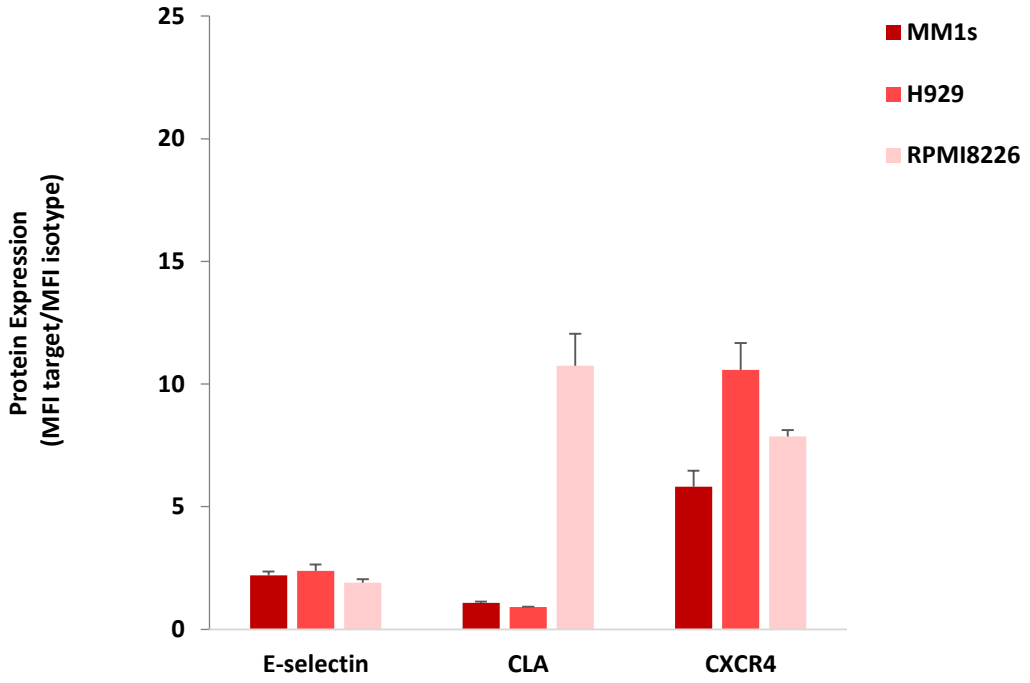


# Aim

To test the role of E-selectin (GMI-1271) and E-selectin/CXCR4 (GMI-1359) antagonists on MM cell trafficking *in vitro* and *in vivo* as a potential approach to overcome bone marrow microenvironment-induced drug resistance

