Epithelial-mesenchymal-transition regulated by Junctional Adhesion Molecule-A (JAM-A) associates with aggressive extramedullary multiple myeloma disease.

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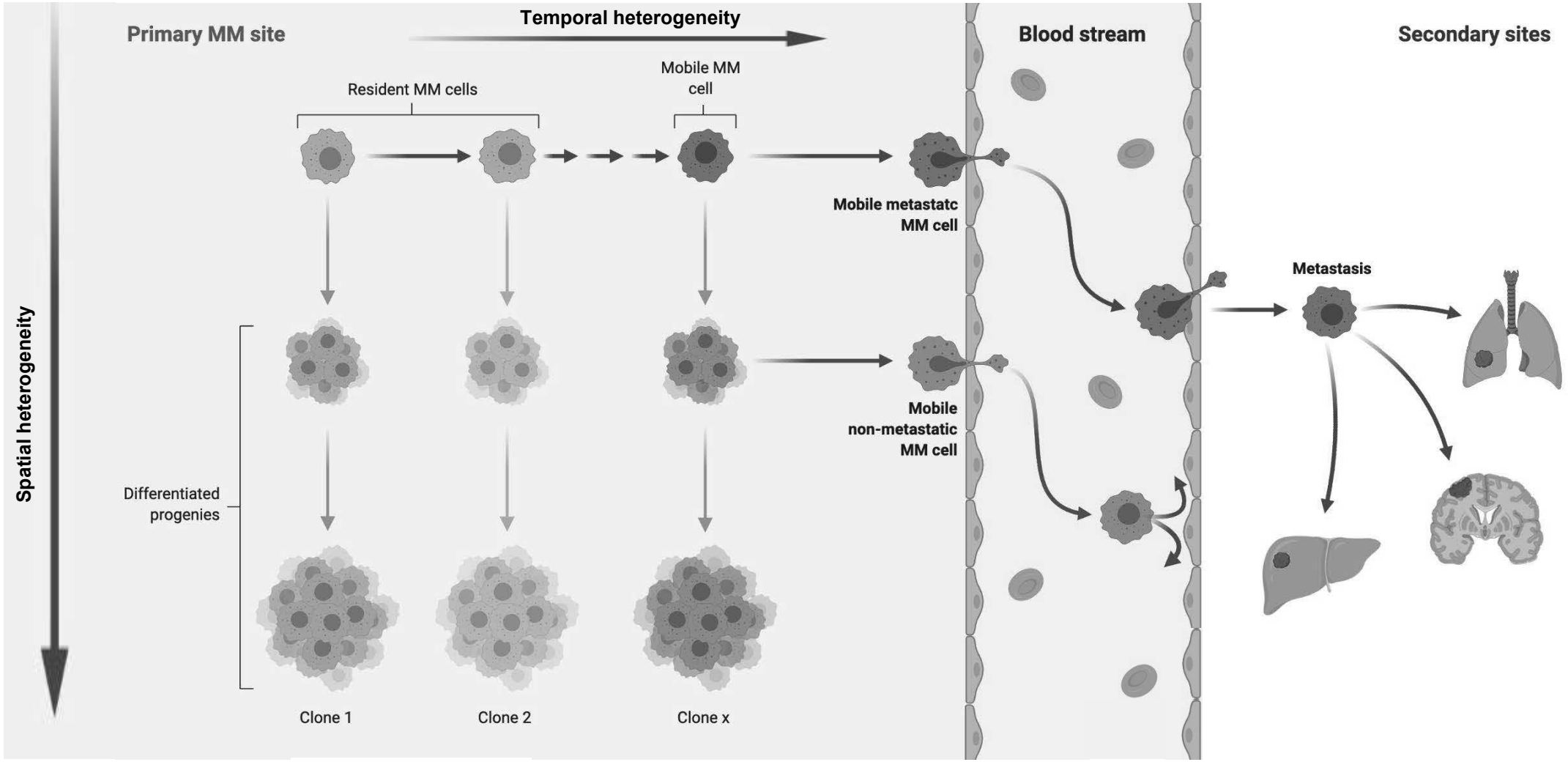
Disclosures

- No relevant conflict of interest to declare for this contents
- Personal financial interests, I received travel grants from:

Amgen Inc., Janssen - Celgene, Bristol-Myers Squibb

MM dissemination: a journey from medullary to extramedullary disease



Instigation

Intrinsic vs. extrinsic mechanisms

Cell-adhesion Dissemination

Fig. created in BioRender.com

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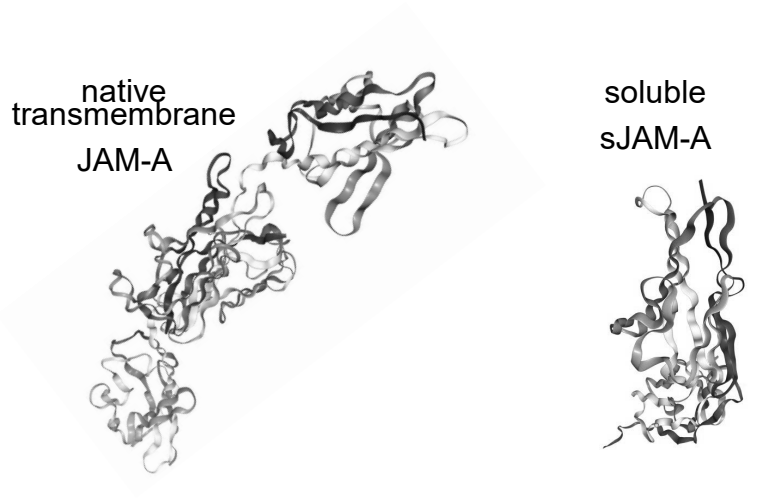
Cell-adhesion

Abstract ID: 1088727, IMW21

Gene	References	*P* value
ITGB2	• Schmidmaier R, *et al.* Int J Oncol 2007	**< .0001**
CXCR4	• Katz BZ. Seminar Cancer Biol, 2010 • Roccaro A, *et al.* Cell Rep, 2015	**< .0001**
SDC1	• Katz BZ. Seminar Cancer Biol, 2010	**< .0001**
CD44	• Katz BZ. Seminar Cancer Biol, 2010	**< .0001**
CXCL12	• Waldschmidt JM, Br J Haematol, 2017	**< .0001**
ITGB1	• Hazlehurst LA, *et al.* Oncogene, 2000	**< .0001**
ITGA4	• Noborio-Atano K, *et al.* Oncogene, 2009 • Waldschmidt JM, Br J Haematol, 2017	**< .0001**
ITGA5	• Andrade VC, *et al.* Leuk Lymphoma, 2010	**=.002**
VCAM1	• Okada T, *et al.* Clin Exp Metastasis, 1999	**=.001**
NCAM1	• Yoshida T, *et al.* PLoS One, 2018	**=.003**
MUC1	• Yin L, *et al.* Br J Haematol, 2017	**=.002**
SELP	• Muz B, *et al.* Biomed Res Int, 2015	**< .0001**
SELE	• Natoni A, *et al.* Leukemia, 2017	**< .0001**
CDH1	• Yao Q, *et al.* Clin Epigenetics, 2018	**< .0001**
CD38	• Nijhof I, *et al.* Blood, 2016	**=.001**
F11R/ JAM-A		**< .0001**

- **Cell-adhesion**
- **Angiogenesis**
- **Hypoxia**



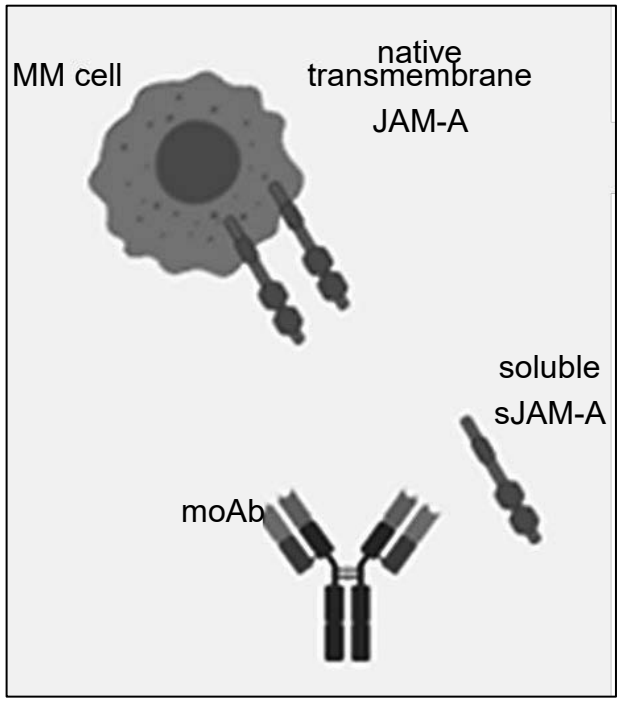


Fig. created in BioRender.com

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Jakob, Franz et al. *Bone* vol. 93 (2016): 155-166.

JAM-A on primary MM PCs and Endothelial Cells correlates with poor OS

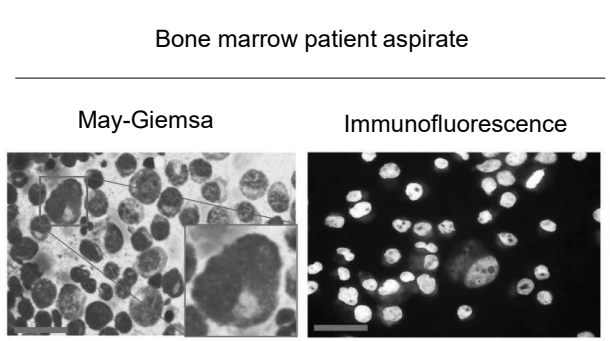
Leukemia nature research

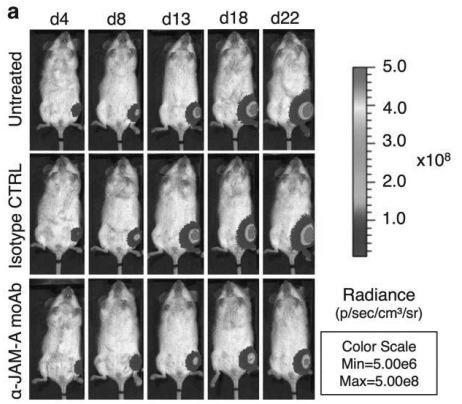
Leukemia (2018) **32**, 736–743

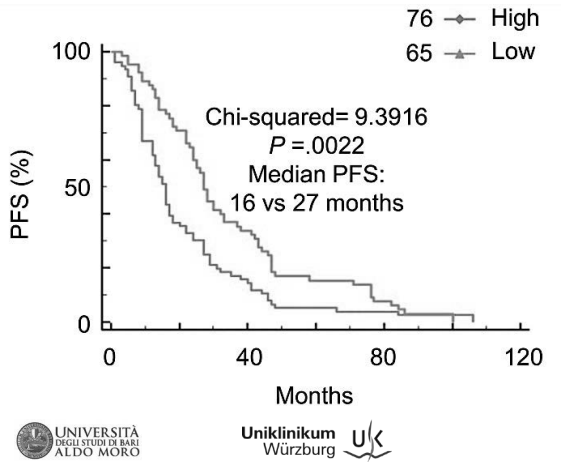
ORIGINAL ARTICLE

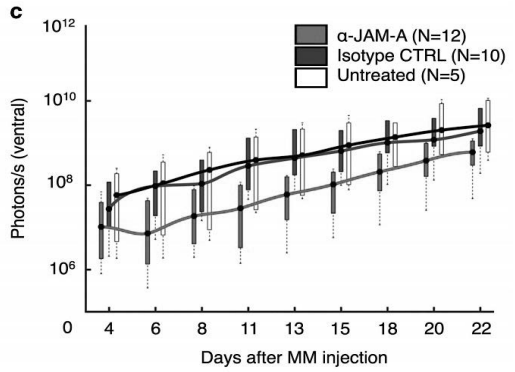
JAM-A as a prognostic factor and new therapeutic target in multiple myeloma

AG Solimando[1,2,3,8], A Brandl[1,2,8], K Mattenheimer[1,2], C Graf[1,2], M Ritz[1,2], A Ruckdeschel[1,2], T Stühmer[4], Z Mokhtari[1,2], M Rudelius[5], J Dotterweich[6], M Bittrich[2], V Desantis[3], R Ebert[6], P Trerotoli[7], MA Frassanito[3], A Rosenwald[5], A Vacca[3], H Einsele[2], F Jakob[6] and A Beilhack[1,2]









