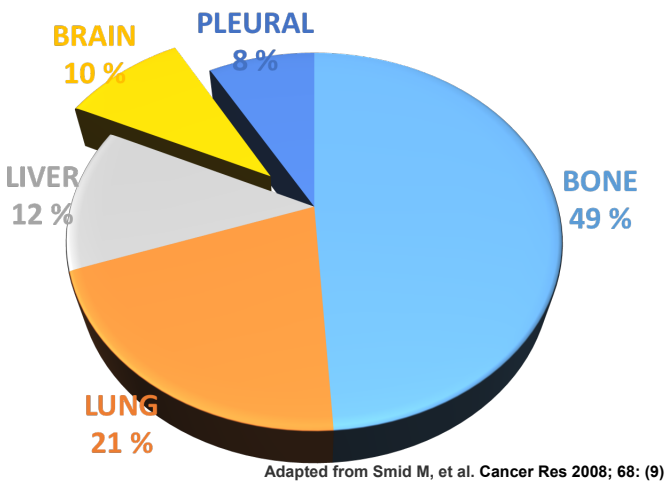


Deciphering the specifically enriched signature associated with breast cancer brain metastasis

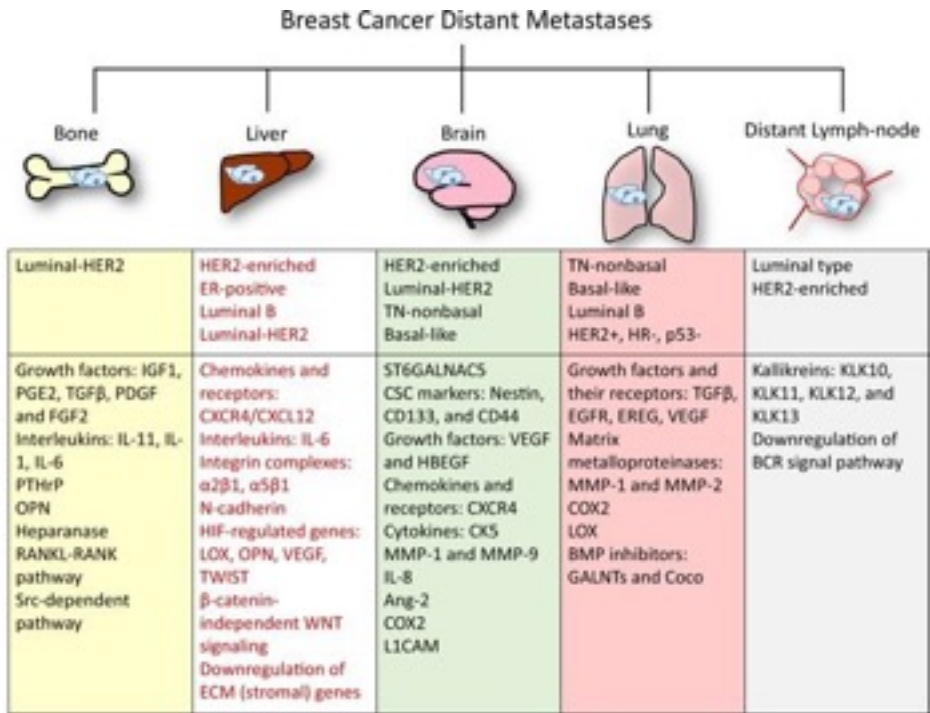
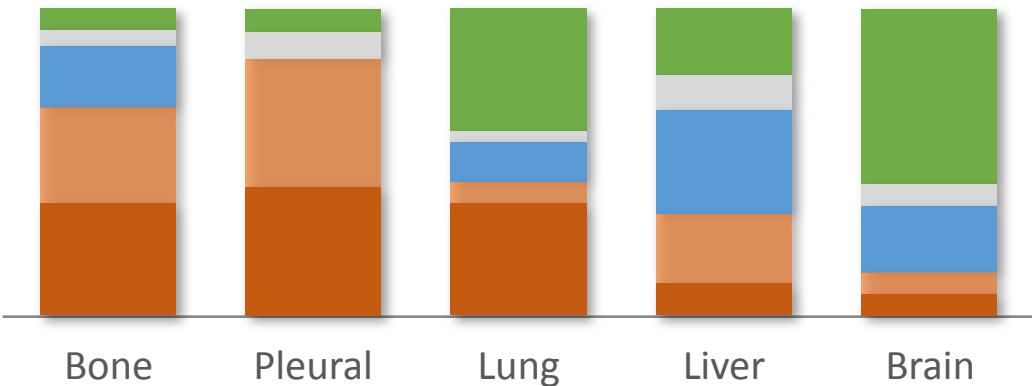
Rita Carvalho
PhD student
rcarvalho@lpatimup.pt