# Expression of cell surface molecules in endothelial, stromal and myeloma cells

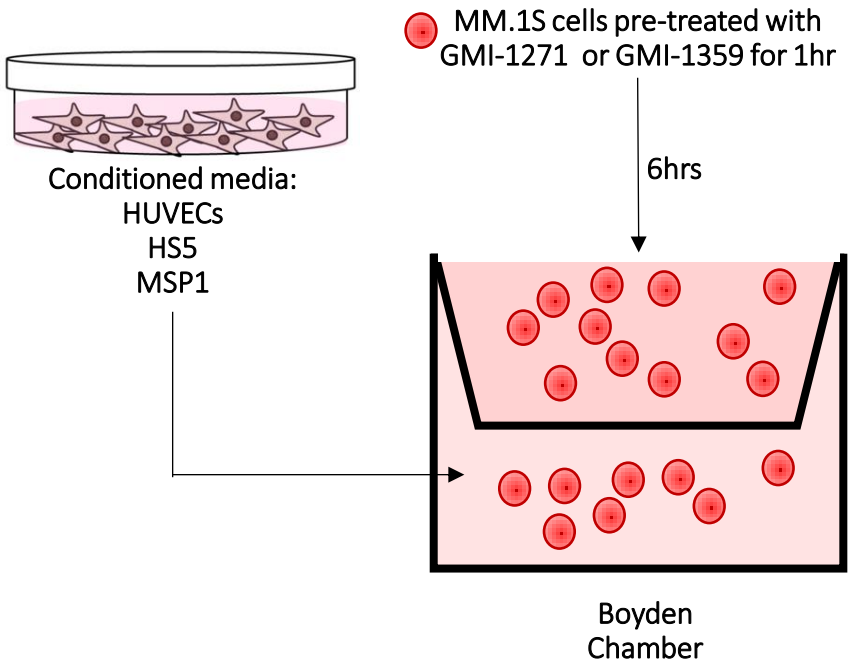


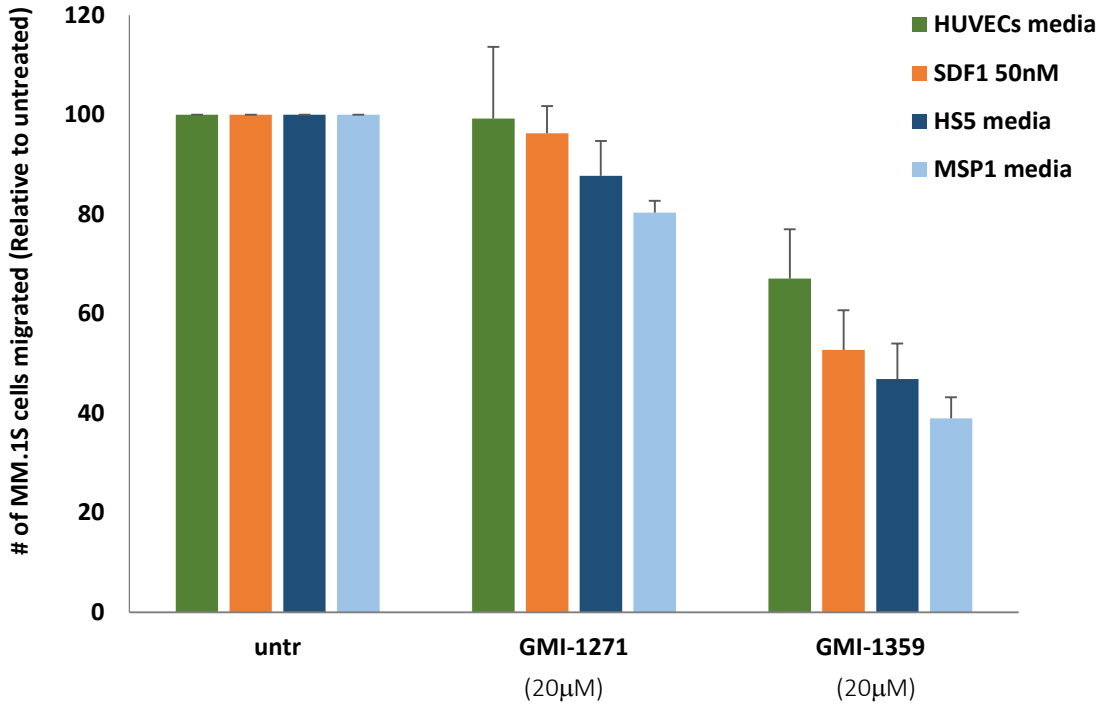




MSP1 – MM-derived stromal cell line (de la Puente P et al. Haematologica 2016 Jul;101(7):e307-11)
**CLA** - Cutaneous Lymphocyte Antigen (Rossiter H et al. **European J Immunol** 1994;24(1): 205-10)
HUVECs – human umbilical vascular endothelial cells
SDF-1 – stromal-derived growth factor-1
HS5 – stromal cell line (normal)