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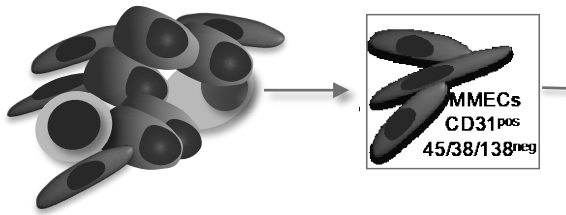
haematologica

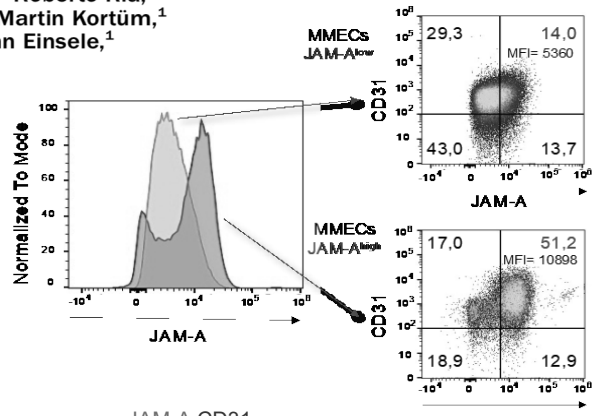
ARTICLE

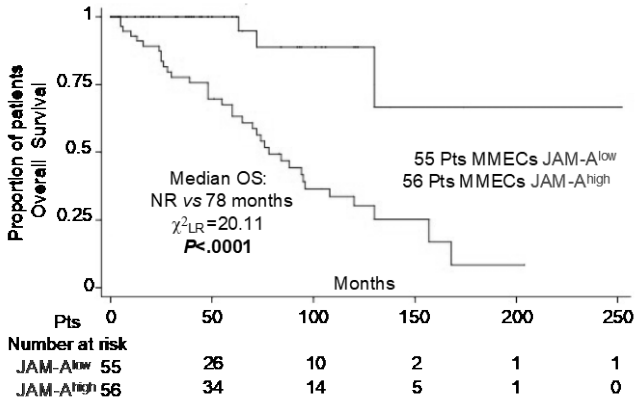
Haematologica 2021
Volume 106(7)1943-1956

Halting the vicious cycle within the multiple myeloma ecosystem: blocking JAM-A on bone marrow endothelial cells restores angiogenic homeostasis and suppresses tumor progression

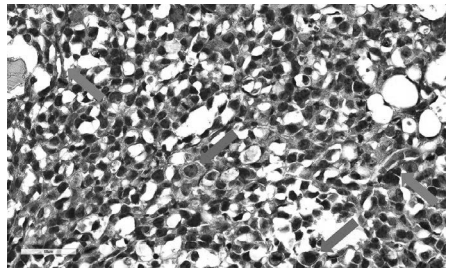
Antonio G. Solimando,[1,2,3] Matteo C. Da Viá,[1,4,5] Patrizia Leone,[3] Paola Borrelli,[6] Giorgio A. Croci,[7,8] Paula Tabares,[1,9] Andreas Brandl,[1,9] Giuseppe Di Lernia,[3] Francesco P. Bianchi,[10] Silvio Tafuri,[10] Torsten Steinbrunn,[1] Alessandra Balduini,[11,12] Assunta Melaccio,[3] Simona De Summa,[13] Antonella Argentiero,[2] Hilka Rauert-Wunderlich,[14] Maria A. Frassanito,[3] Paolo Ditonno,[2] Erik Henke,[15] Wolfram Klapper,[7] Roberto Ria,[3] Carolina Terragna,[16] Leo Rasche,[1] Andreas Rosenwald,[14] K. Martin Kortüm,[1] Michele Cavo,[16] Domenico Ribatti,[17] Vito Racanelli,[3] Hermann Einsele,[1] Angelo Vacca[3] and Andreas Beilhack[1,9]



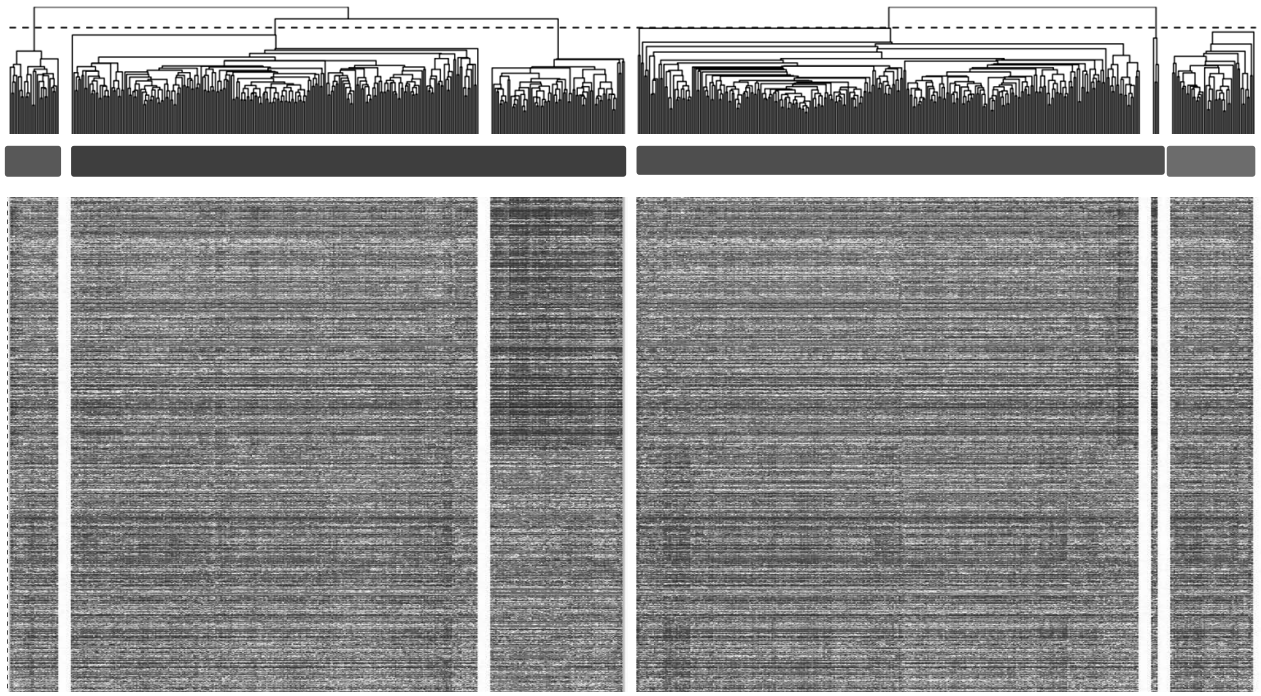




JAM-A CD31



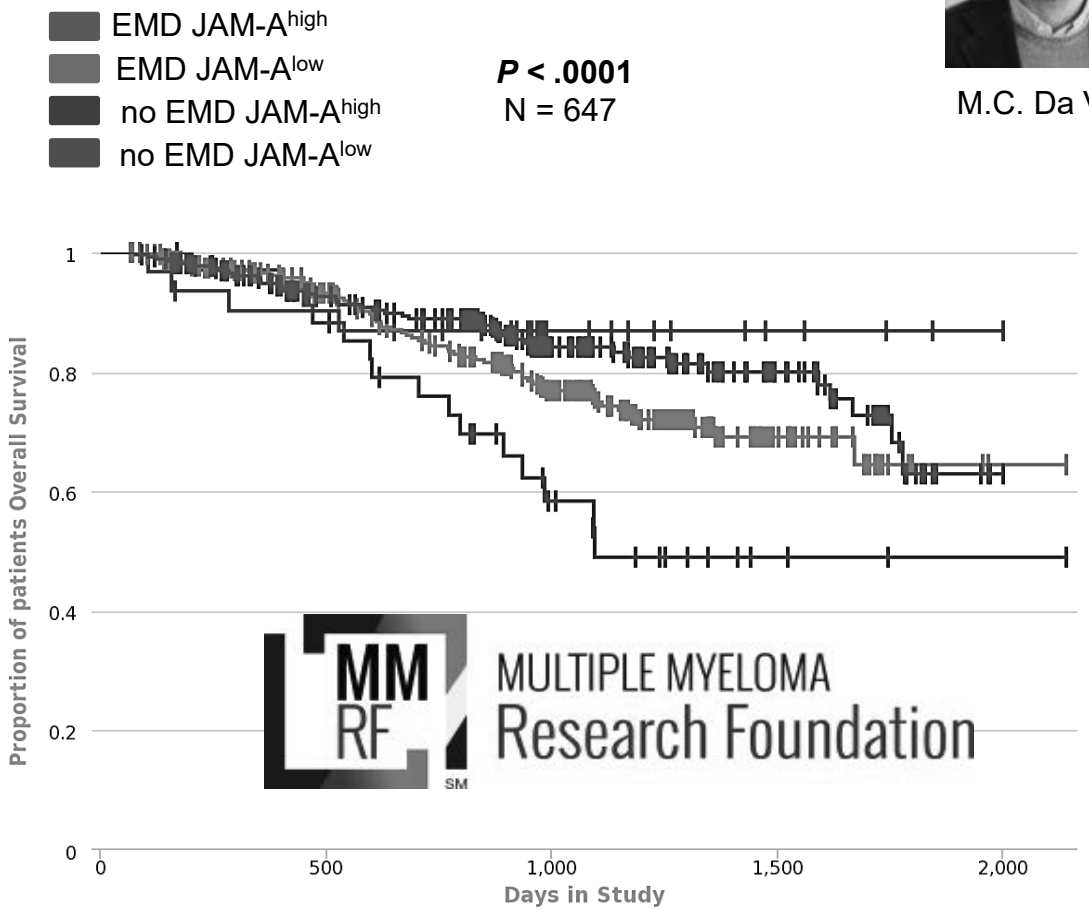
JAM-A + NDMM with EMD display a unique gene-expression signature



CELL CYCLE
PROLIFERATION

EMT
FOCAL ADHESION
PI3K-AKT

M.C. Da Vià



https://research.themmrf.org/rp/terms

Those data were also generated as part of the MMRF Personaliyed Medicine Initiative