Breast Cancer Metastasis



luminal A luminal B erbb2 normal basal



Adapted from Wenjing Chen et al. Npj Precision Oncology, 2018

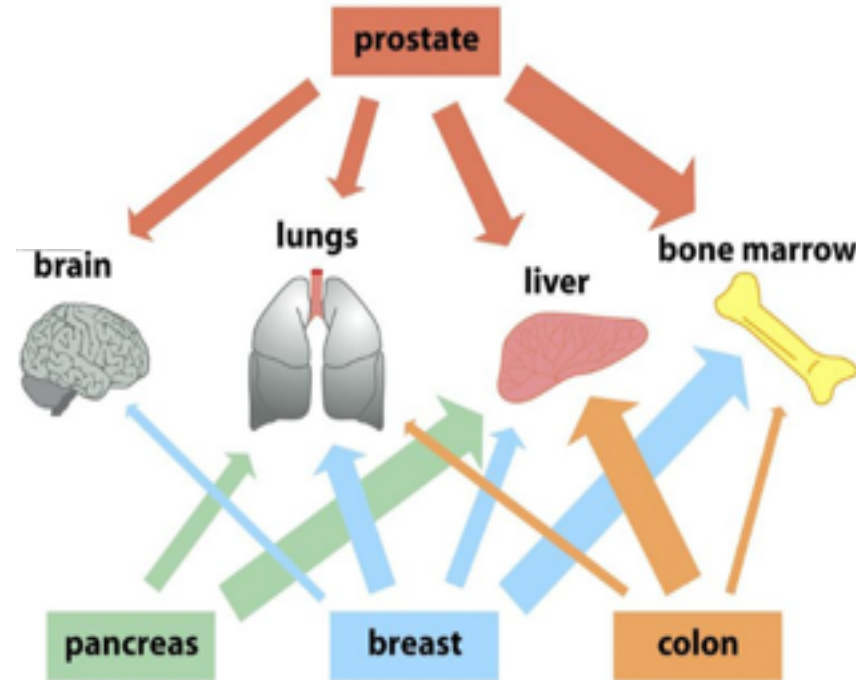
“Seed and soil” Theory

“Seed and soil” theory:

Organ specificity depends on the tumor cell (seed) and on the organ microenvironment at metastatic sites (soil).



STEPHEN PAGET, M.A., F.R.C.S.
(Founder of the Research Defence Society).



“ So, just landing in a tissue is not sufficient for cancer cells to develop a secondary tumor; rather, some property of the tissue itself must sustain the new growth ”

(Paget, 1889, Lancet 1:571)

ARTICLE

doi:10.1038/nature15756

Tumour exosome integrins determine organotropic metastasis

Ayuko Hoshino^{1*}, Bruno Costa-Silva^{1*}, Tang-Long Shen^{1,2*}, Gonçalo Rodrigues^{1,3}, Ayako Hashimoto^{1,4}, Milica Tešić Mark⁵, Henrik Molina⁶, Shinji Kohsaka⁶, Angela Di Giannatale¹, Sophia Ceder⁷, Swarnima Singh¹, Caitlin Williams¹, Nadine Soplog⁸, Kunihiro Uryu⁹, Lindsay Pharmed⁹, Tari King⁹, Linda Bojmar^{1,10}, Alexander E. Davies¹², Yonathan Araso¹, Tuo Zhang¹², Haiying Zhang¹, Jonathan Hernandez^{1,13}, Joshua M. Weiss¹, Vanessa D. Dumont-Cole¹⁴, Kimberly Kramer¹⁴, Leonard H. Wexler¹⁴, Aru Narendran¹⁵, Gary K. Schwartz¹⁶, John H. Healey¹⁷, Per Sandstrom¹⁸, Knut Jørgen Labori¹⁸, Elin H. Kure¹⁸, Paul M. Grandgenett²⁰, Michael A. Hollingsworth²⁰, Maria de Sousa^{1,3}, Sukhwinder Kaur²¹, Maneesh Jain²¹, Kavita Mallia²¹, Surinder K. Batra²¹, William R. Jarnagin¹², Mary S. Brady^{1,22}, Øystein Fodstad^{22,24}, Volkmar Müller²⁵, Klaus Pantel²⁶, Andy J. Minn²⁷, Mina J. Bissell¹⁰, Benjamin A. Garcia²⁸, Yibin Kang^{29,30}, Vinagolu K. Rajasekhar³¹, Cyrus M. Ghajar³², Irina Matei¹, Hector Peinado^{1,12}, Jacqueline Bromberg^{14,23} & David Lyden^{1,14}



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Author manuscript

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Nat Cell Biol. 2015 June ; 17(6): 816–826. doi:10.1038/ncb3169.

Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver

Bruno Costa-Silva¹, Nicole M. Aiello², Allyson J. Ocean³, Swarnima Singh¹, Haiying Zhang¹, Basant Kumar Thakur^{1,4}, Annette Becker¹, Ayuko Hoshino¹, Milica Tešić Mark⁵, Henrik Molina⁶, Jenny Xiang⁶, Tuo Zhang⁶, Till-Martin Theilen¹, Guillermo Garcia-Santos¹, Caitlin Williams¹, Yonathan Araso¹, Yujie Huang¹, Gonçalo Rodrigues^{1,7}, Tang-Long Shen⁸, Knut Jørgen Labori⁹, Inger Marie Bowitz Lothe^{10,11}, Elin H. Kure¹¹, Jonathan Hernandez¹², Alexandre Doussot¹², Saya H. Ebbesen¹, Paul M. Grandgenett¹³, Michael A. Hollingsworth¹³, Maneesh Jain¹⁴, Kavita Mallia¹⁴, Surinder K. Batra¹⁴, William R. Jarnagin¹², Robert E. Schwartz¹⁵, Irina Matei¹, Héctor Peinado^{1,16}, Ben Z. Stanger^{2,19}, Jacqueline Bromberg^{17,19}, and David C. Lyden^{1,18,19}



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Nat Med. Author manuscript; available in PMC 2018 March 18.

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Nat Med. 2017 October ; 23(10): 1176–1190. doi:10.1038/nm.4400.