# In the presence of SDF-1, GMI-1359 inhibits MM cell chemotaxis more effectively than GMI-1271

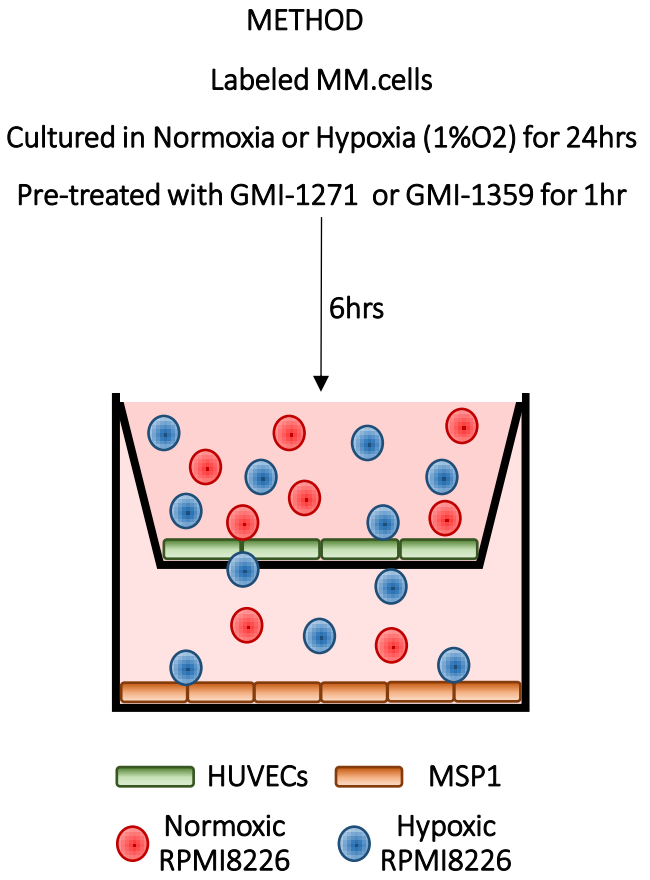
METHOD

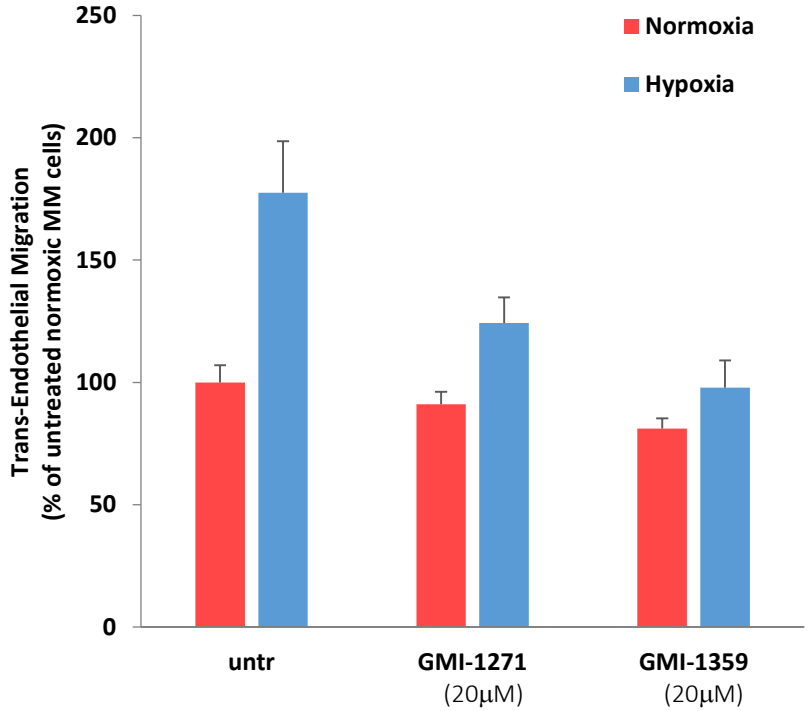


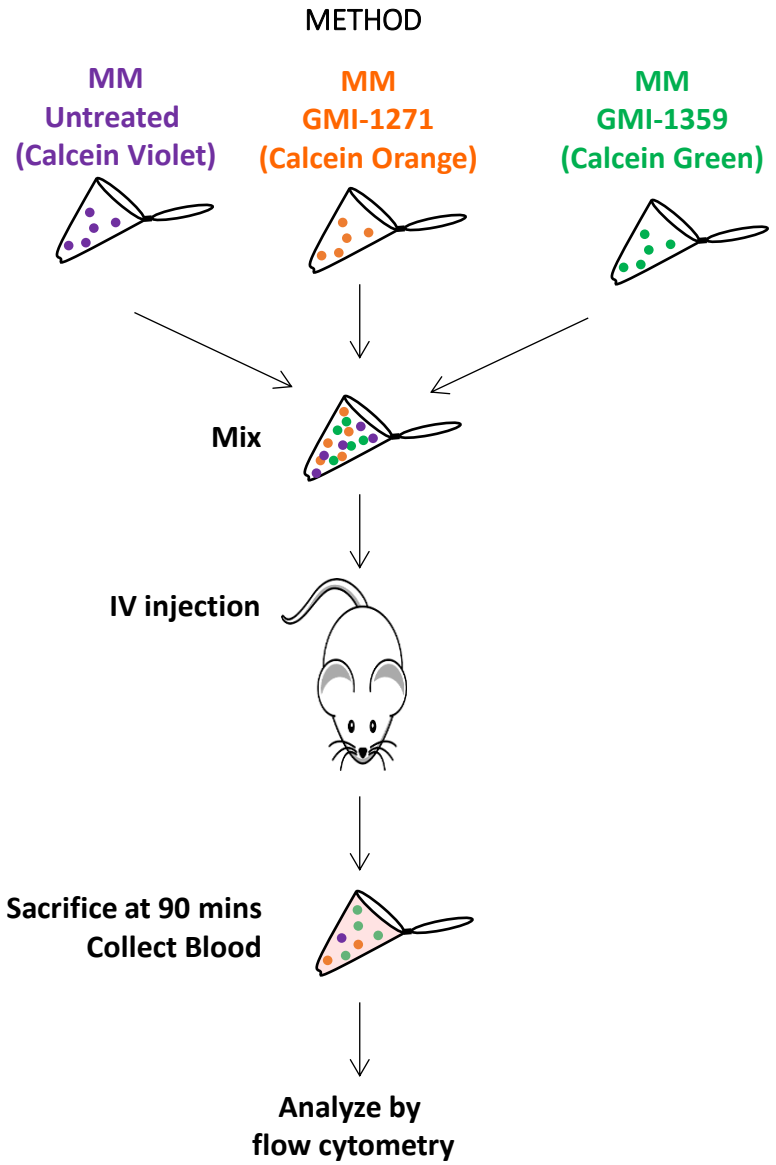

HUVECs – human umbilical vascular endothelial cells
SDF1 – stromal-derived growth factor-1
