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Activated Leukocyte cell adhesion molecule (ALCAM) as a potential MRI biomarker for detection of brain metastases

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Alexandr A. Khrapitchev, Nicola R. Sibson

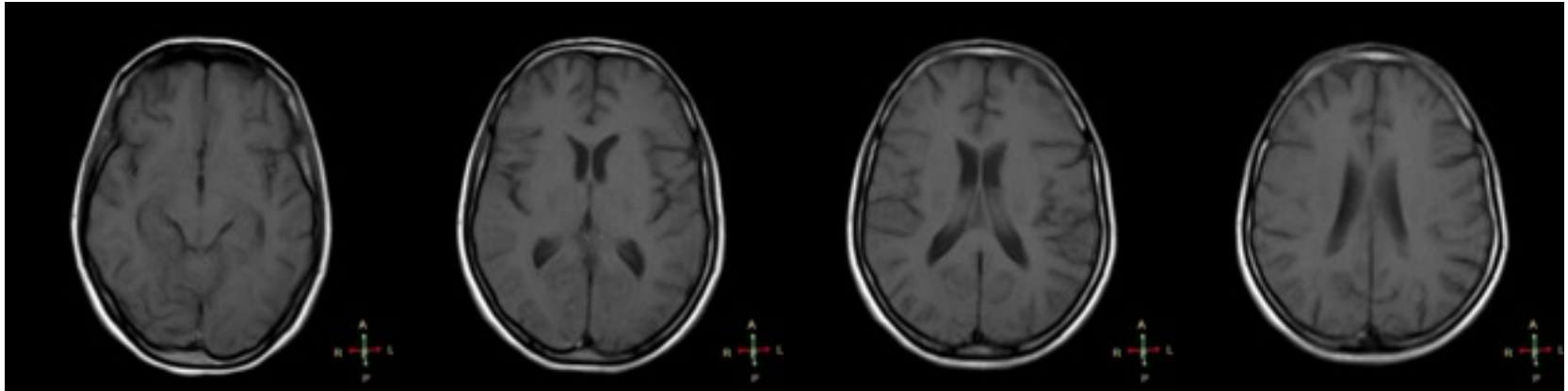
Department of Oncology, University of Oxford, UK

8th Annual Brain Metastases Congress

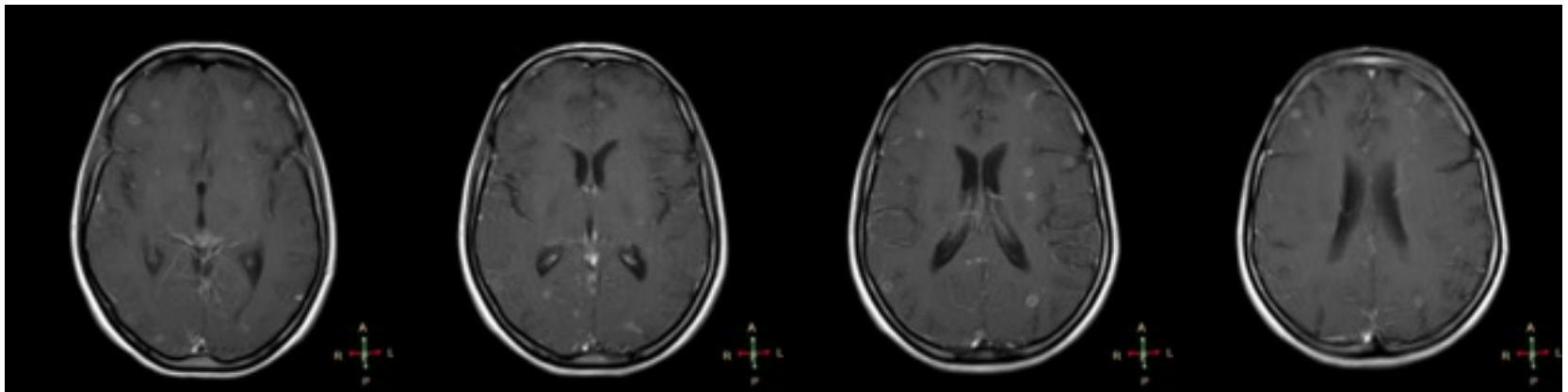
22nd September 2018

Case study: breast cancer brain metastases

T_1 - pre contrast



T_1 - post contrast

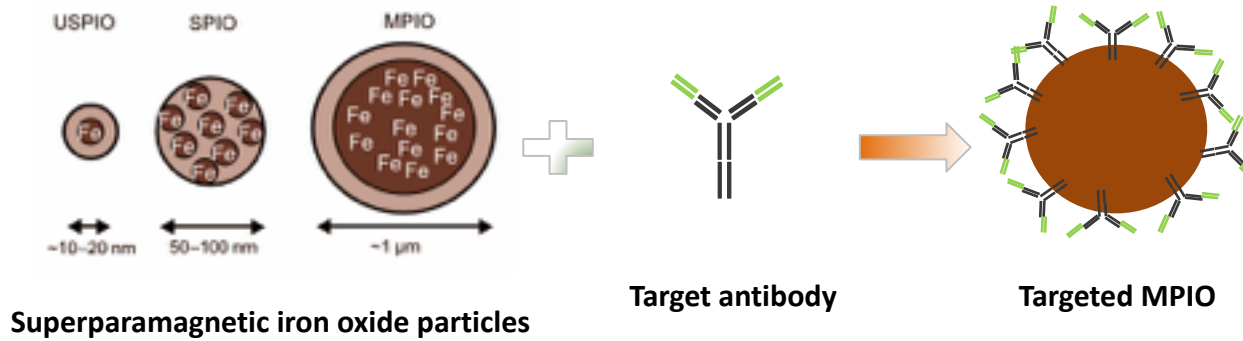


Case courtesy of Dr Ahmed Abdrabou, Radiopaedia.org, rID: 25497

Limitations of conventional MRI:

- Often identifies late-stage of disease which is beyond therapy (>5mm diameter) → **Early detection**
- Limited information about cellular and molecular level → **Identify specific molecular process**

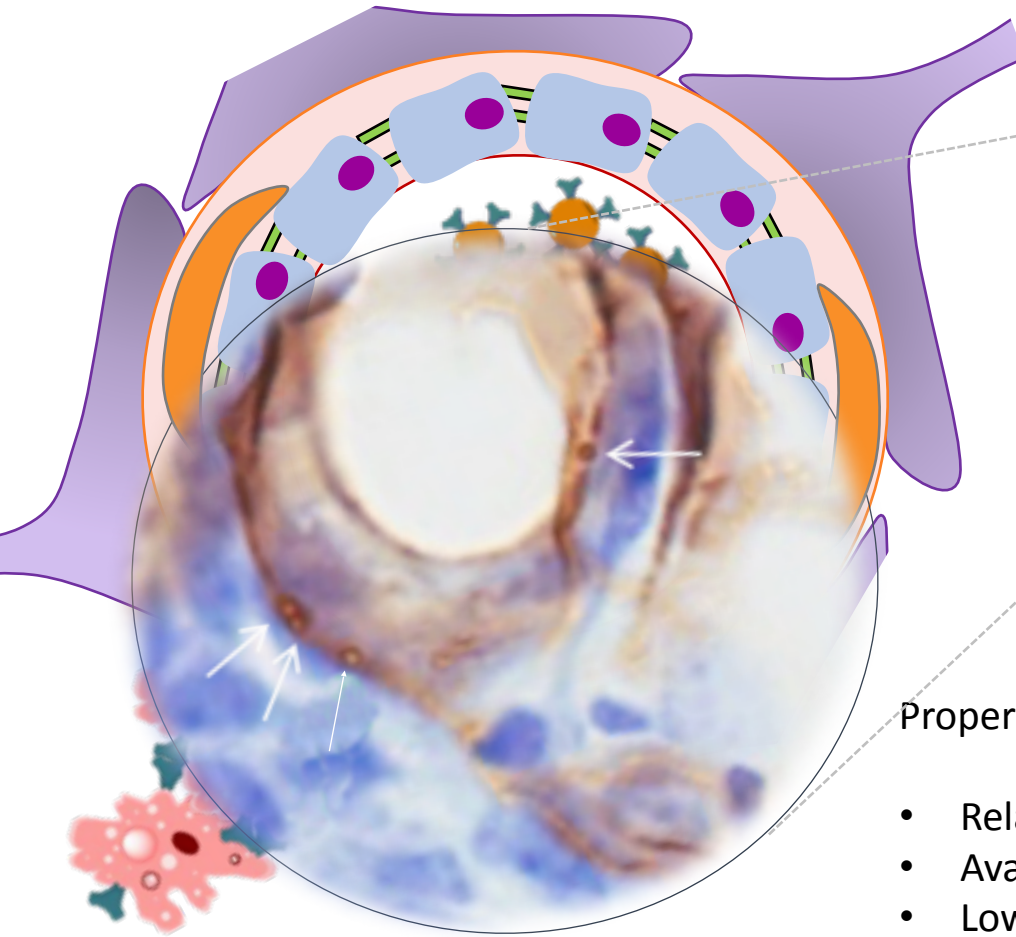
Detection of brain metastases using targeted molecular imaging