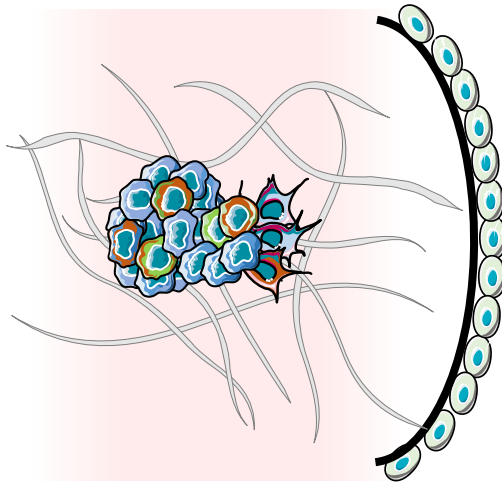
KLF4-dependent perivascular cell plasticity mediates pre-metastatic niche formation and metastasis

Meera Murgai¹, Wei Ju¹, Matthew Eason¹, Jessica Kline¹, Daniel Beury¹, Sabina Kaczanowska¹, Markku M Miettinen², Michael Kruhlak³, Haiyan Lei¹, Jack F Shern¹, Olga A. Cherepanova^{4,5}, Gary K Owens⁴, and Rosandra N Kaplan¹

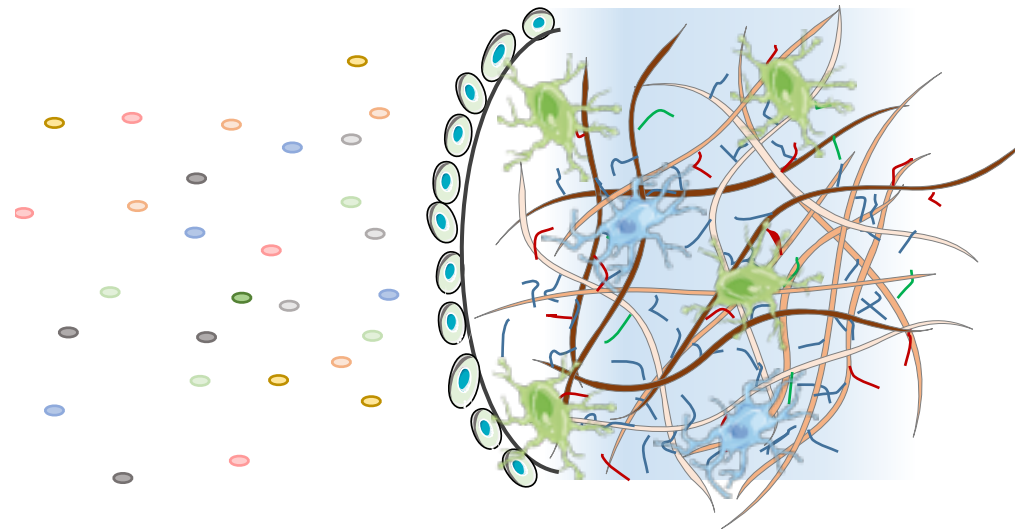
AIM

We aim to disclose the specifically enriched **secretome signature** associated with breast cancer brain metastasis and elucidate the paracrine communication between cancer cells and brain pre-metastatic niche.

Brain Metastatic Breast Cancer Cells

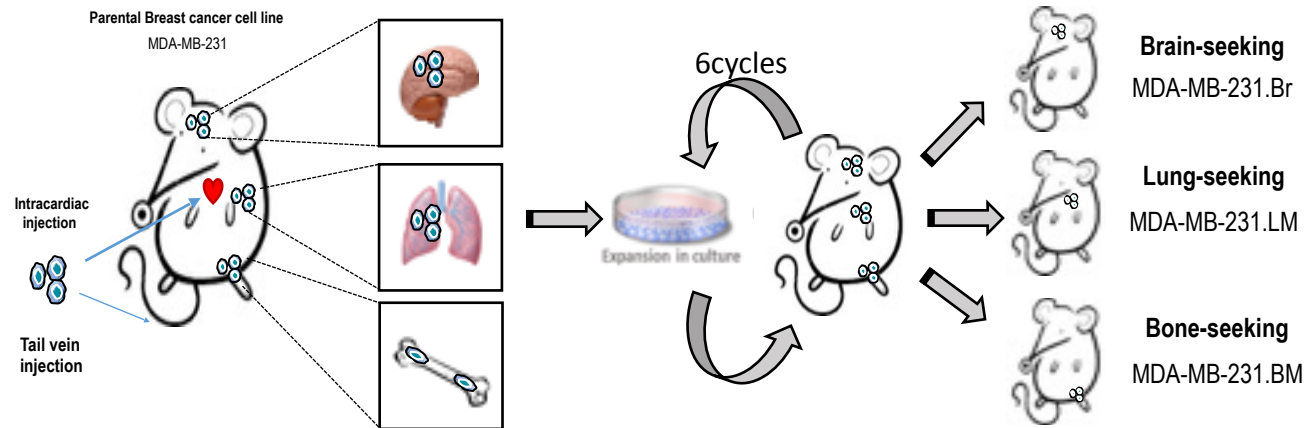


Brain Pre-Metastatic Niche



Specifically enriched genes in Breast Cancer Metastatic Cells

Breast Cancer Metastatic Cell Model



[Genes that mediate breast cancer metastasis to the brain.](#)

Bos Pd et al. Nature. 2009 Jun 18;459(7249)

[Genes that mediate breast cancer metastasis to lung.](#)

Minn AJ, et al Nature. 2005 Jul 28;436(7050):518-24.