HS5 – stromal cell line (normal)
MSP1 – MM-derived stromal cell line (de la Puente P et al. Haematologica. 2016 Jul;101(7):e307-11)

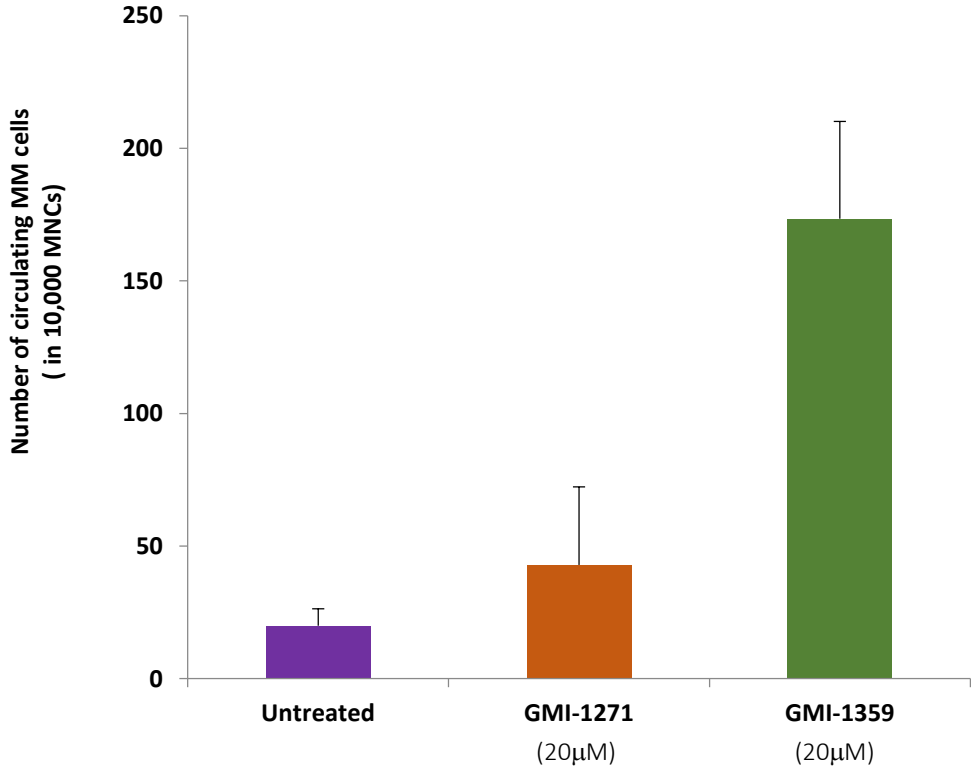
# GMI-1359 inhibits MM cell trans-endothelial migration more effectively than GMI-1271, especially under hypoxic conditions