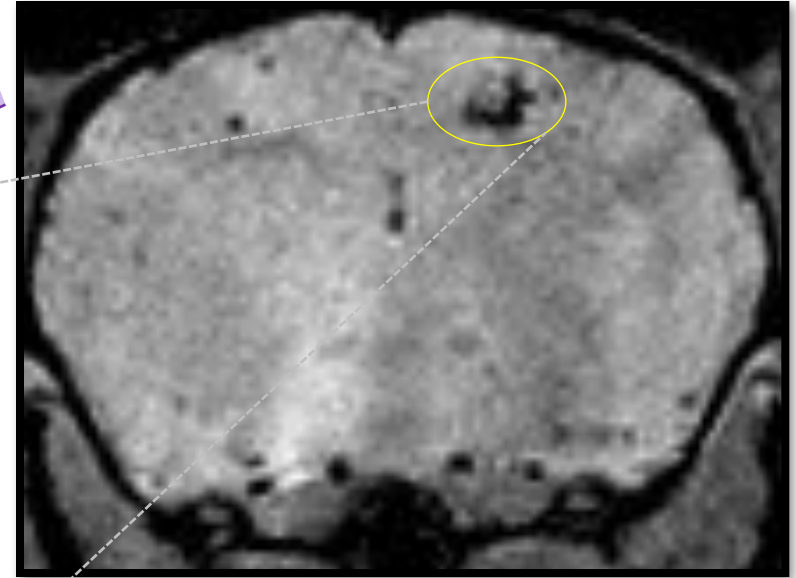
Modo et al. Mol imaging 2005

Detection of brain metastases using targeted molecular imaging

Blood brain barrier



Metastatic brain lesion

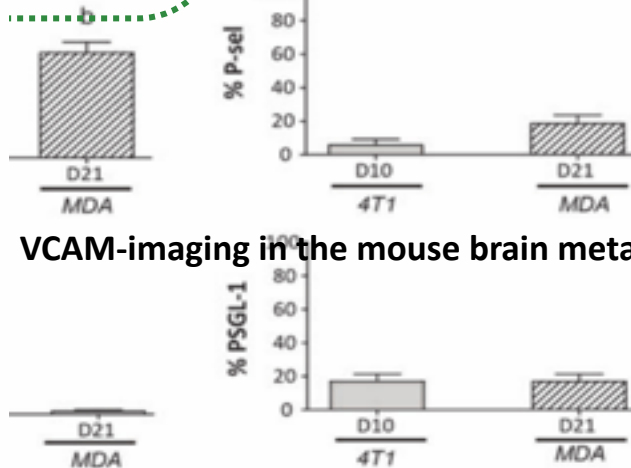
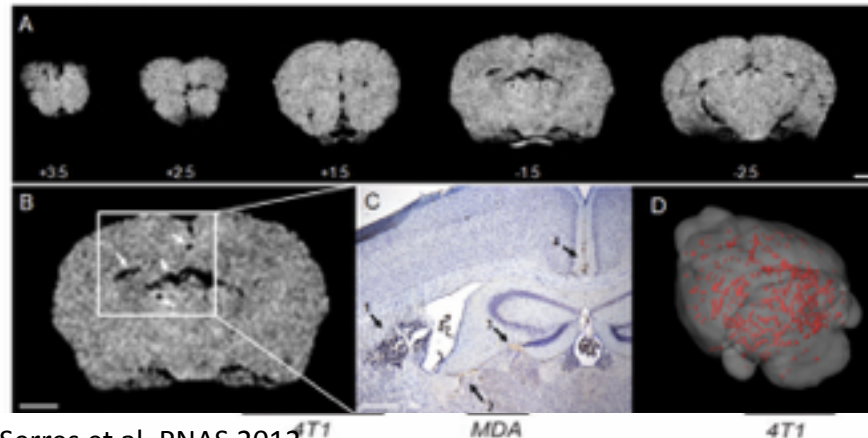
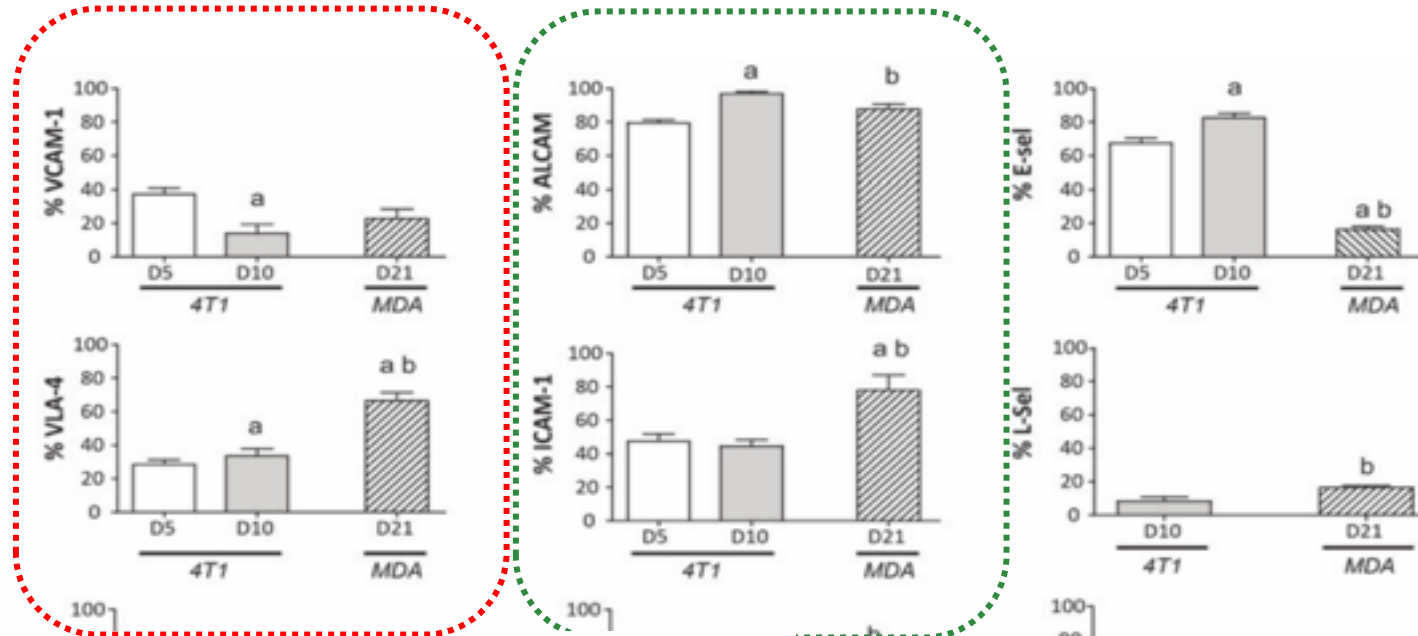