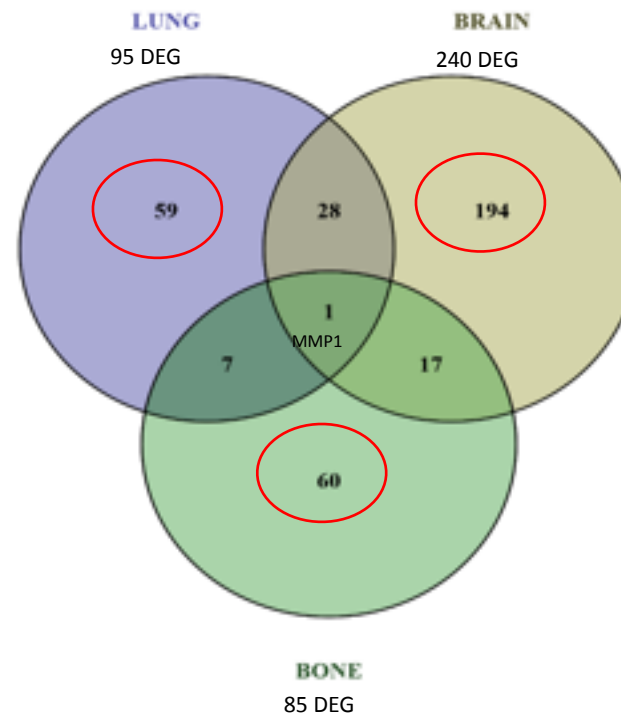
[A multigenic program mediating breast cancer metastasis to bone.](#)

Kang Y et al. Cancer Cell. 2003 Jun;3(6):537-49.

Provided by Massagué J

Gene ontology signatures

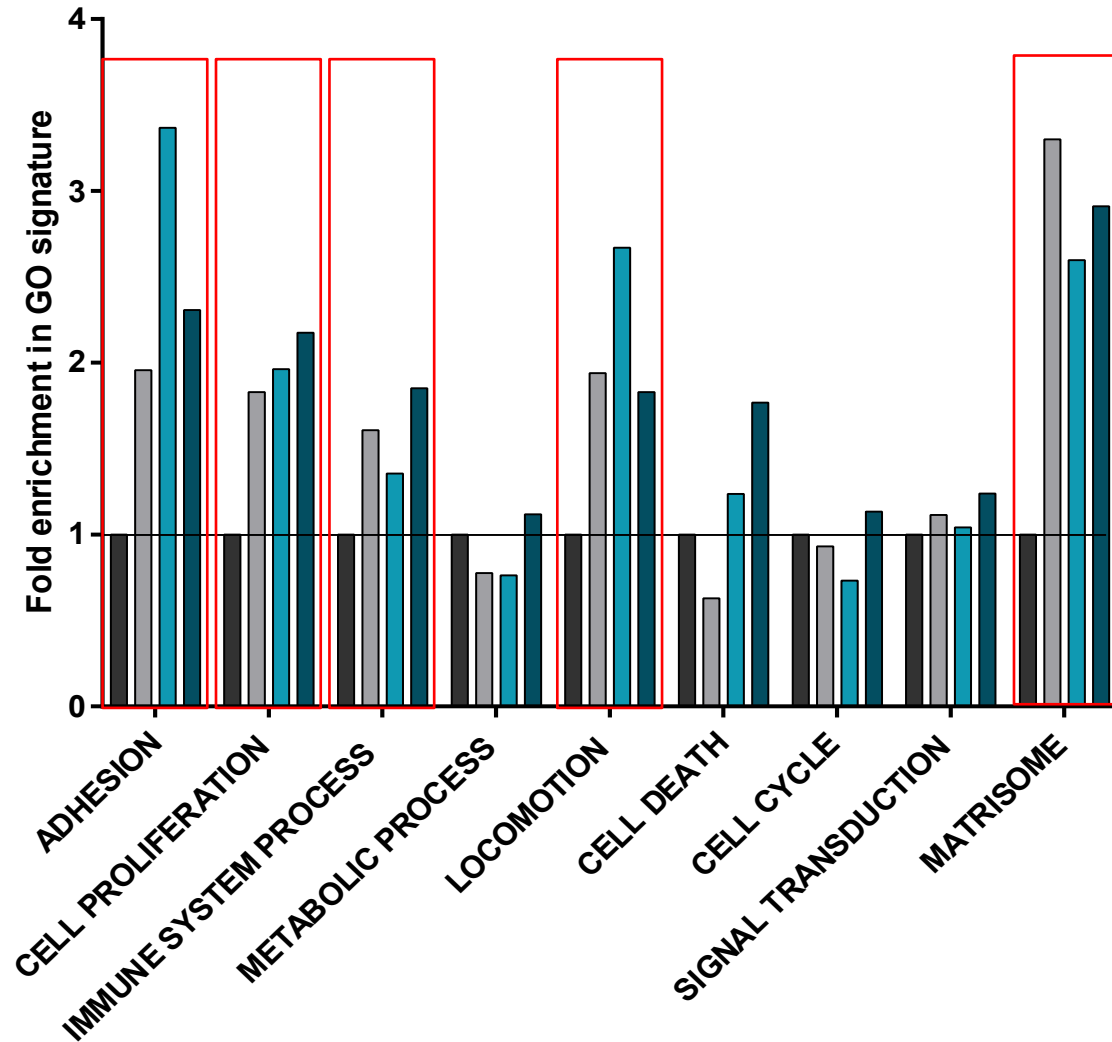
Biological Adhesion
Cell proliferation
Immune system process
Metabolic process
Locomotion
Cell death
Cell cycle
Signal transduction
Matrisome



Significantly deregulated genes (DEG)