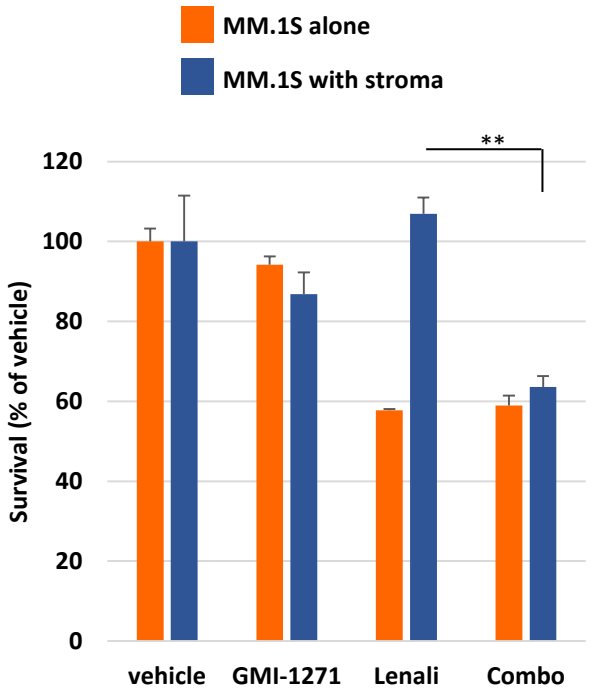
# GMI-1359 inhibits extravasation of MM cells to the bone marrow *in vivo*