Properties of a suitable *in vivo* MRI biomarker :

- Relative abundance at early stages of disease
- Available to the ligand outside the CNS parenchyma
- Low or absent constitutive expression on healthy cells

Functional role of endothelial adhesion molecules in the early stages of brain metastasis

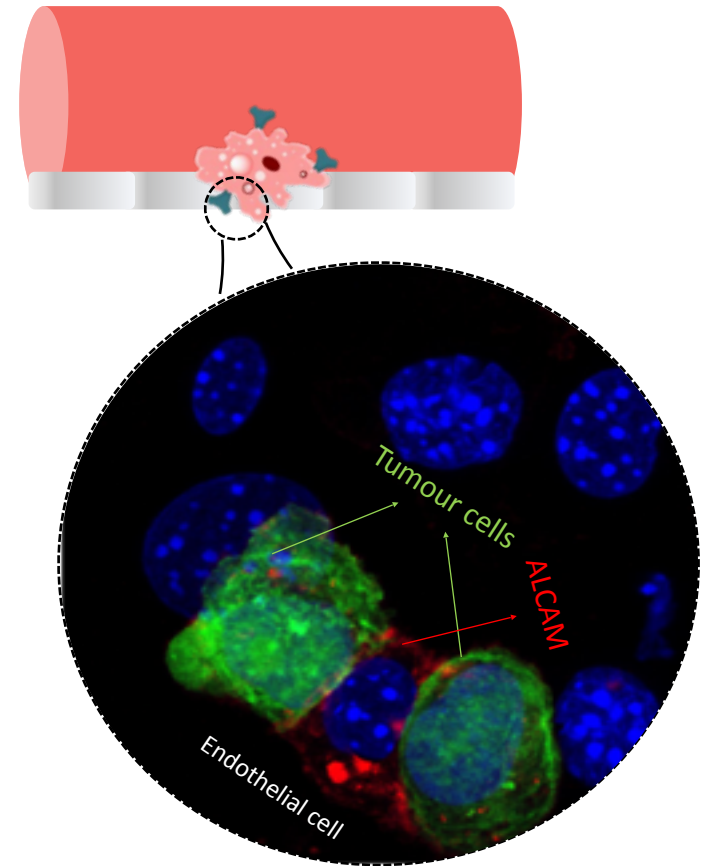
Sarmiento-soto et al. Neuro-Onc 2014



VCAM-imaging in the mouse brain metastases model

Activated cell adhesion molecule (ALCAM) and metastasis

- ALCAM (CD166, MEMD) is a part of cell surface immunoglobulin superfamily
- Involves in both homotypic (ALCAM-ALCAM) and heterotypic (ALCAM-CD6)
- Has a role in cell adhesion/migration



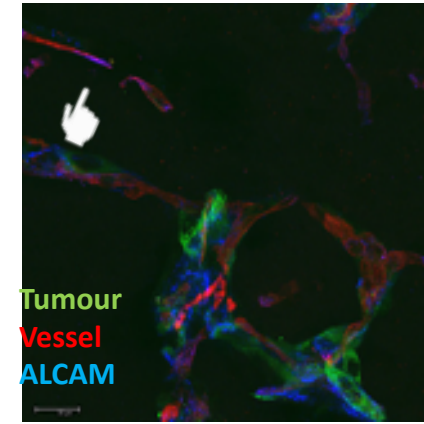
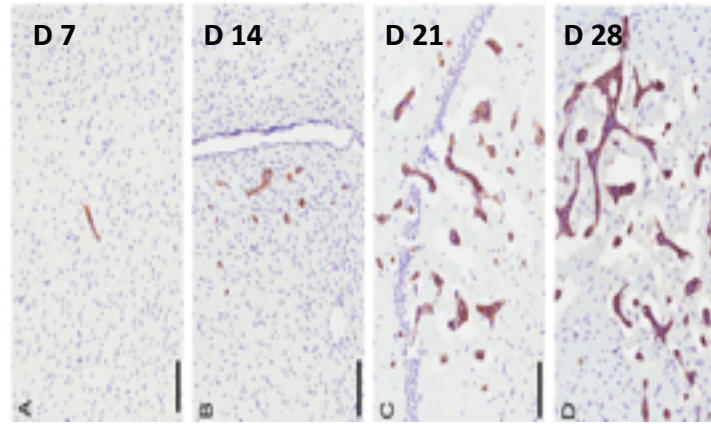
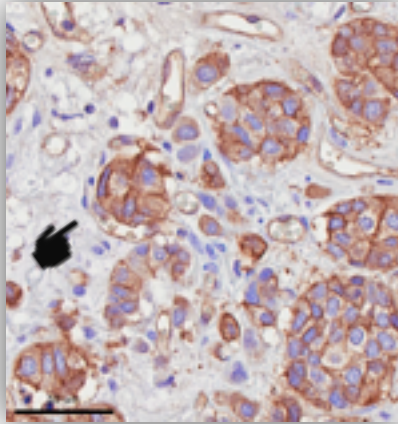
Homotypic ALCAM-ALCAM interaction