**231 metastatic breast cancer cells
vs.
231 parental breast cancer cells**

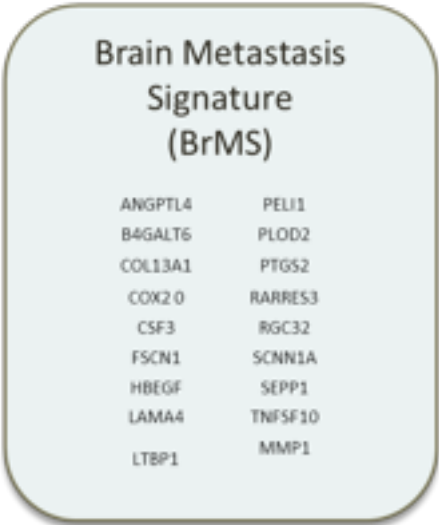
In Silico - Gene Ontology Signature Profile of Breast Cancer Metastatic Cells



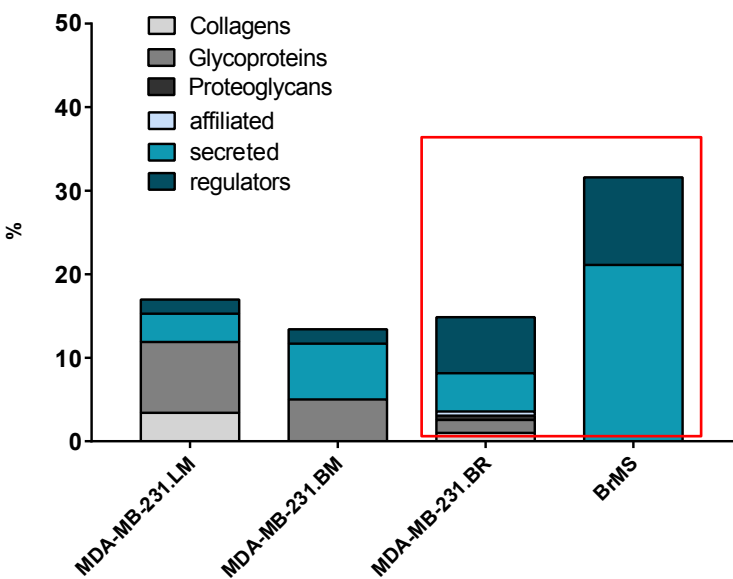
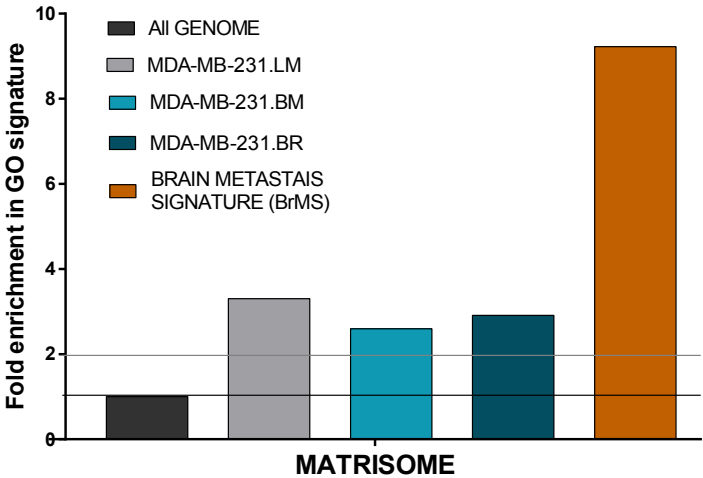
Breast cancer metastatic cells show an enrichment in genes associated with:

- **ADHESION**
- **CELL PROLIFERATION**
- **MATRISOME**
- **IMMUNE SYSTEM**
- **LOCOMOTION**

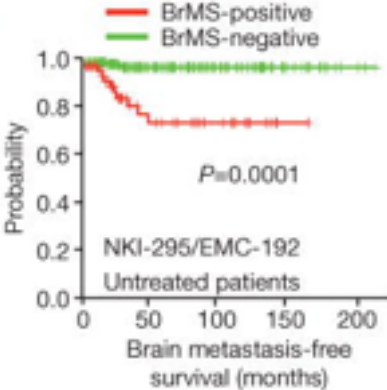
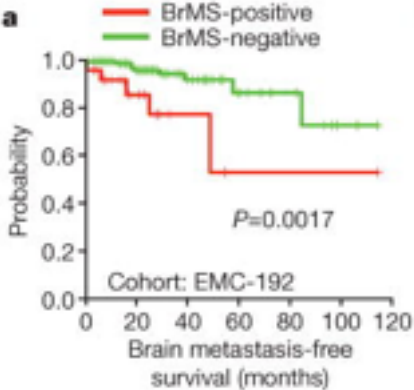
Matrisome profile and ECM remodelling enrichment in brain metastatic breast cancer cells



Bos Pd et al. Nature. 2009 Jun 18;459(7249)

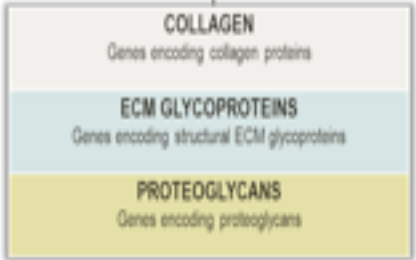
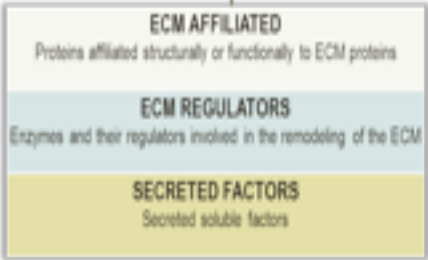


Secreted factors and ECM regulators are crucial for ECM remodeling



MATRISOME ASSOCIATED

genes encoding ECM-associated proteins
including ECM-affiliated proteins, ECM regulators
and secreted factors