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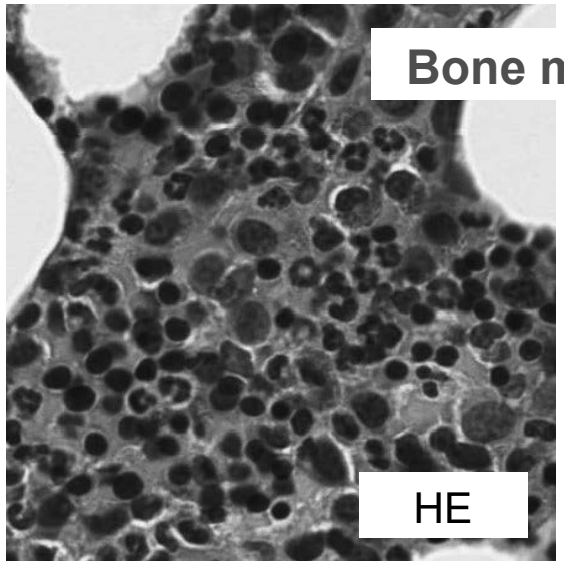
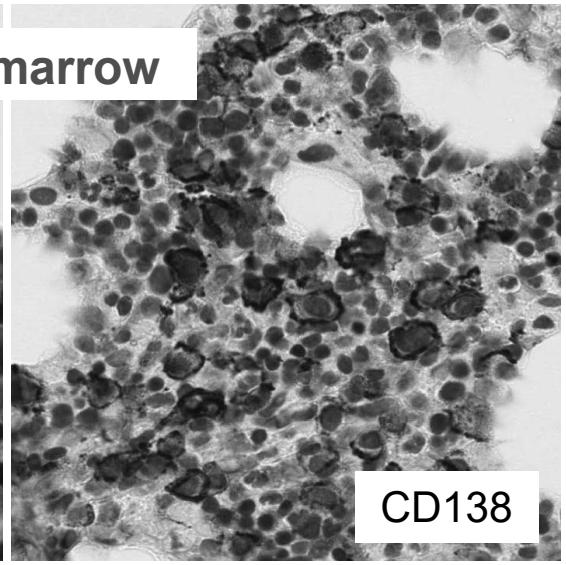
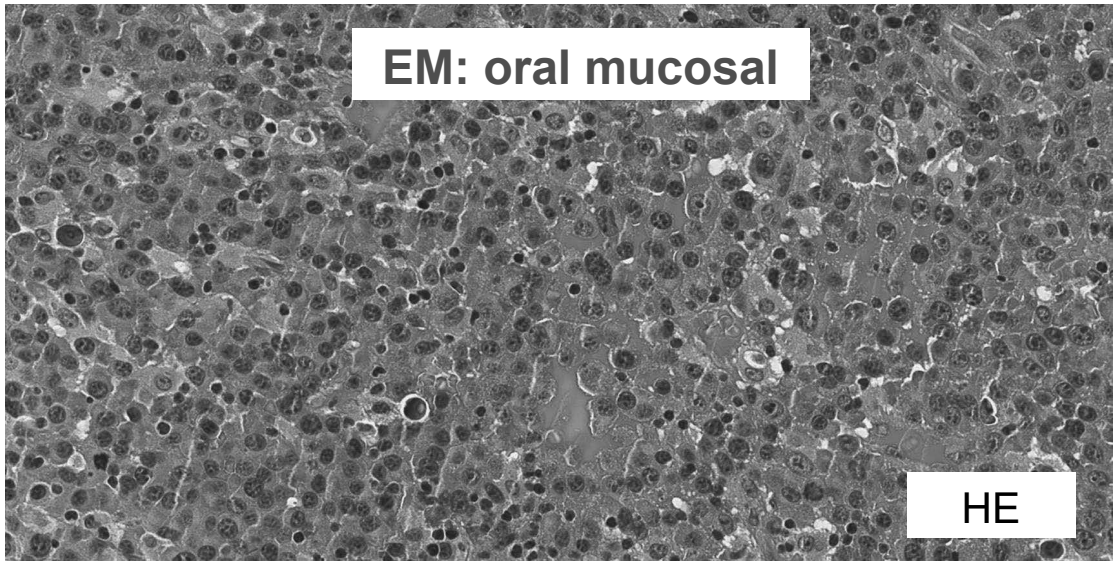
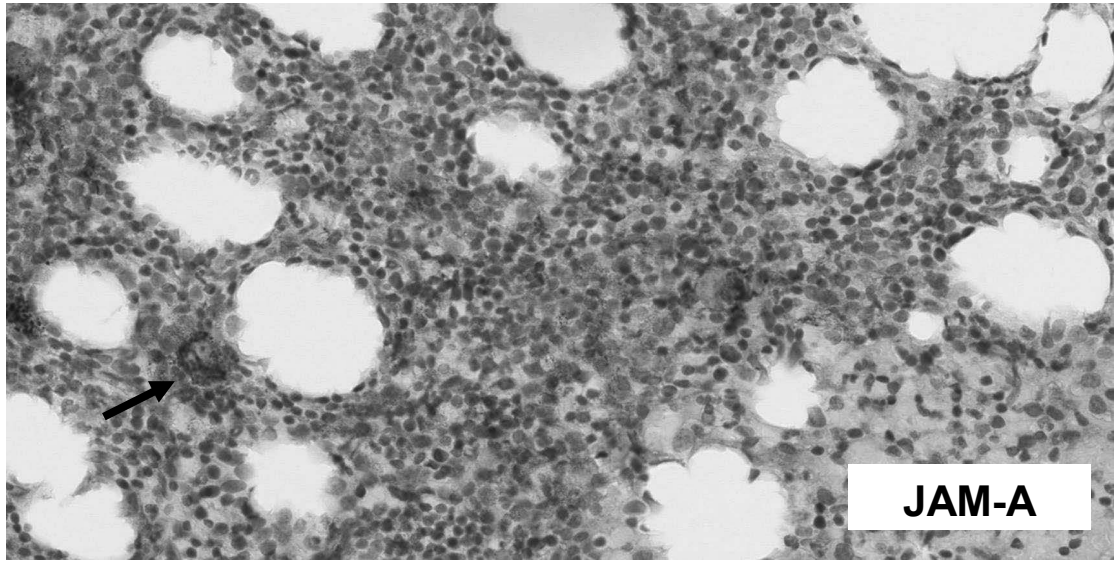
Unpublished data

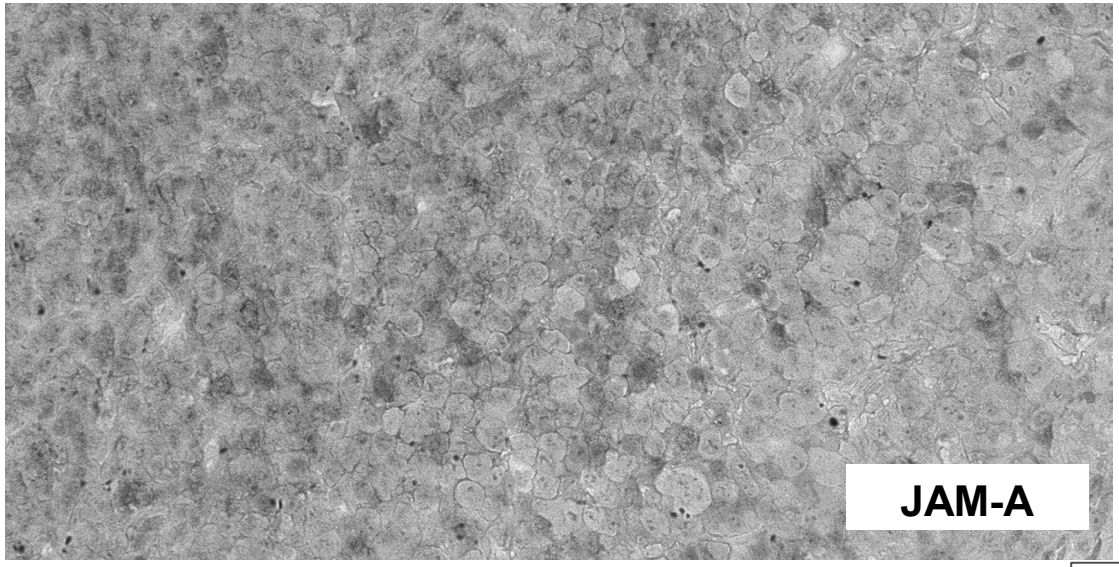
Case 1 – MGUS IgG in BM, oral mucosal infiltrate, moderate cytologic atypia; low JAM-A expression











G. Croci

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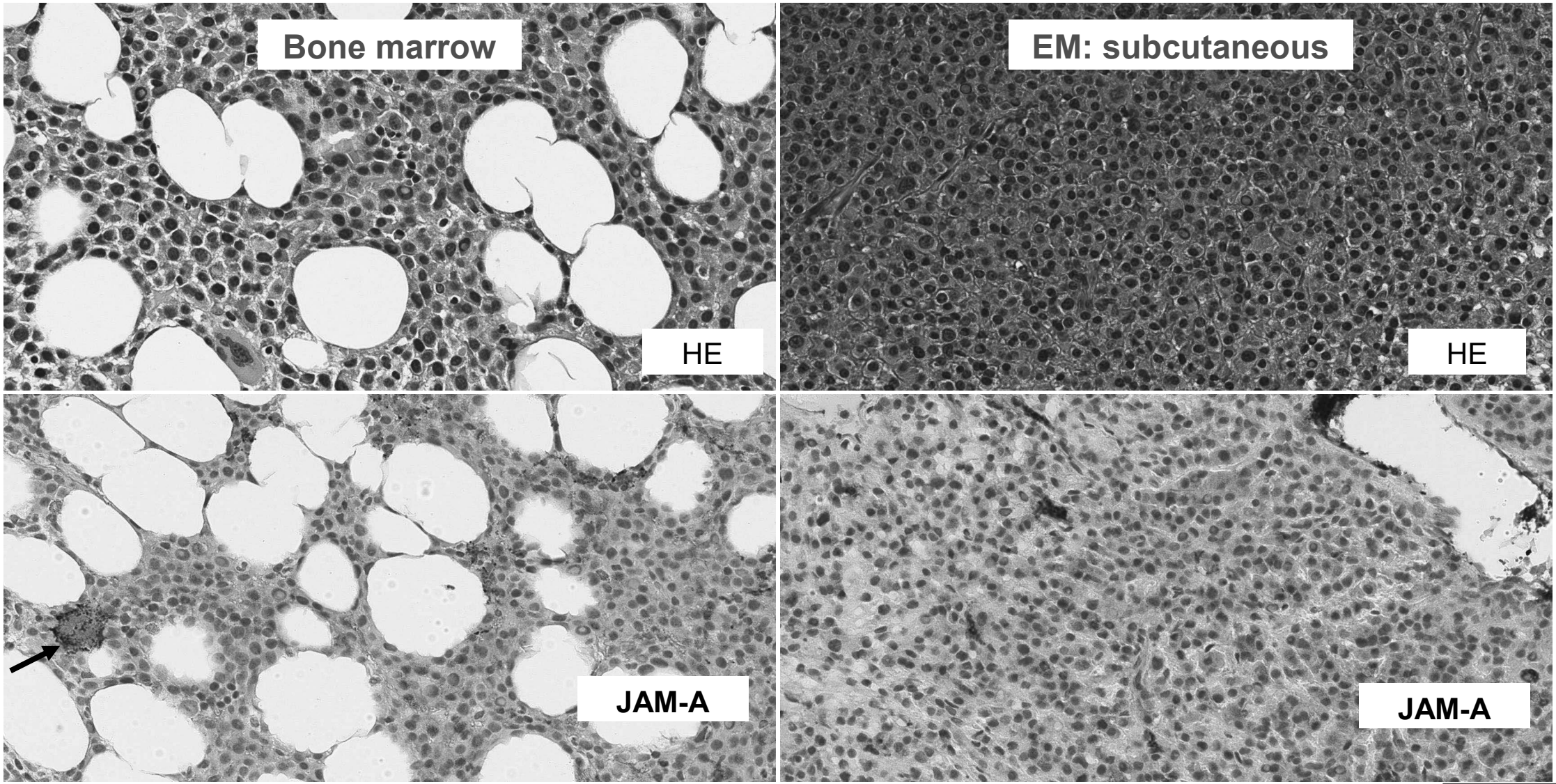
Case 2 –MM in BM, subcutaneous localization; mild atypia, Dutcher bodies; low JAM-A expression EM > BM



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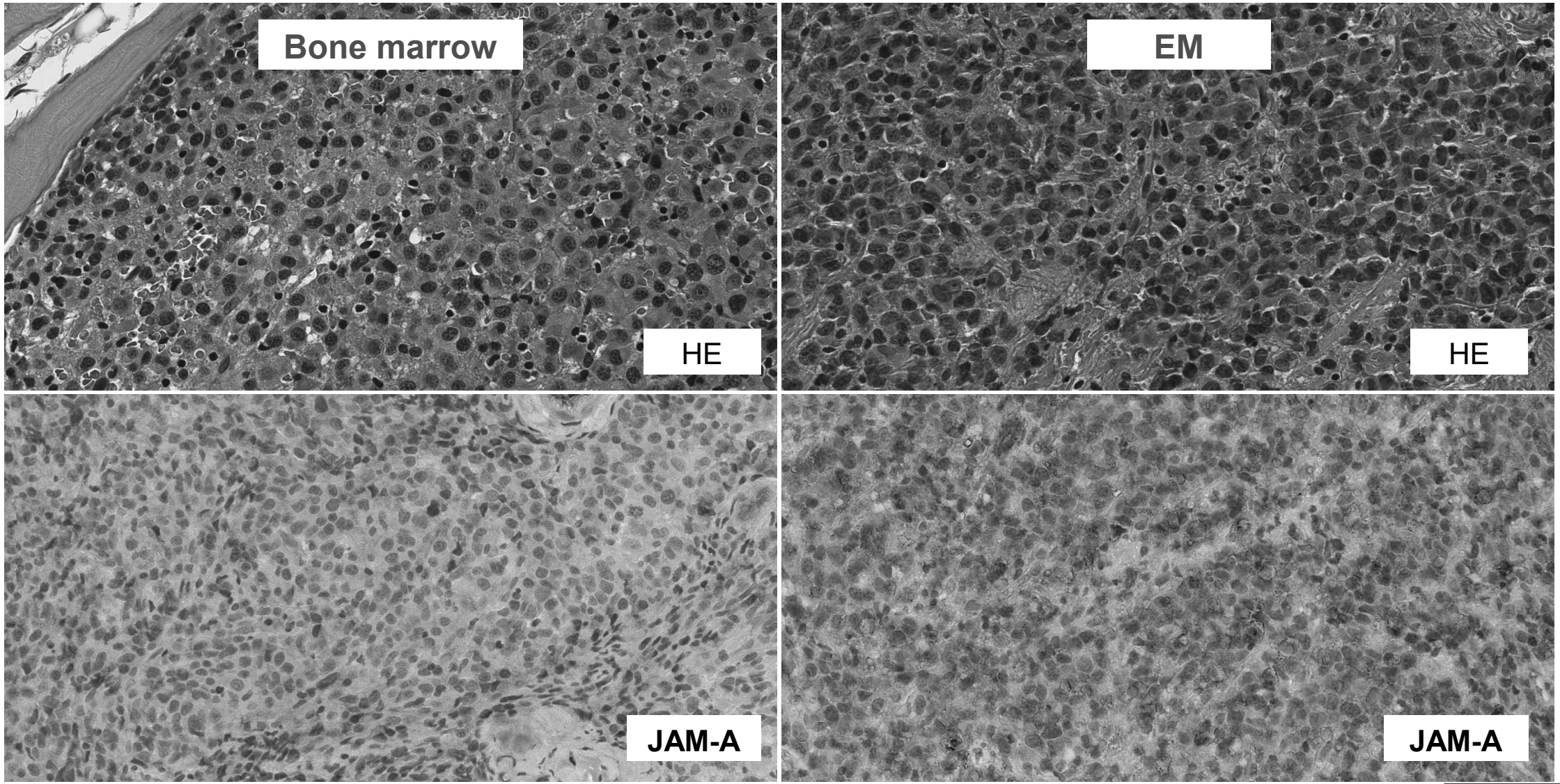
Case 3 –MM in BM, pleural localization; moderate atypia; moderate JAM-A expression EM > BM