ALCAM expression in brain metastases samples with different origin

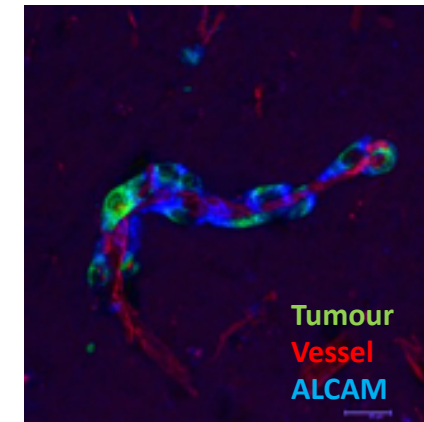
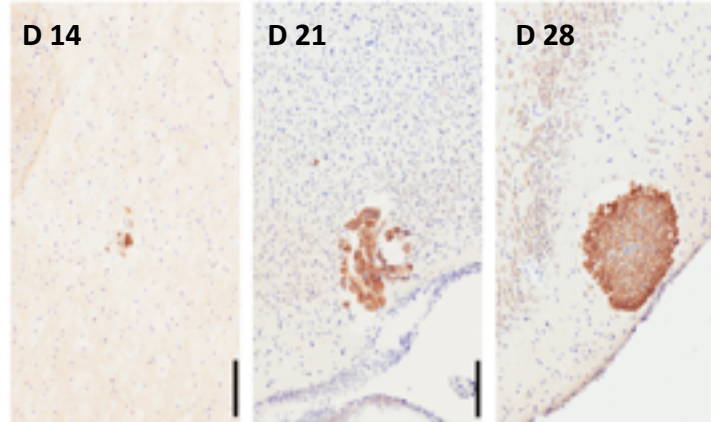
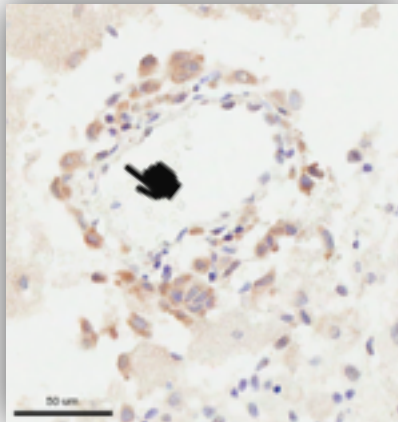
Human brain metastasis biopsy

Mouse brain metastases model

Breast

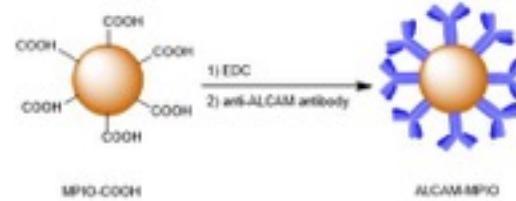


Melanoma

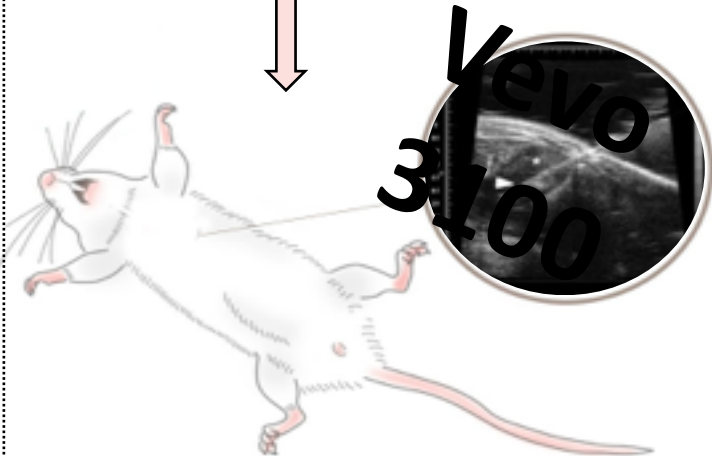
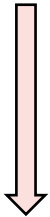


- ALCAM is present **at early stages** of brain metastasis formation
- ALCAM is expressed on tumour associated **vessels**
- ALCAM is **absent** on healthy cells

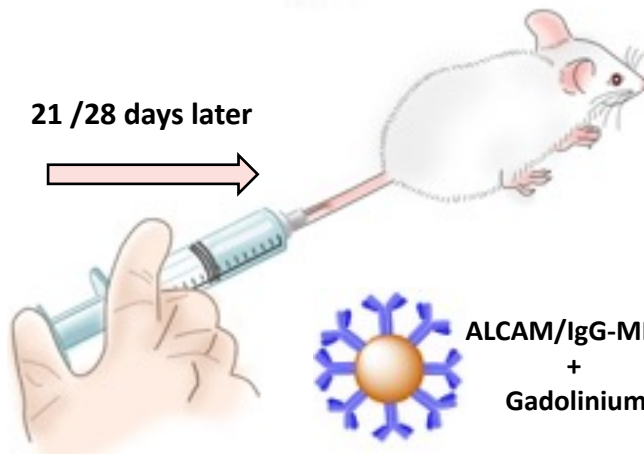
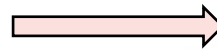
Brain metastases model experimental plan