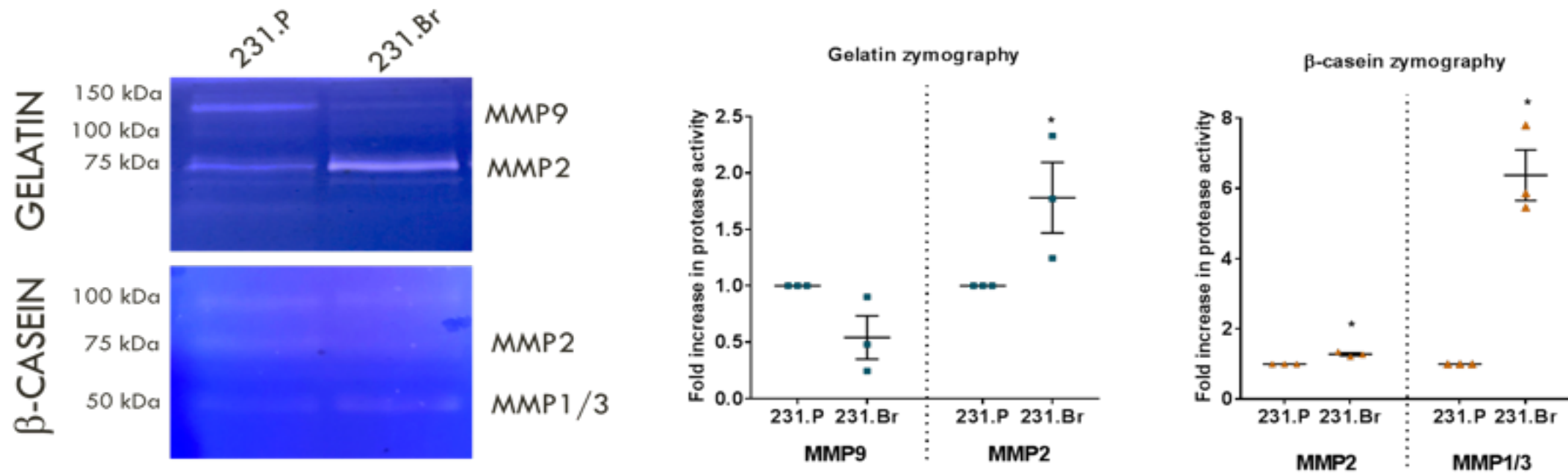
REGULATORS

ADAMs
CST
CTS
HYAL
LOXL
MMPs
SERPIN
TGM

SECRETED

ANGPT	IFNA
BMP	IL
CCL	NRG
CRHBP	PDGF
CSF	S100
CXCL	TGF
EGFL	TNFSF
FGF	VEGF
GDF	WNT

Protease activity in brain metastatic breast cancer cells



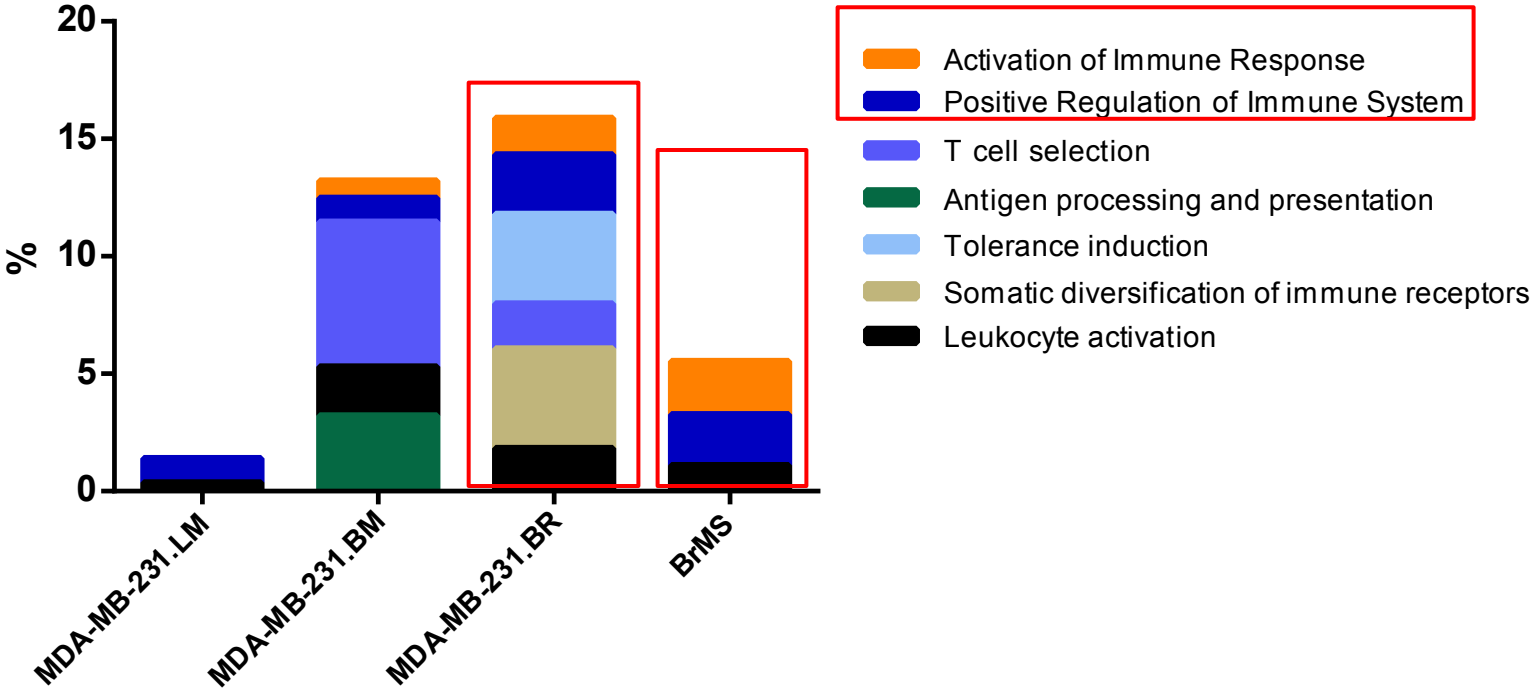
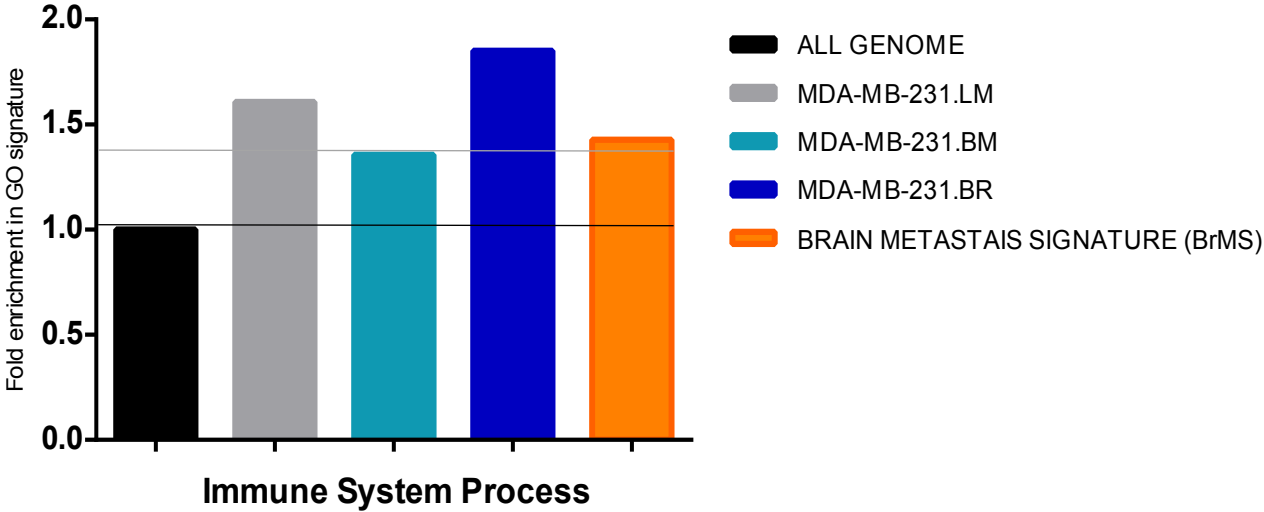