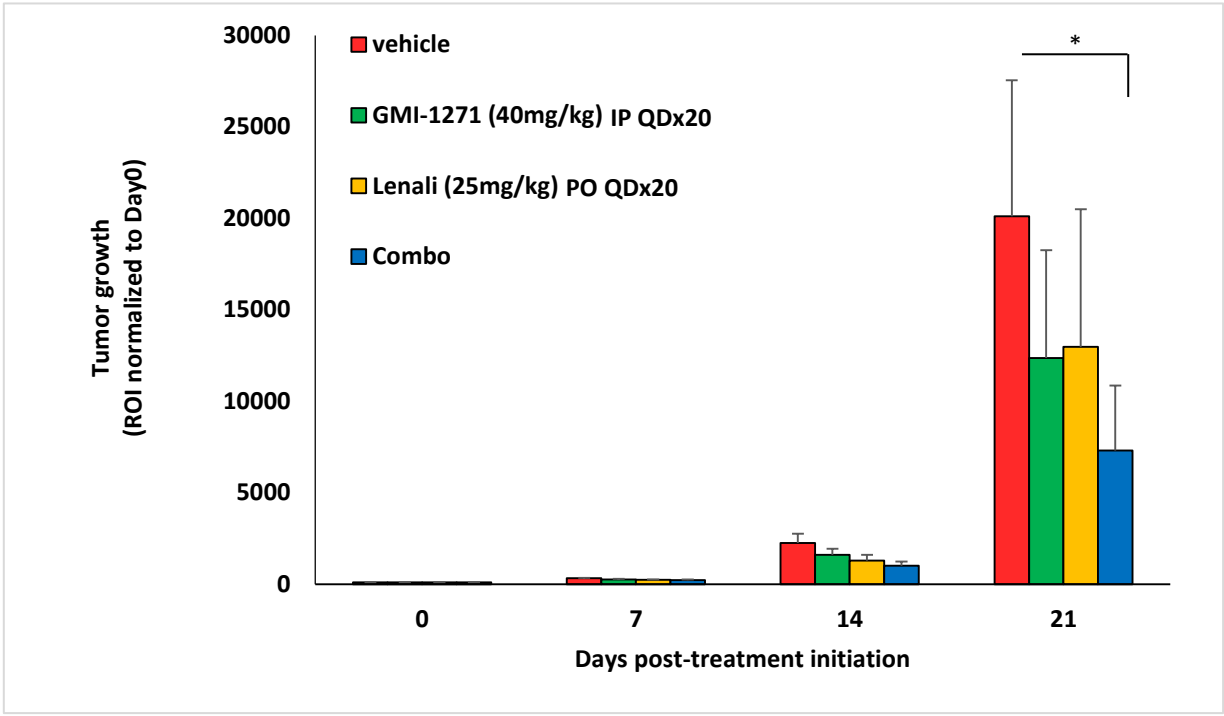



# GMI-1271 in combination with lenalidomide overcomes stroma-induced drug resistance *in vitro* and inhibits tumor growth *in vivo*