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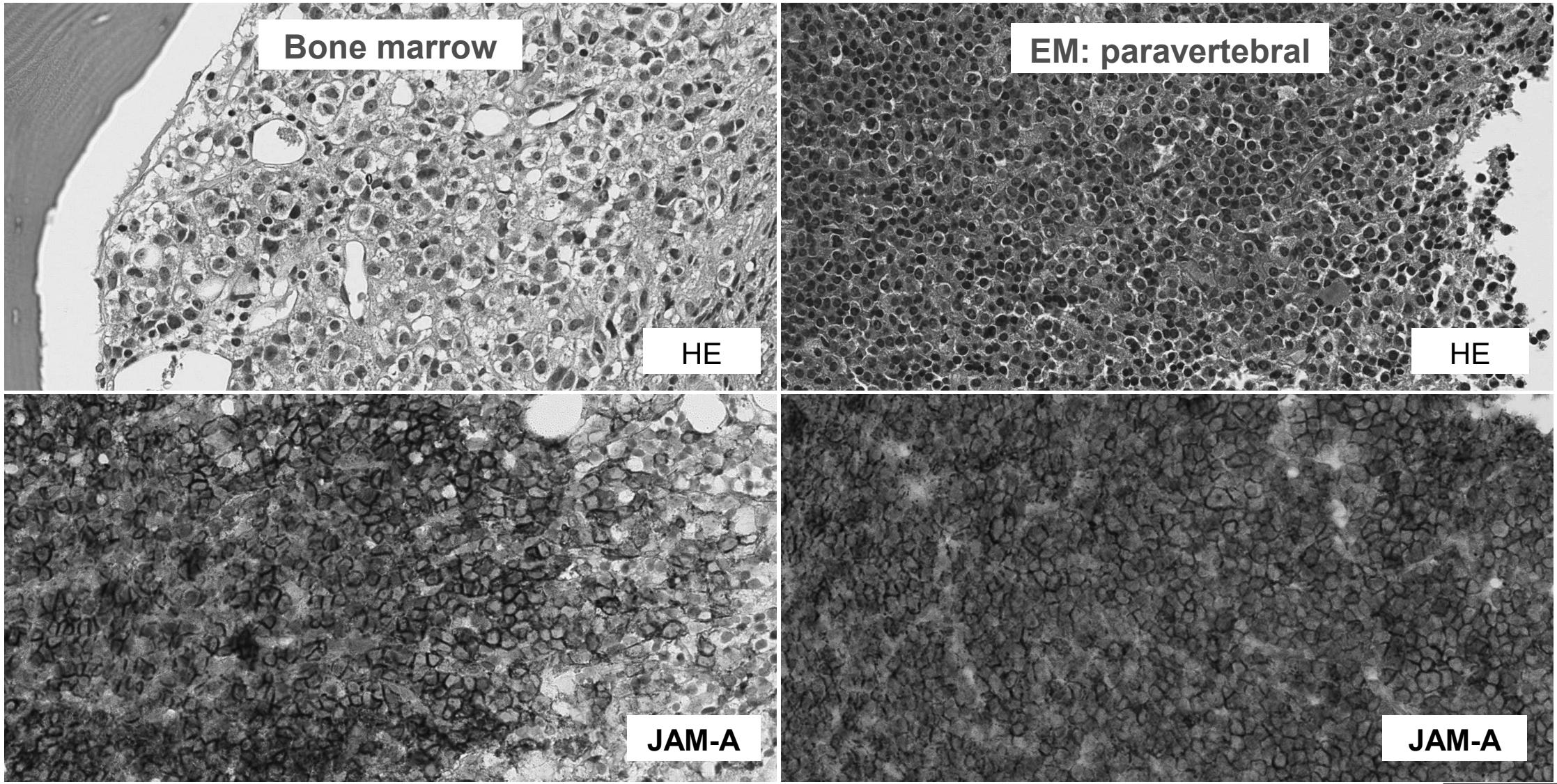
Case 4 – Pleomorphic / plasmablastic MM in BM and paravertebral; high JAM-A expression EM > BM



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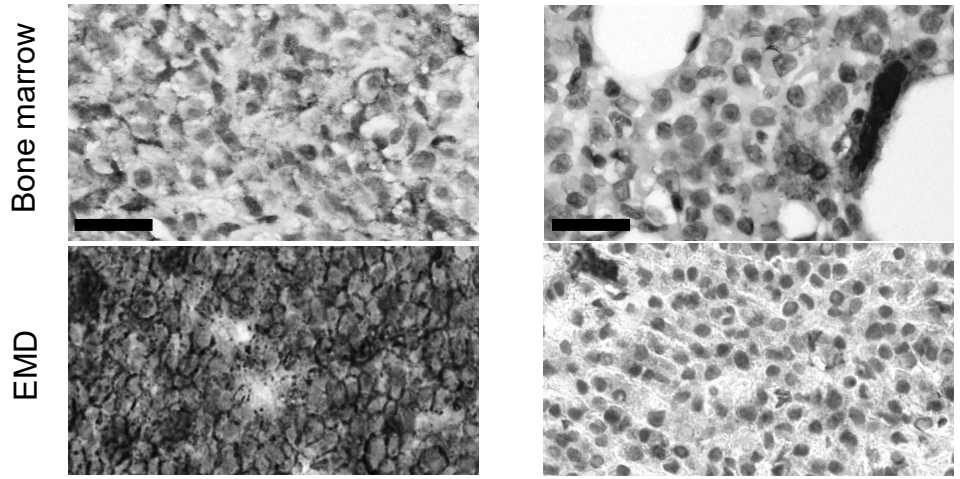
JAM-A is differentially expressed in patients with extramedullary MM disease

A



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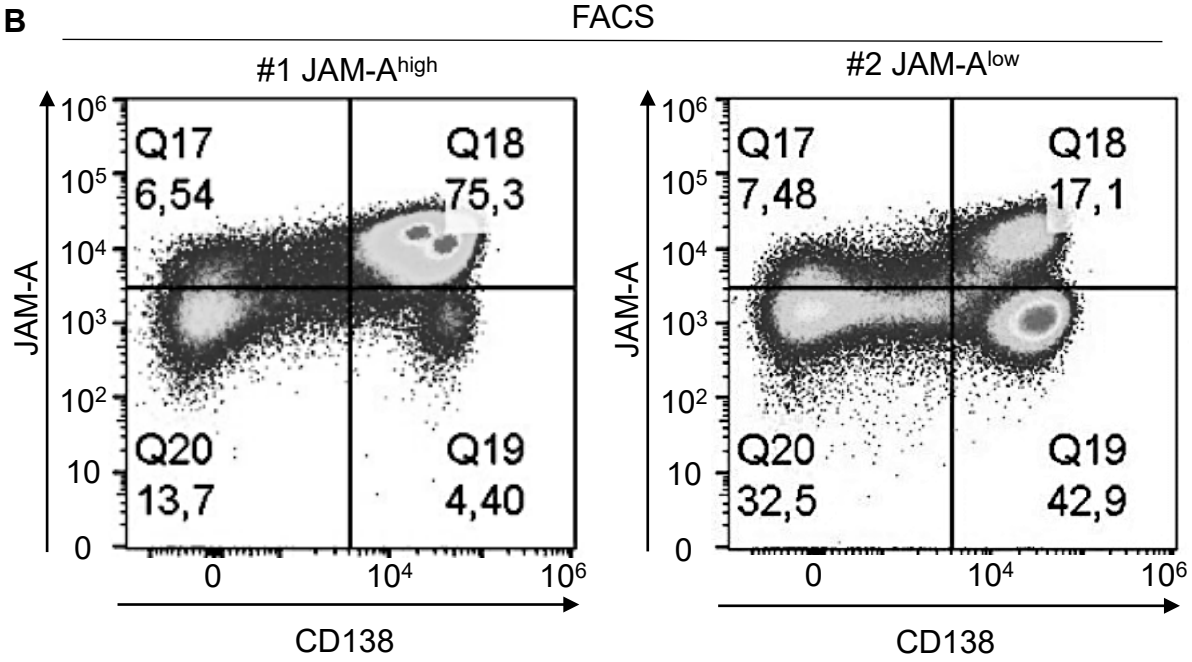
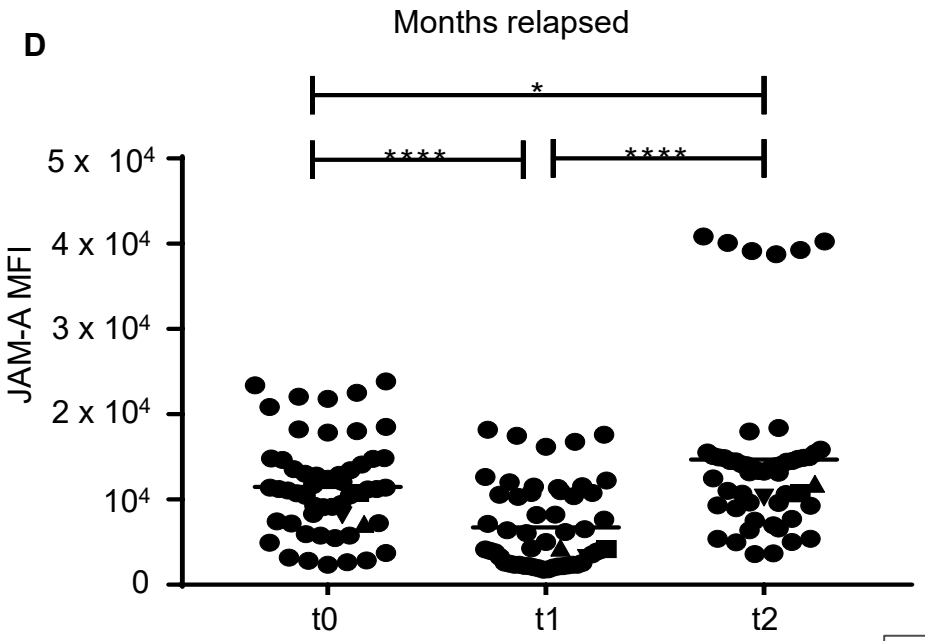