- MDA-MB-231-Br
- H1-DL2



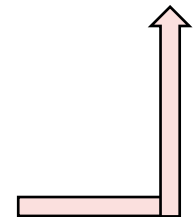
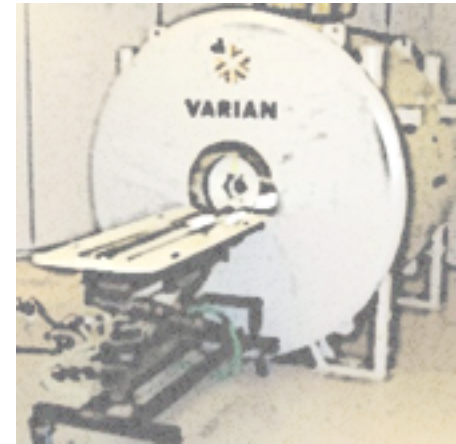
21 / 28 days later



ALCAM/IgG-MPIO
+
Gadolinium

7.0 T magnet

- T_2^*W MGE3D
TR/TE/TE₂ = 48.8/4.0/7.0 ms,
6 echoes , 30 min
- T_1W spin echo multi-slice,
pre/post Gd



ALCAM-MPIO imaging in brain metastases models

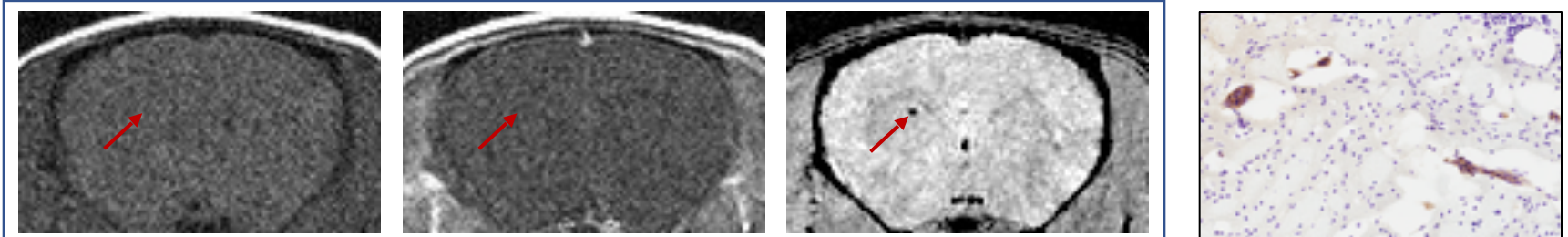
T₁W-Pre Gd

T₁W-Post Gd

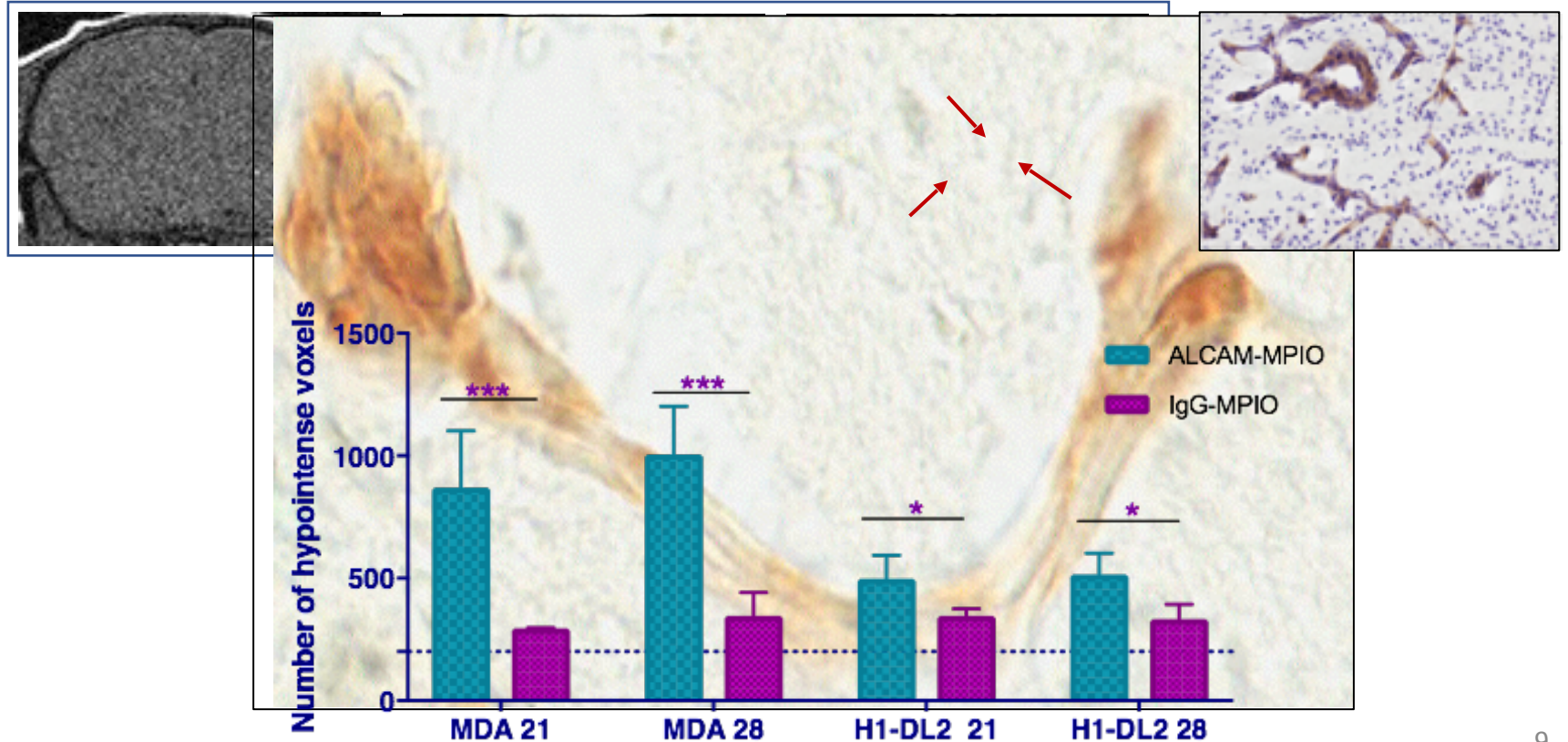
MGE3D

ALCAM/Cresyl violet

Day 21



Day 28





Conclusions

- ❖ ALCAM is up-regulated on vessels associated with brain metastases.
- ❖ ALCAM-MPIO contrast agent enables detection of breast cancer brain metastases at early stages of development with no evidence of gadolinium enhancement.
- ❖ Minimal contrast effects from IgG-MPIO in control group indicates high specificity of ALCAM-MPIO.