*In vitro* – MTT assay

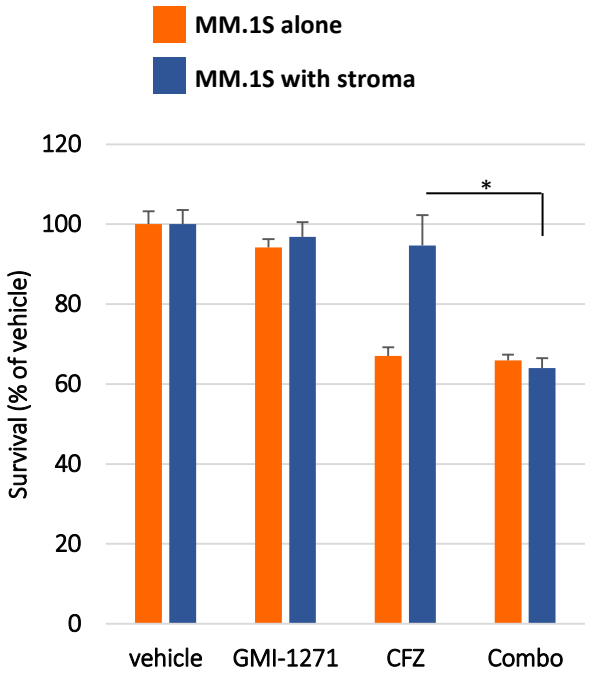



*In vivo* - Human Xenograft Disseminated Mouse Model

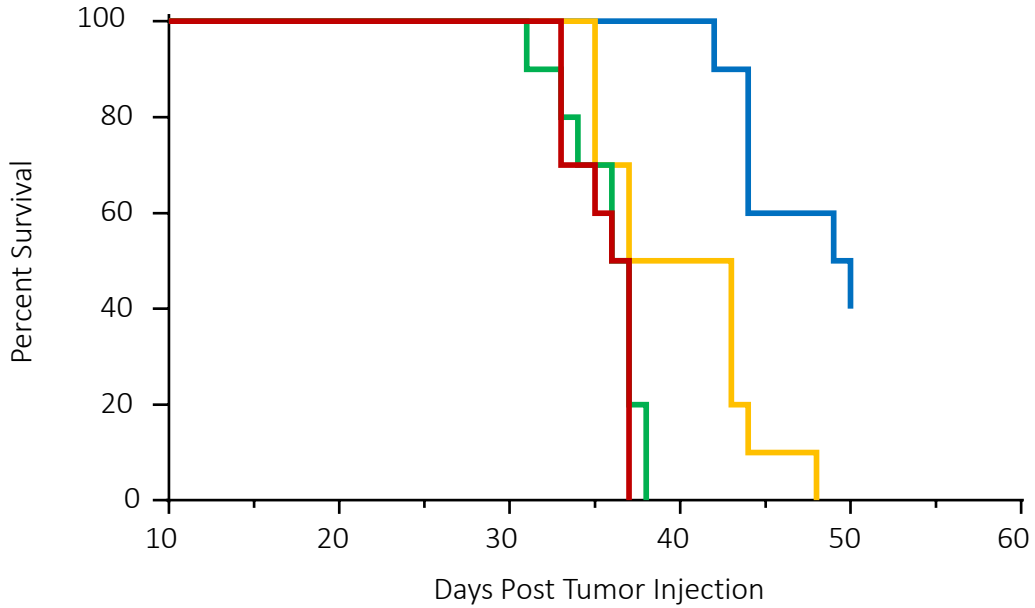


# GMI-1271 in combination with carfilzomib (CFZ) overcomes stroma-induced drug resistance *in vitro* and prolongs mice survival