Gelatin and b-casein zymography to detect protease activity in the conditioned medium from parental (231.P) and brain tropic (231.Br) breast cancer cells cultured in collagen type I.

Immune system process genes enrichment in metastatic breast cancer cells

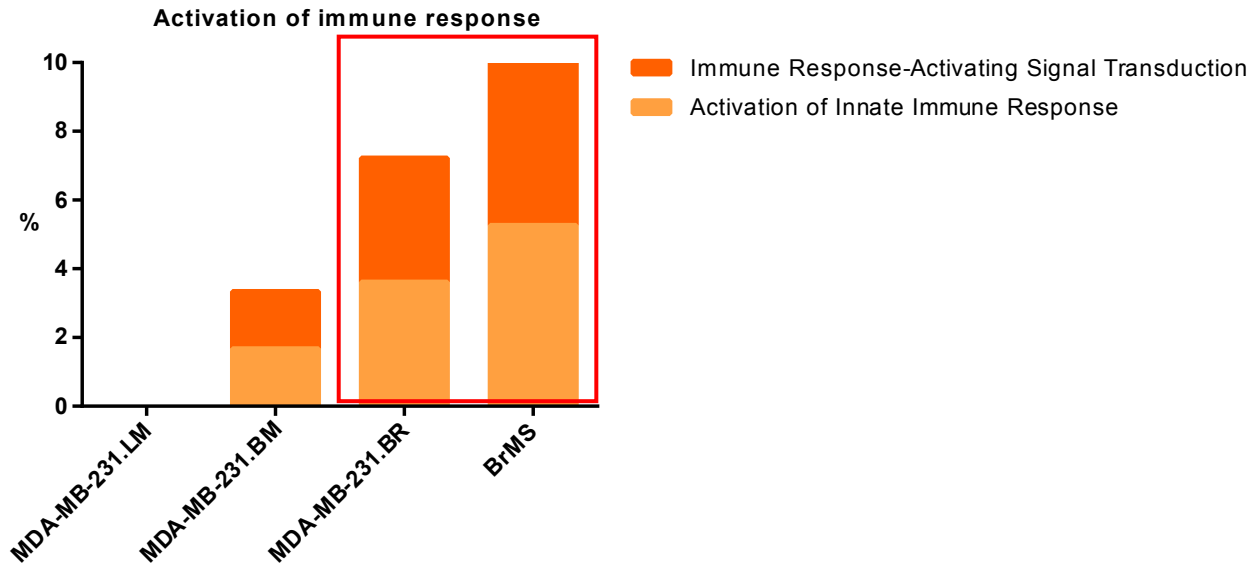
Brain Metastasis Signature (BrMS)