- ❖ Next, ALCAM would be evaluated in lung (SEBTA-001) brain metastases model.
- ❖ Earlier detection of brain metastases may yield substantial gains for both the application of current therapies and the development of new metastasis-inhibiting agents.

Experimental neuroimaging group members

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Dr Francisco Perez-Balderas

Dr Luca Bau

Vinton Cheng

Axel de Bernardi



Oxford-Radcliffe scholarship



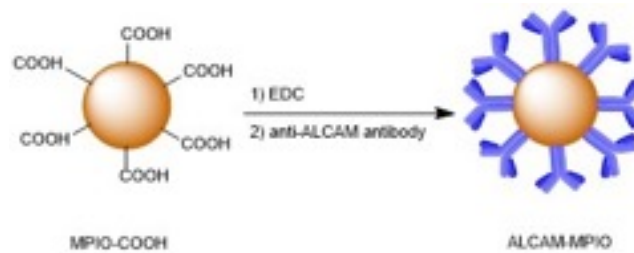
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Morgan Ray Schweitzer

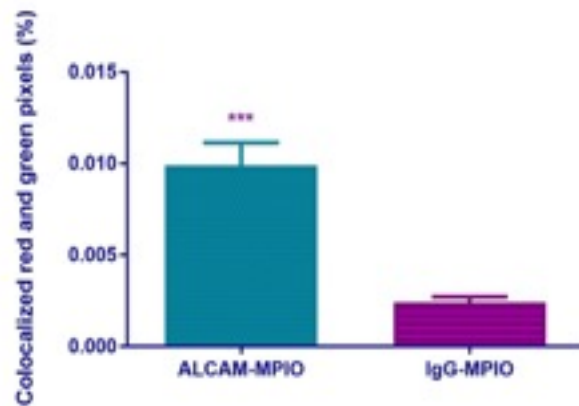
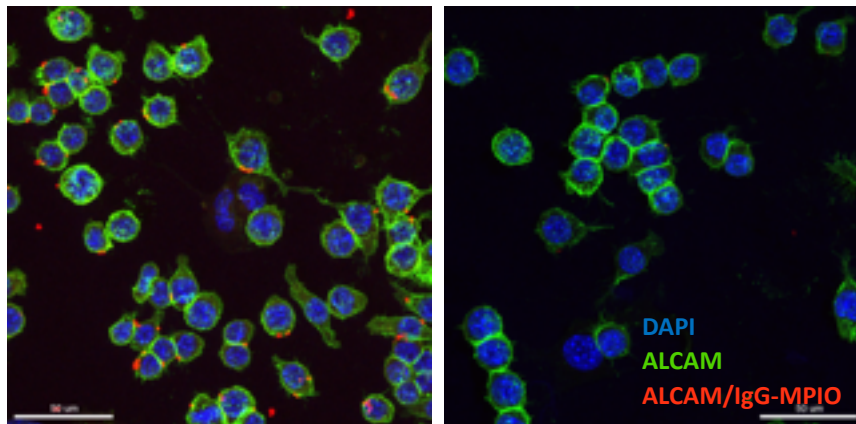
THANK YOU

[niloufar.zarghami@oncology.ox.ac.uk](mailto:niloufar.Zarghami@oncology.ox.ac.uk)