C

	*Cox model for Overall Survival			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
PCs JAM-A surface expression (JAM-A^high vs JAM-A^low)	9.14 (2.80-29.76)	**<0.001**	9.11 (2.79-29.76)	**<0.001**
Bone Lesion (Yes vs No)	1.31 (0.60-2.89)	0.489	-	-
Hb (<10 vs >/-10 g/dL)	1.44 (0.75-2.77)	0.271	-	-
R-ISS **R-Stage I** **R-Stage II** **R-Stage III**	 1 1.37 (0.55-3.39) 2.11 (0.76-5.86)	 0.494 0.149	-	-
Sex (M vs F)	0.58 (0.29-1.13)	0.110	0.65 (0.33-1.30)	0.233
Chronic kidney disease (Yes vs No)	2.04 (1.05-3.96)	**0.033**	2.11 (1.08-4.10)	**0.027**
Age	0.98 (0.94-1.02)	0.542	0.99 (0.95-1.04)	0.984

D



****** *P* < .0001**
*** *P* = .0371**
N=60

Unpublished data

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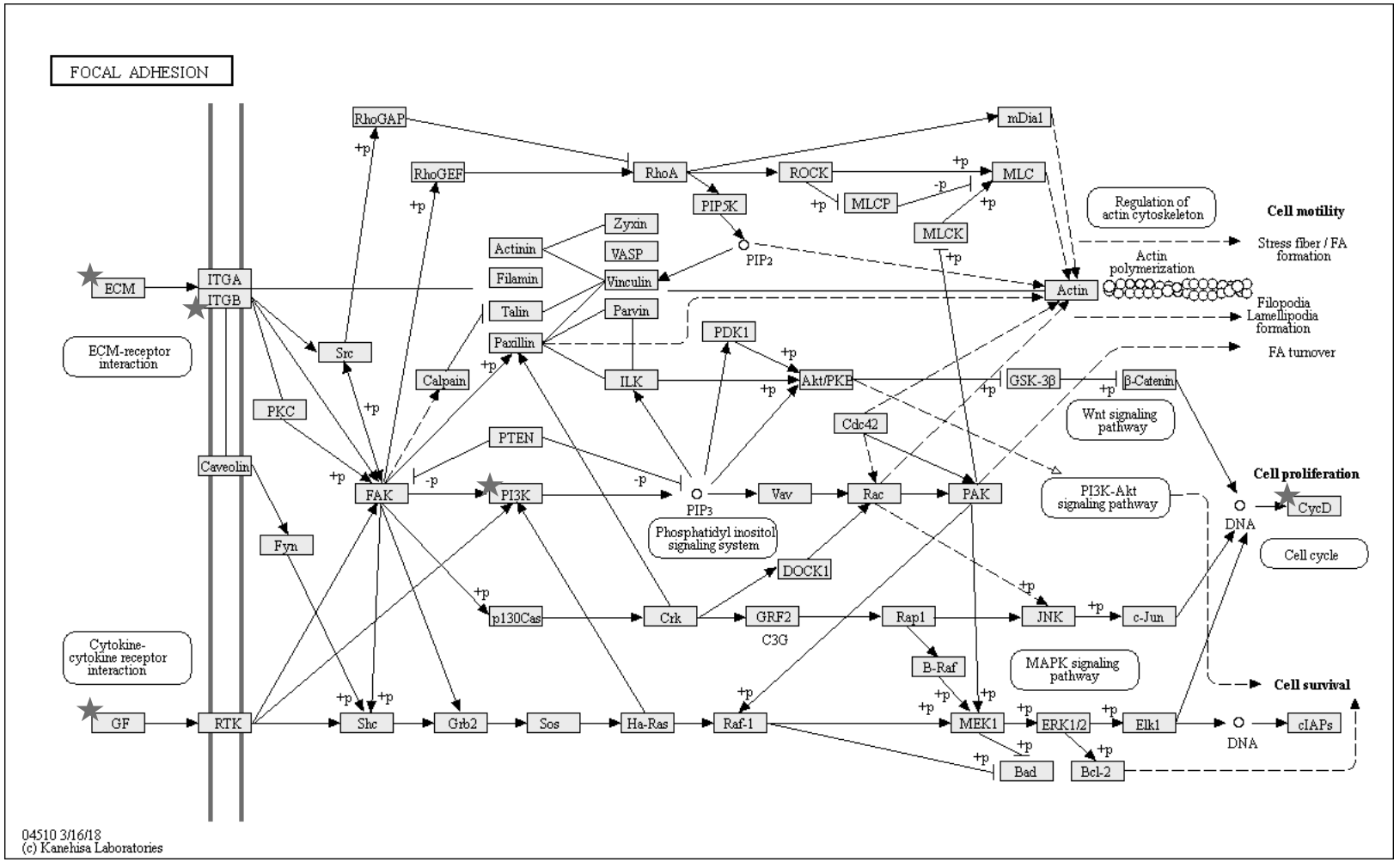
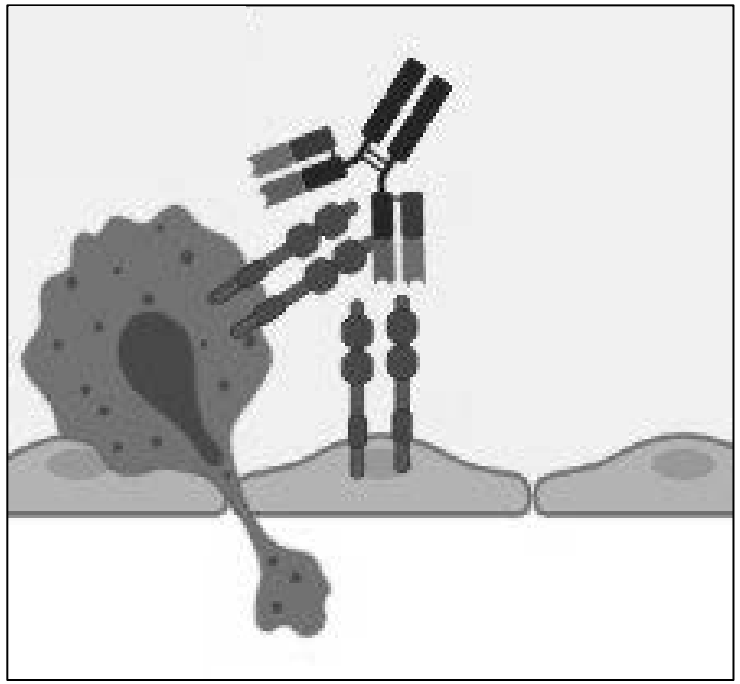
Enriched genes in focal adhesion, PI3K/mTOR pathway, and regulation of actin cytoskeleton



Context dependent and dynamic JAM-A expression on bone marrow endothelial cells and invasive MM cells



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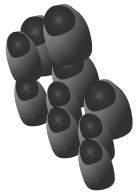
Unpublished data

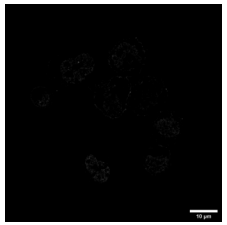
JAM-A mediates acquisition of EMT-like features in MM cells in vitro (I)

KMS12 JAM-A^{low}



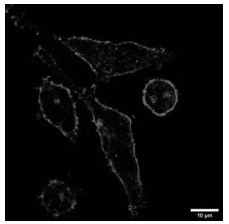
JAM-A

KMS12 E.V.



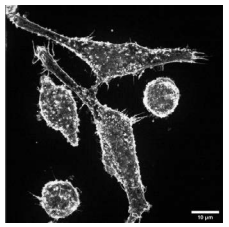
JAM-A

KMS12 JAM-A^{+}

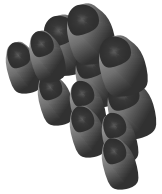


Z-projections

KMS12 JAM-A^{+}

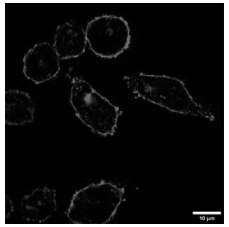


MM.1S JAM-A^{high}



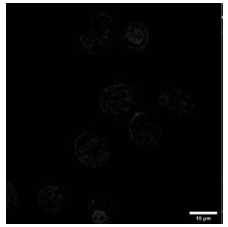
JAM-A

MM.1S wild type



JAM-A

MM.1S shJAM-A



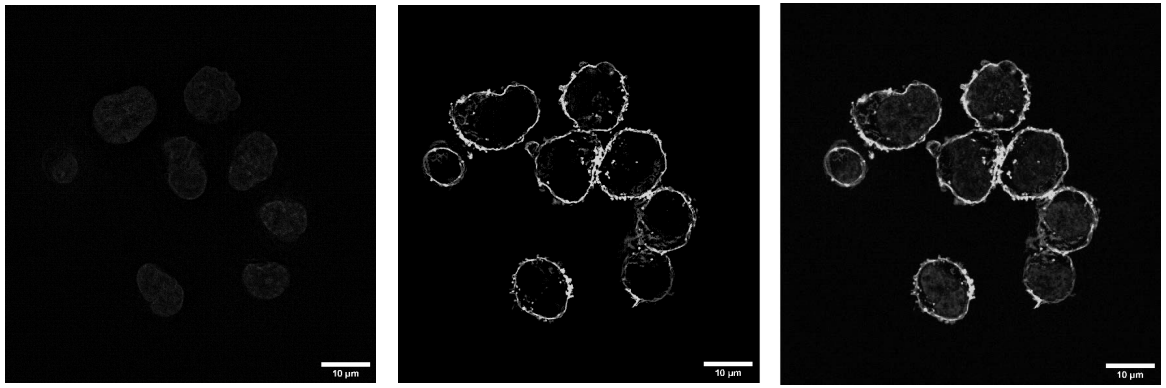
U. Terpitz

Nucleus

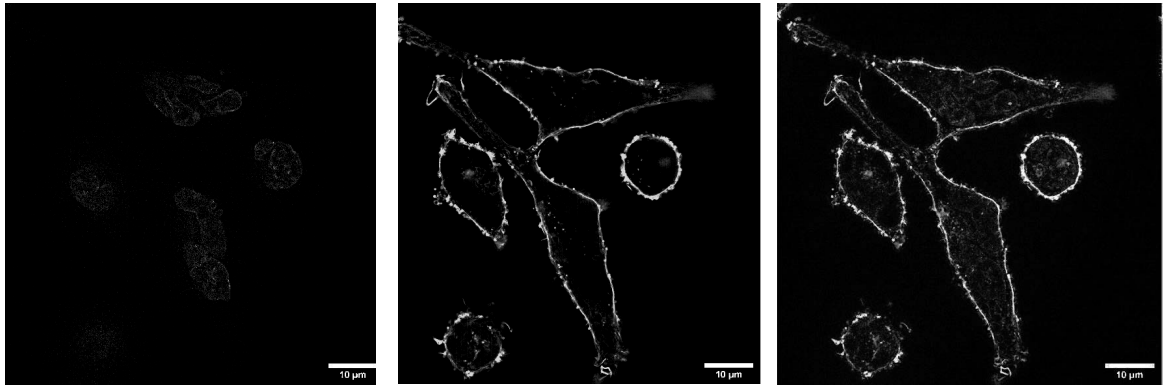
Actin

Merge

KMS12 E.V.