*In vitro* – MTT assay



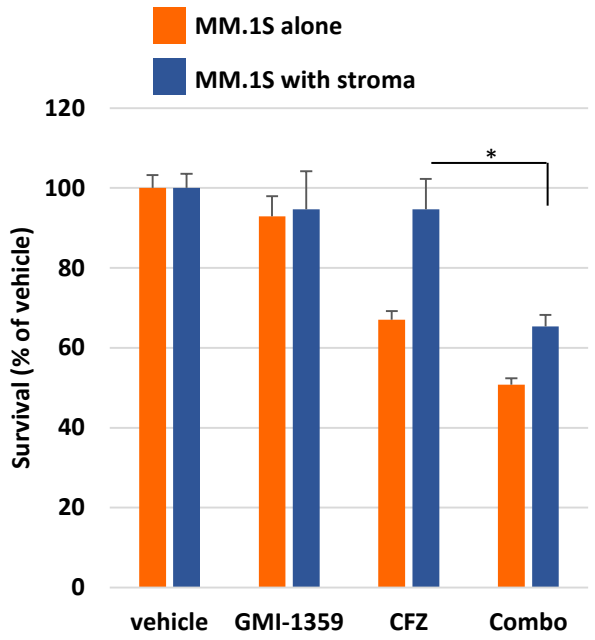

*In vivo* - Syngeneic 5TGM1 Disseminated Mouse Model



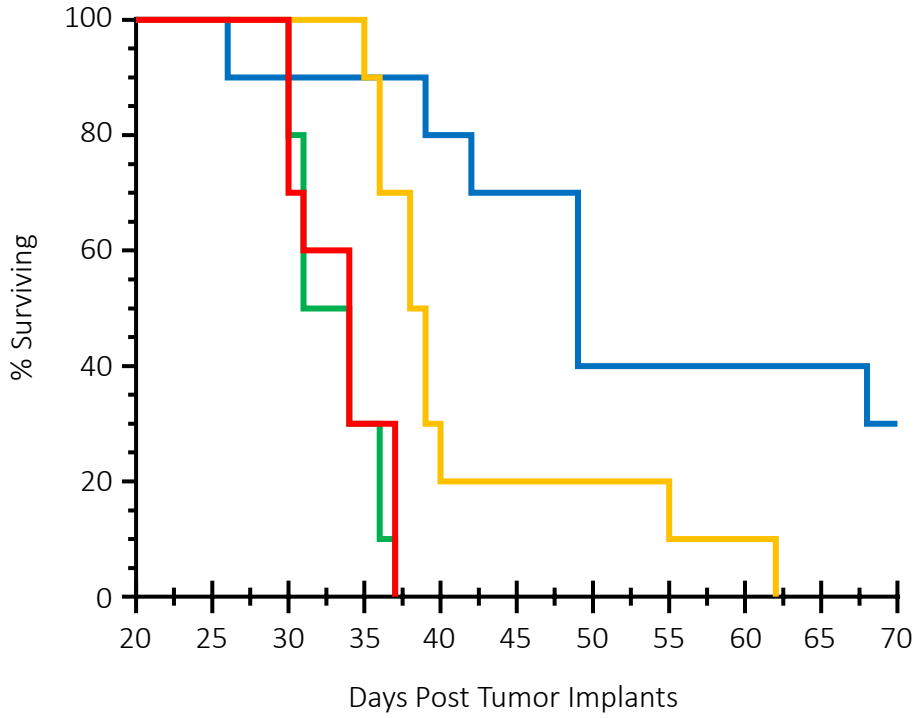

| | Treatment | N | MST (days) | P vs saline | P vs CFZ |
|---|---|---|---|---|---|
| | saline | 10 | 36.5 | -- | |
| | GMI-127140 mg/kg IP QDx14 | 10 | 36.5 | 0.5212 | |
| | CFZ 3 mg/kg IV QDx2 | 10 | 40.0 | 0.0274 | -- |
| | GMI-1271 + CFZ | 10 | 49.5 | 0.0001 | 0.0006 |

# GMI-1359 in combination with carfilzomib (CFZ) overcomes stroma-induced drug resistance *in vitro* and prolongs mice survival

*In vitro* – MTT assay

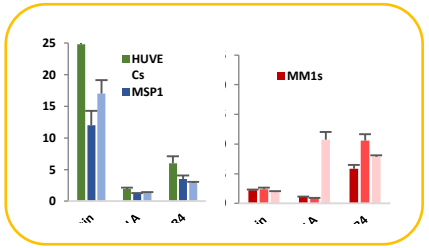



*In vivo* - Syngeneic 5TGM Disseminated Mouse Model

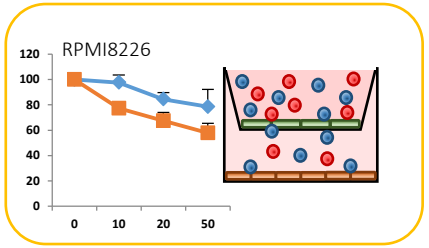



| | Treatment | N | MST (days) | P vs saline | P vs CFZ |
|---|---|---|---|---|---|
| | saline | 10 | 32.5 | -- | |
| | GMI-1359 40 mg/kg IP QDx14 | 10 | 34 | 0.5215 | |
| | CFZ 3 mg/kg IV QDx2 | 10 | 38.5 | 0.0002 | -- |
| | GMI-1359 + CFZ | 10 | 49 | 0.0001 | 0.014 |

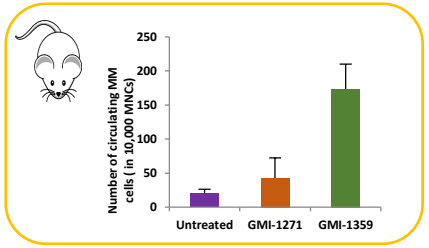
# Summary



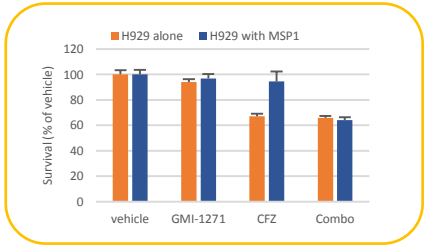

- Endothelial cells (HUVECs) and stromal cells (MSP-1 and HS5) express high levels of E-selectin
- CXCR4 is highly expressed on MM cell lines; CLA is highly expressed in RPMI8226



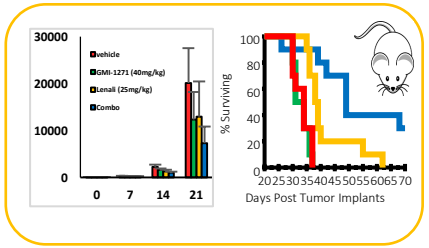

- *In vitro,* MM cell adhesion, chemotaxis, and trans-endothelial migration is decreased by GMI-1271 and even further by GMI-1359, in the presence of SDF-1




- *In vivo*, GMI-1359 significantly inhibits extravasation of MM cells to the bone marrow




- *In vitro,* GMI-1271 and GMI-1359 combined with either lenalidomide or carfilzomib overcome stroma-mediated drug resistance




- *In vivo*, GMI-1271 in combination with lenalidomide reduces tumor growth
- Mice survival is prolonged by GMI-1271 combined with carfilzomib, and even further by GMI-1359 combined with carfilzomib

# Acknowledgements


Azab Lab

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*Thank you for your attention!*