ANGPTL4	PELI1
B4GALT6	PLOD2
COL13A1	PTGS2
COX20	RARRES3
CSF3	RGC32
FSCN1	SCNN1A
HBEGF	SEPP1
LAMA4	TNFSF10
LTBP1	MMP1

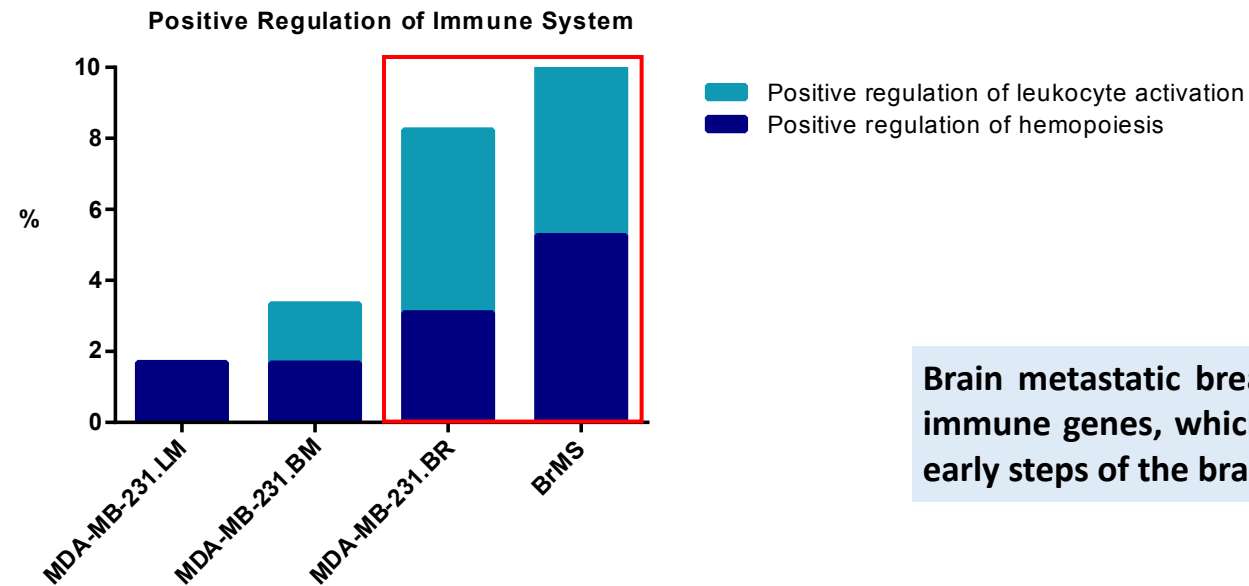
Bos Pd et al. Nature. 2009 Jun 18;459(7249)



Immune system process enrichment in brain metastatic breast cancer cells



Activation of Immune Response	Positive Regulation of Immune System
Immune Response – Activating signal transduction	Positive regulation of leukocyte activation
Activation of innate immune response	Positive Regulation of hemopoiesis

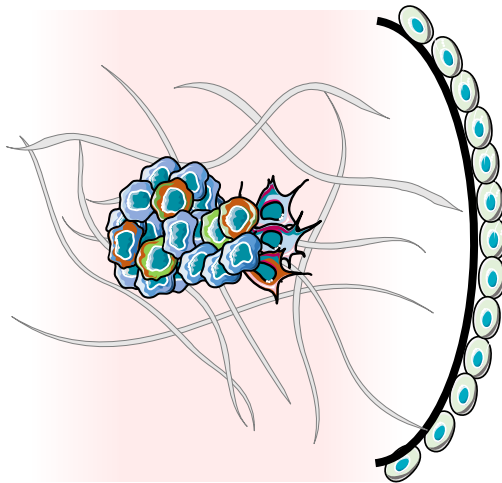


Brain metastatic breast cancer cells and BrMS show a significant enrichment of immune genes, which can point for the importance of microglia activation in the early steps of the brain metastatic cascade.

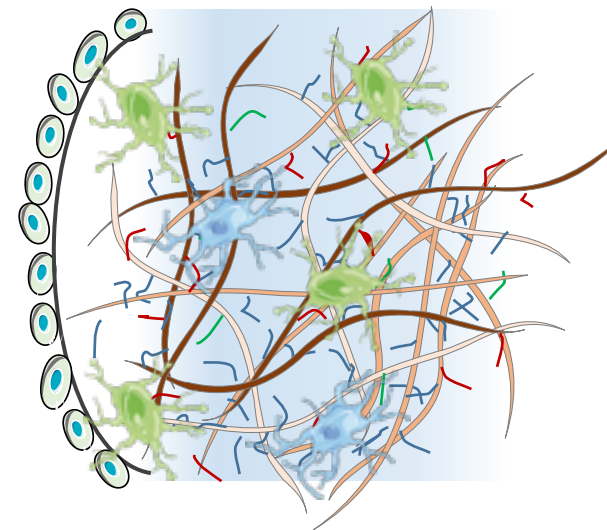
Conclusion

- Brain metastatic cells have an enrichment in matrisome associated regulators, that are crucial for ECM remodeling.
- The brain metastatic cells show an enrichment in genes associated with immune system, that are involved in the activation of microglia and neuroinflammation which occurs in the early steps of the brain metastatic cascade.

Brain Metastatic Breast Cancer Cells



Brain Pre-Metastatic Niche



Brain tissue
remodeling

Extracellular vesicles or
soluble factors?





EPIC GROUP

Joana Paredes
Ana Ribeiro
Bárbara Sousa
Joana Pereira
Mónica Oliveira
André Vieira
Maria Rita
Rita Canário
Carolina Noronha
Raquel Seruca