KMS12 JAM-A^{+}

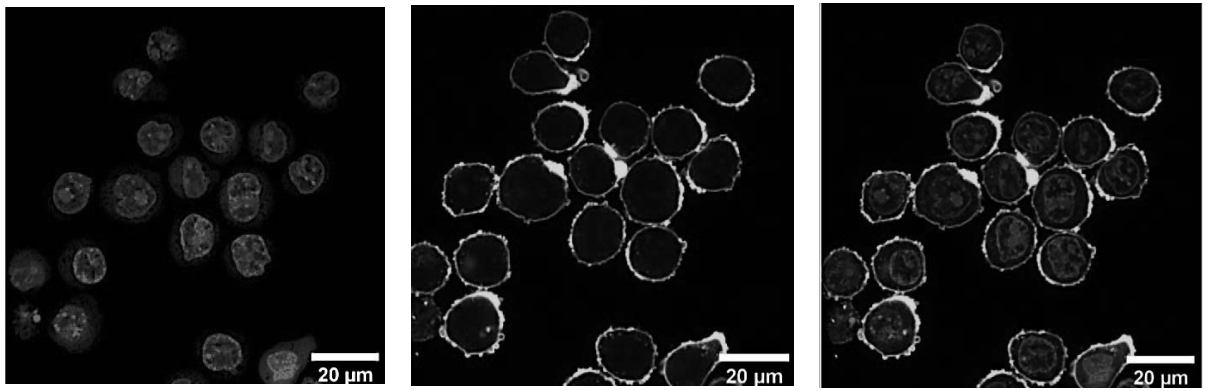


Nucleus

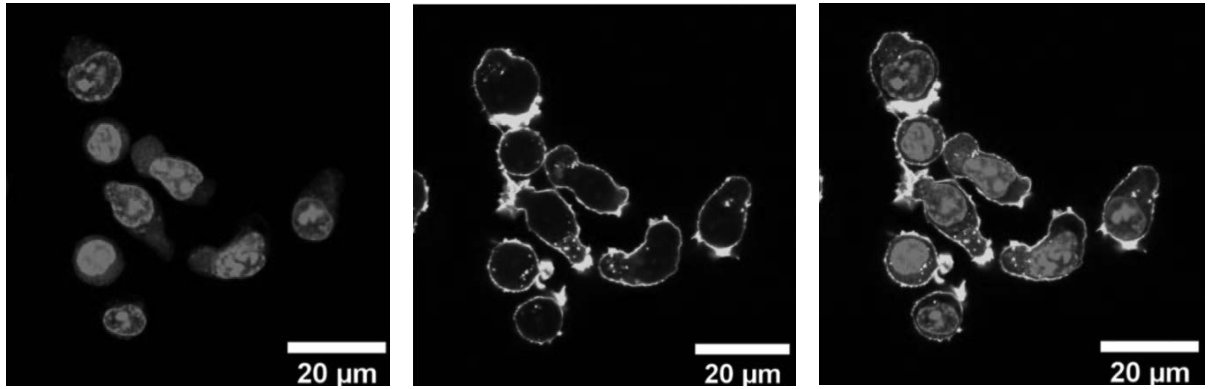
Actin

Merge

MM.1S shJAM-A



MM.1S wild type



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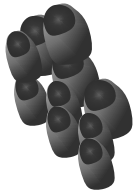
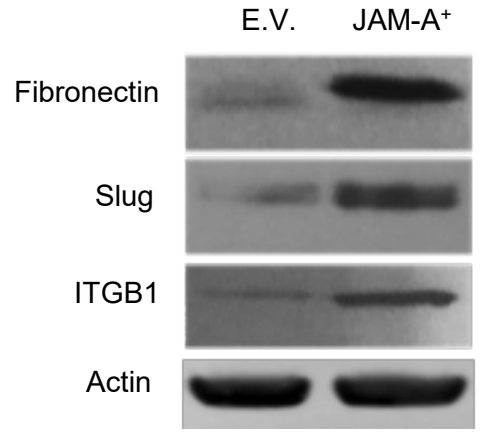
Antonio G. Solimando

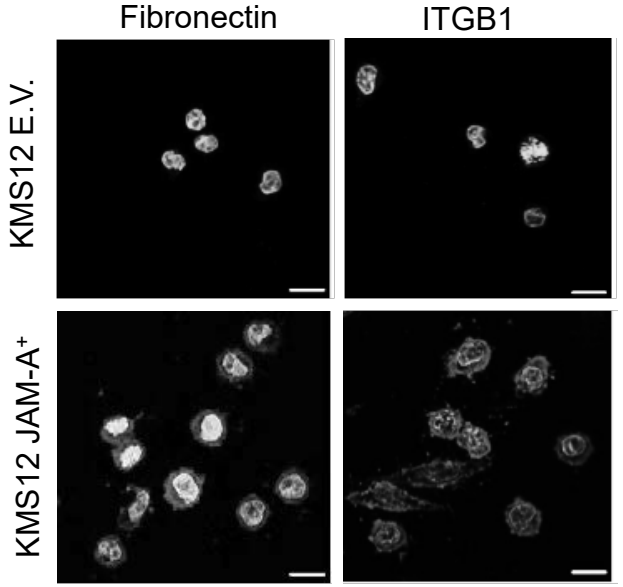
Unpublished data

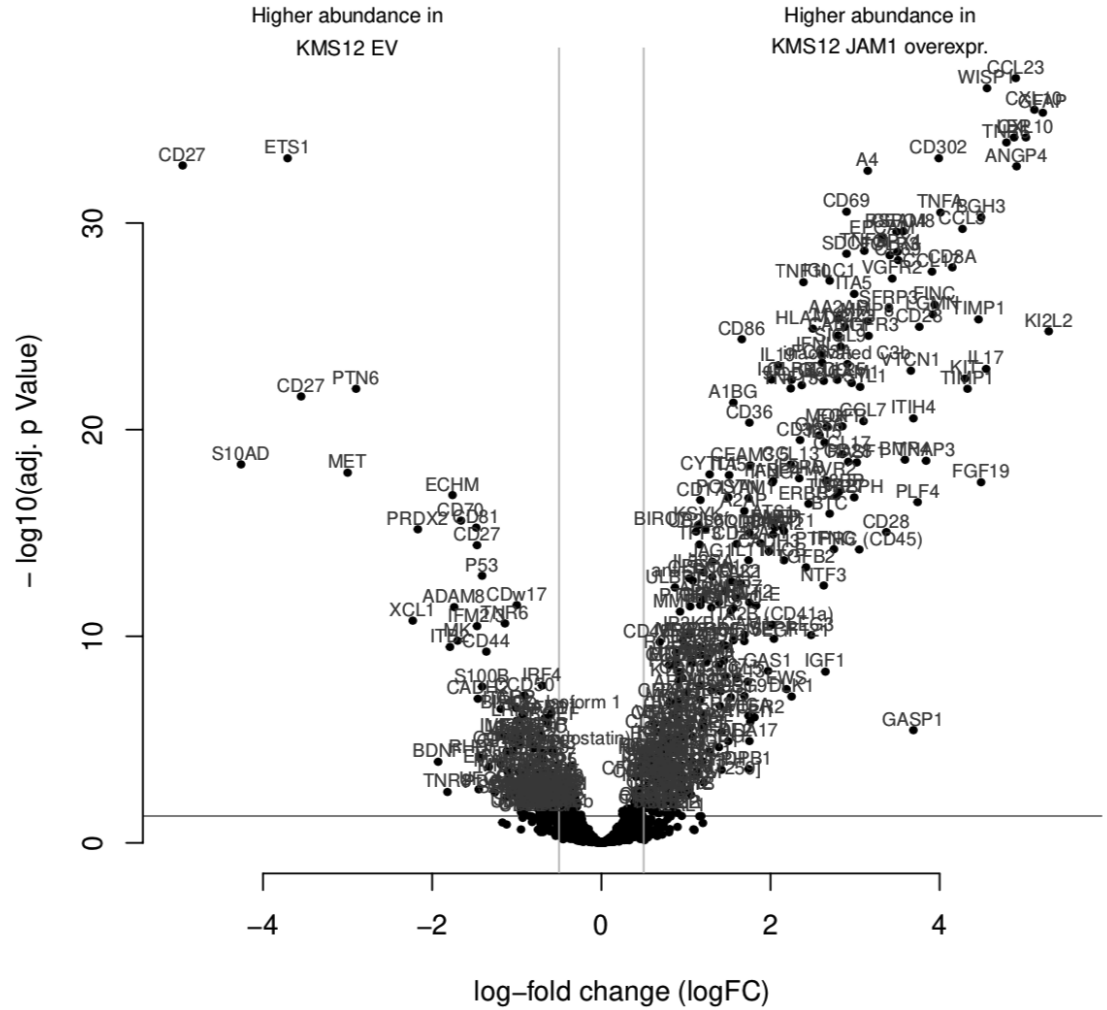
JAM-A mediates acquisition of EMT-like features in MM cells (II)

KMS12 JAM-A^{low}









Unpublished data

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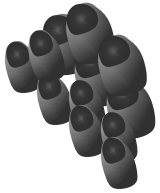
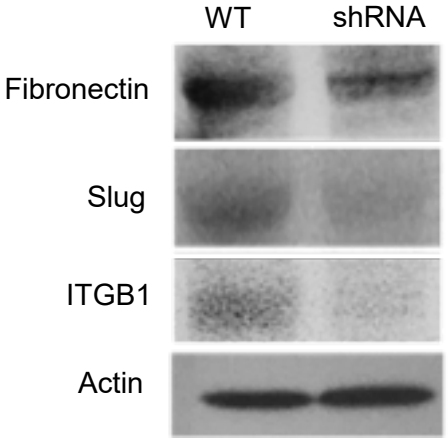
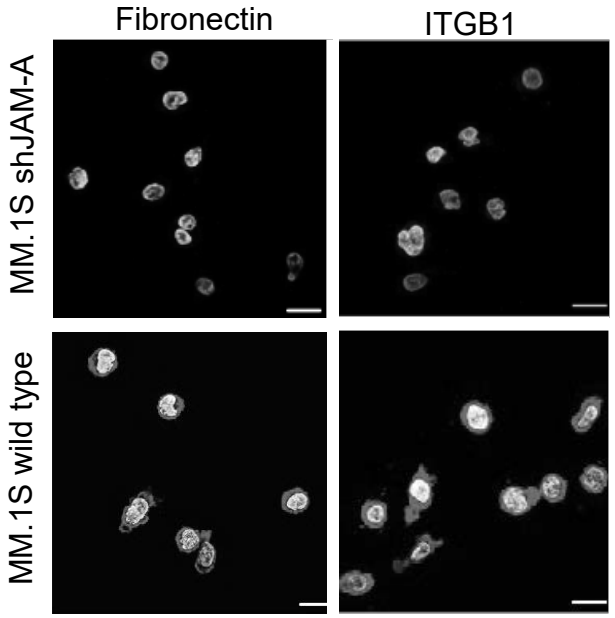
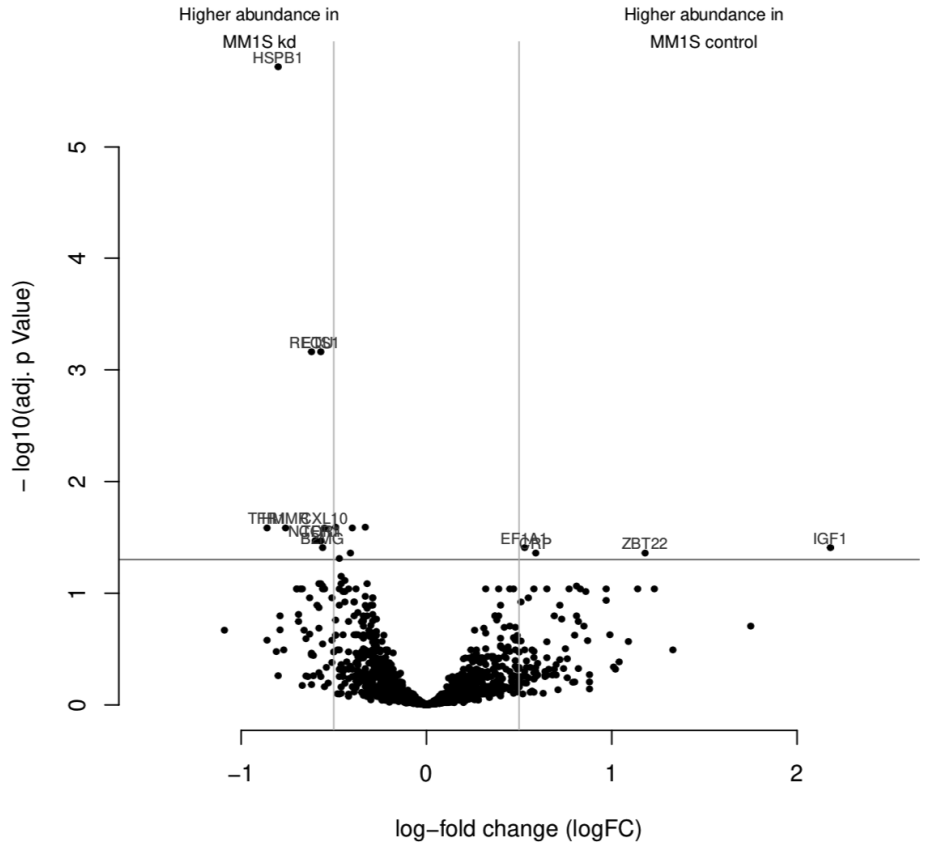
JAM-A mediates acquisition of EMT-like features in MM cells (III)

MM.1S JAM-A^{high}









KEGG

hsa04060	Cytokine-cytokine receptor interaction	30	263	2.24e-26
hsa04514	Cell adhesion molecules (CAMs)	11	139	6.08e-08
hsa04657	IL-17 signaling pathway	9	92	2.50e-07
hsa04010	MAPK signaling pathway	13	293	8.01e-07
hsa04630	Jak-STAT signaling pathway	10	160	1.28e-06
hsa04668	TNF signaling pathway	7	108	3.93e-05
hsa04510	Focal adhesion	9	197	3.04e-05

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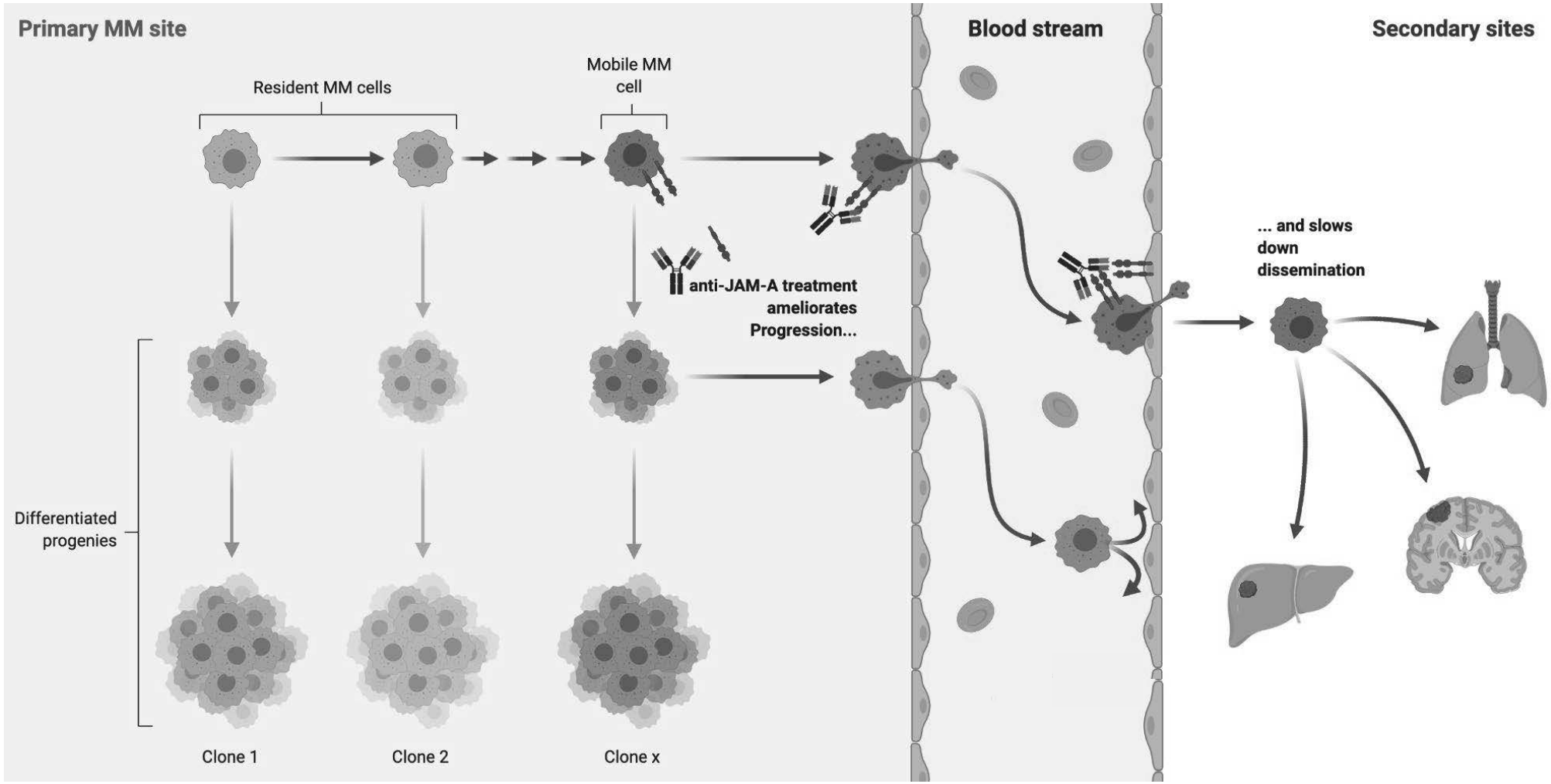
Unpublished data

JAM-A regulation of EMT in MM dissemination as druggable target



- JAM-A as a potential modulator of MM-TME dynamics, anchoring connections, context dependency
- Inhibiting JAM-A could restricts MM progression, potentially influencing EMD progression: a novel theragnostic window

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FORTITher Forschungsverbund Tumordiagnostik für Individualisierte Therapie

ISTITUTO TUMORI "GIOVANNI PAOLO II"
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

SPP 2084 Colonization and interaction of tumor cells in the bone microenvironment
ubone CONSORTIUM

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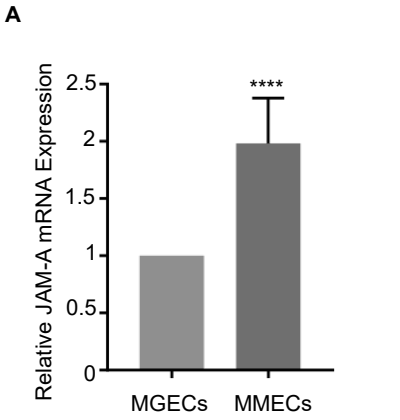
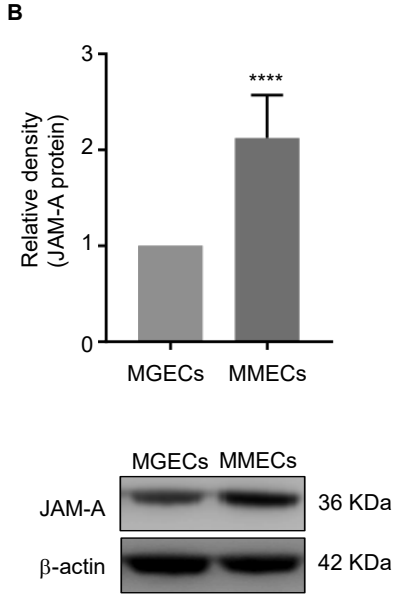
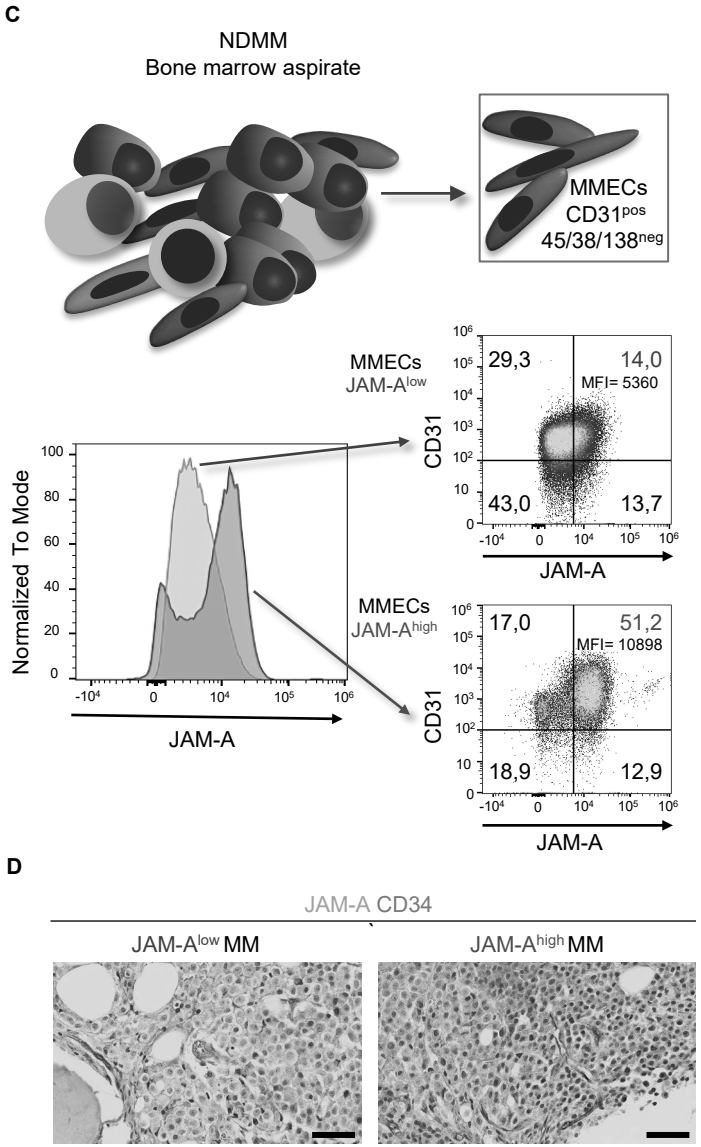
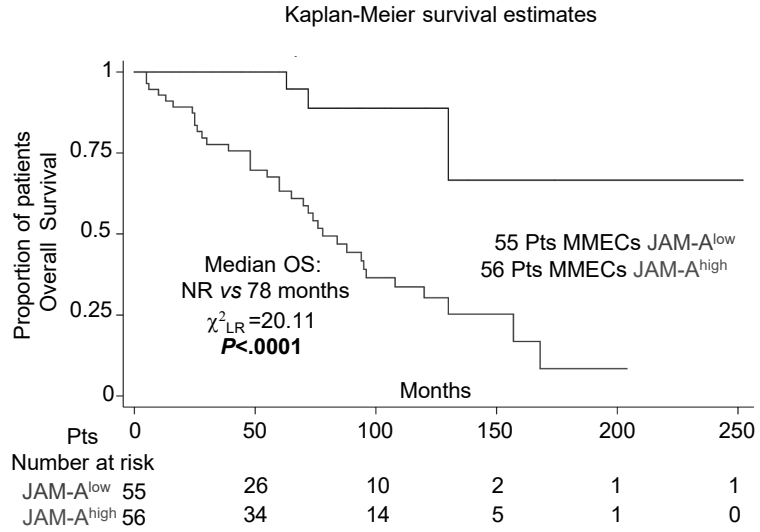
MMRF MULTIPLE MYELOMA Research Foundation

Elevated JAM-A expression on BM primary MM endothelial cells (MMECs) in newly diagnosed patients correlates with poor OS









	*Cox model for Overall Survival			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
MMECs JAM-A surface expression (JAM-A^{high} vs JAM-A^{low})	9.14 (2.80-29.76)	**<0.001**	9.11 (2.79-29.76)	**<0.001**
Bone Lesion (Yes vs No)	1.31 (0.60-2.89)	0.489	-	-
Hb (<10 vs >/-10 g/dL)	1.44 (0.75-2.77)	0.271	-	-
R-ISS **R-Stage I** **R-Stage II** **R-Stage III**	 1 1.37 (0.55-3.39) 2.11 (0.76-5.86)	 0.494 0.149	-	-
Sex (M vs F)	0.58 (0.29-1.13)	0.110	0.65 (0.33-1.30)	0.233
Chronic kidney disease (Yes vs No)	2.04 (1.05-3.96)	**0.033**	2.11 (1.08-4.10)	**0.027**
Age	0.98 (0.94-1.02)	0.542	0.99 (0.95-1.04)	0.984

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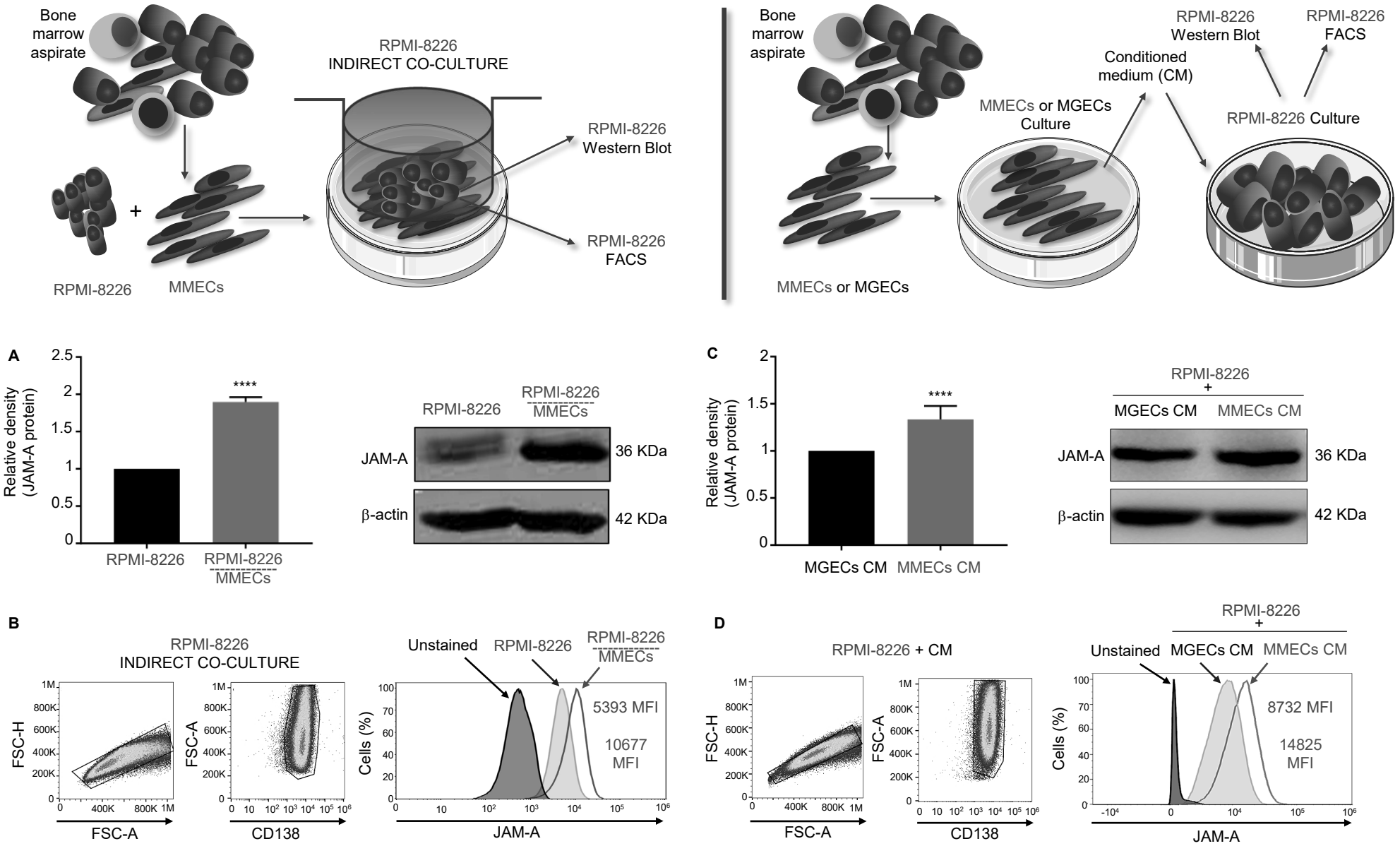
MMECs enhance JAM-A expression on MM-cells



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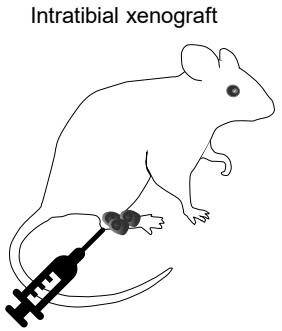
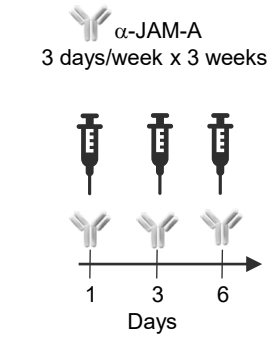
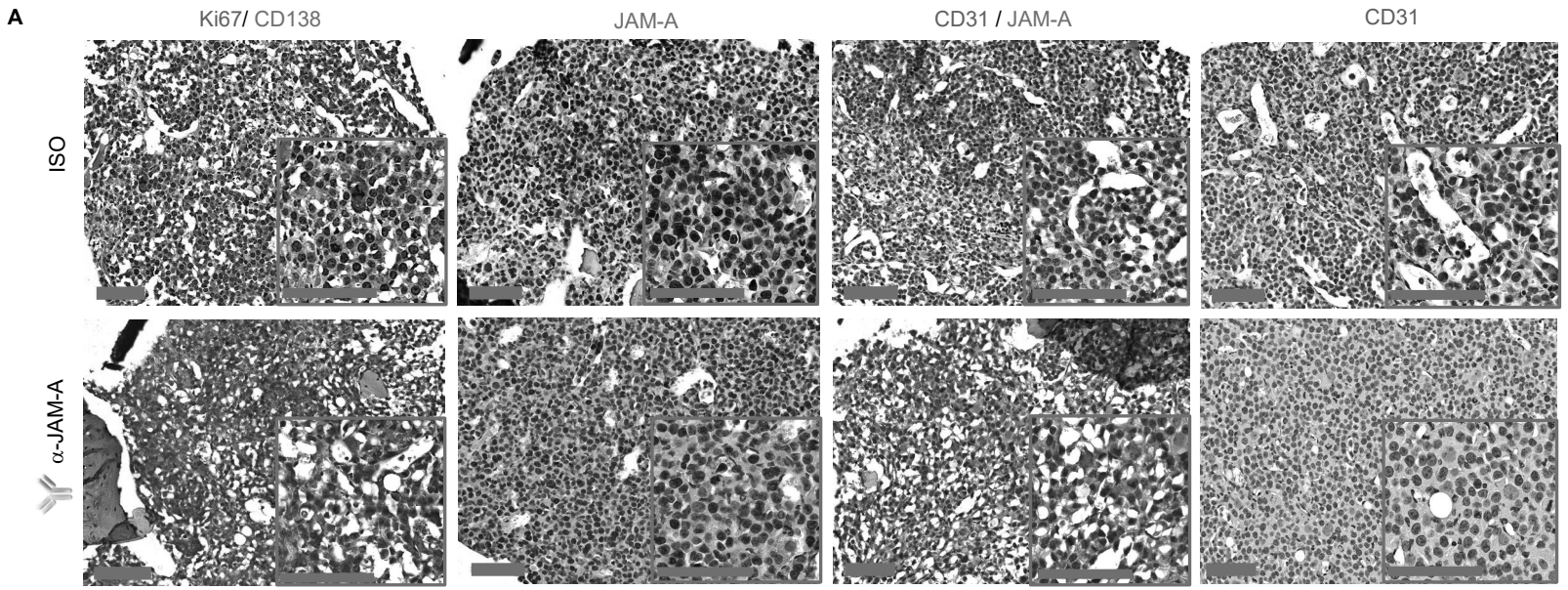
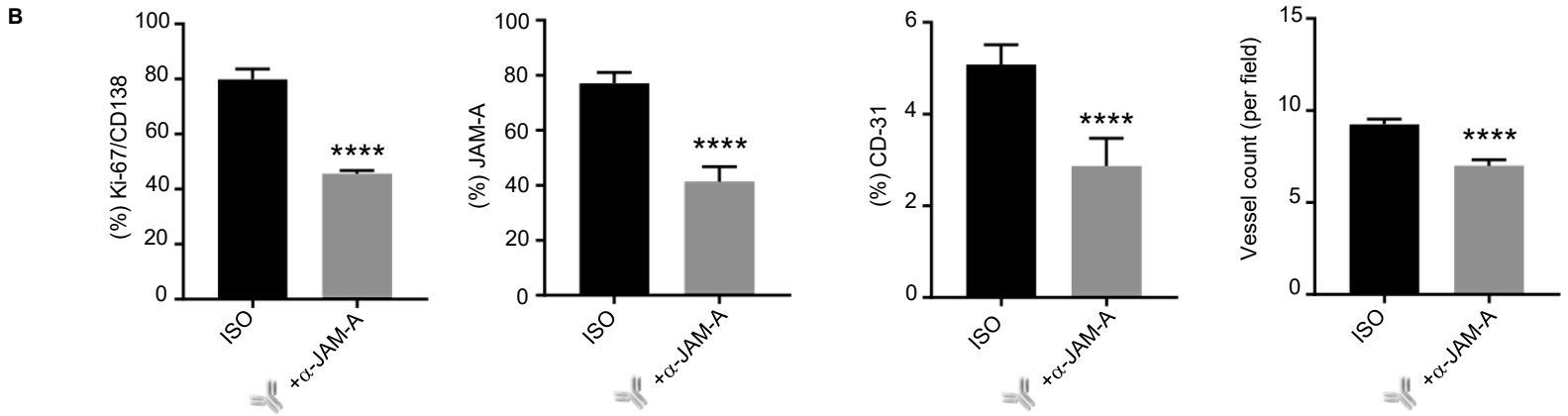
JAM-A inhibition reduces MM proliferation and vasculature in intratibial MM *in vivo* model









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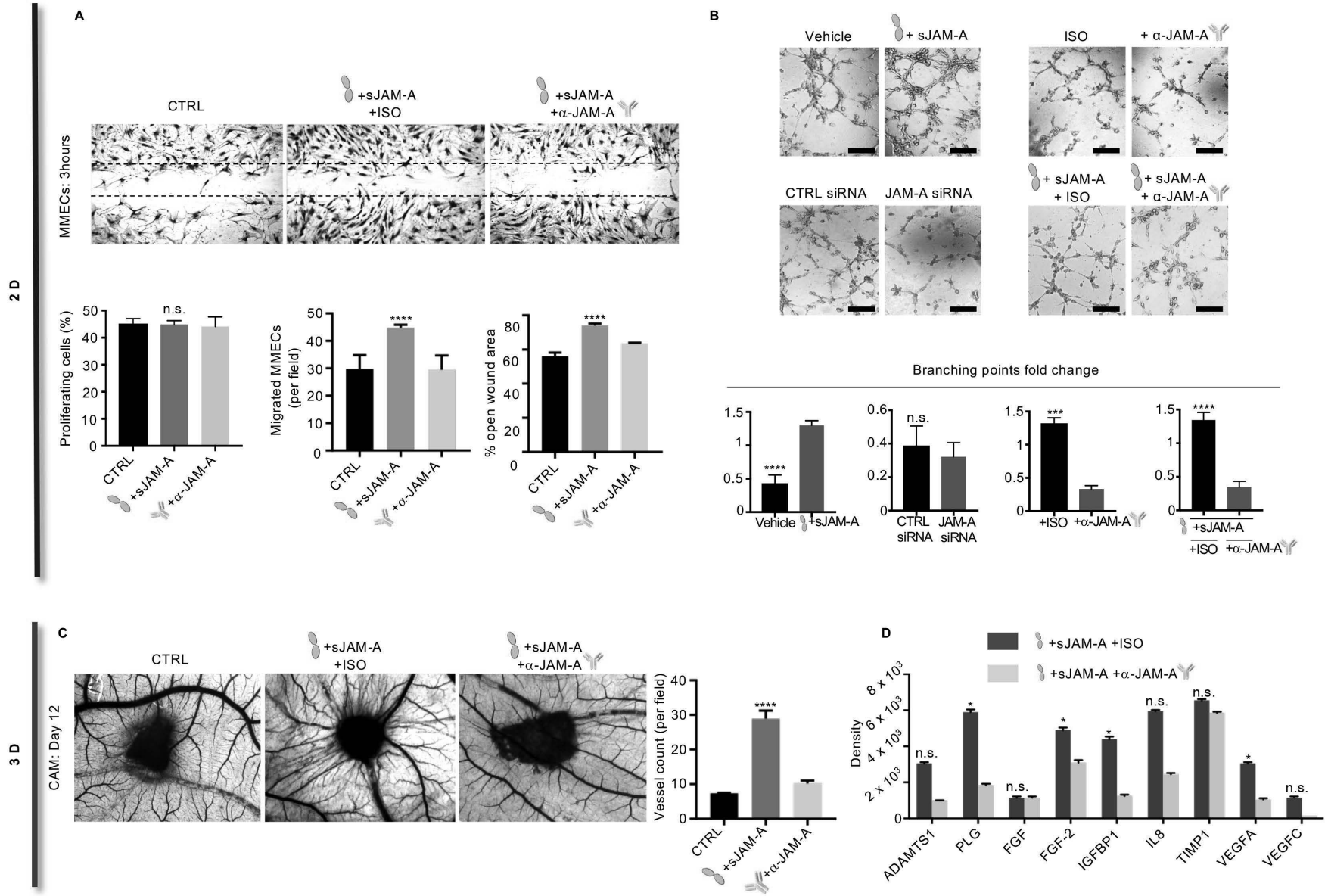
Pivotal role of JAM-A in MM associated angiogenesis in 2D and 3D conditions



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Conclusions

- JAM-A is a potent driver of MM-associated angiogenesis, besides impacting patient's prognosis
- Inhibiting JAM-A restricts angiogenesis in vitro, in embrio and in vivo and MM progression, and influencing EMD progression