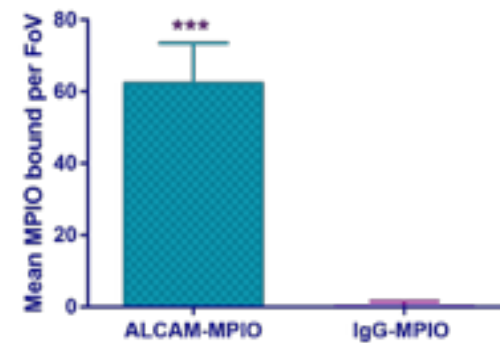
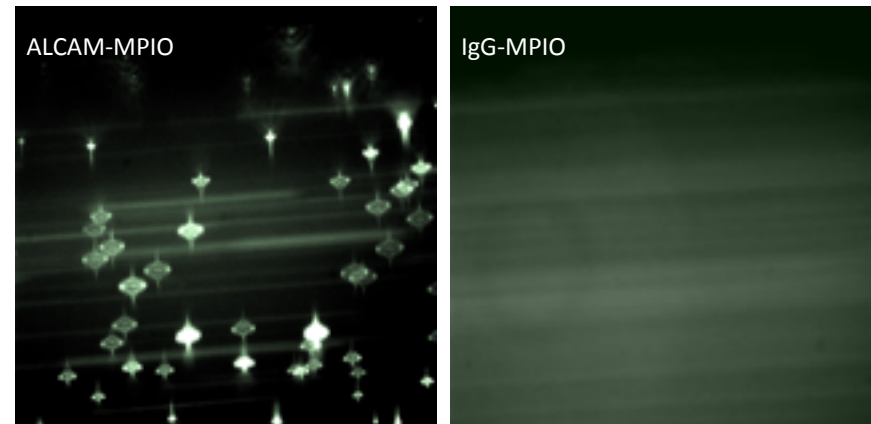
Binding under **static** condition

Pre-treated mouse endothelial cells with 10 ng TNF- α

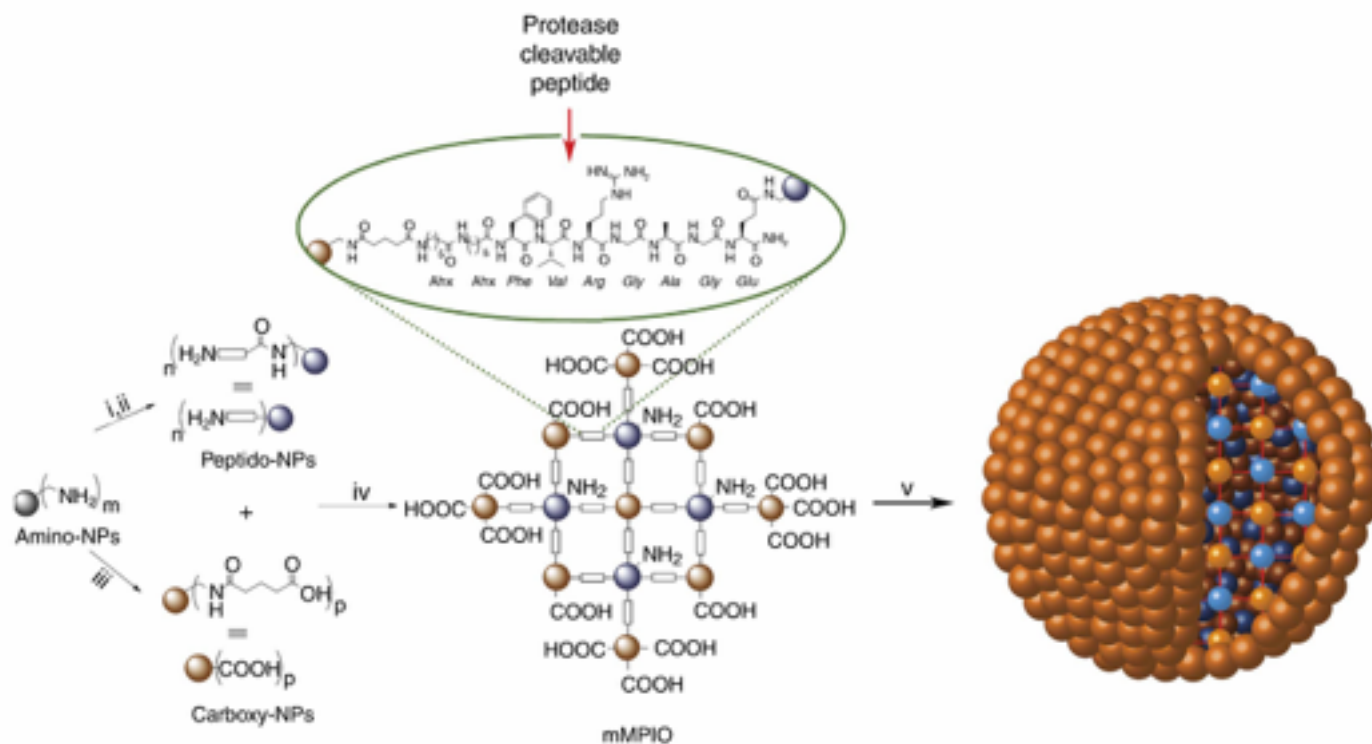


Binding under **flow** condition

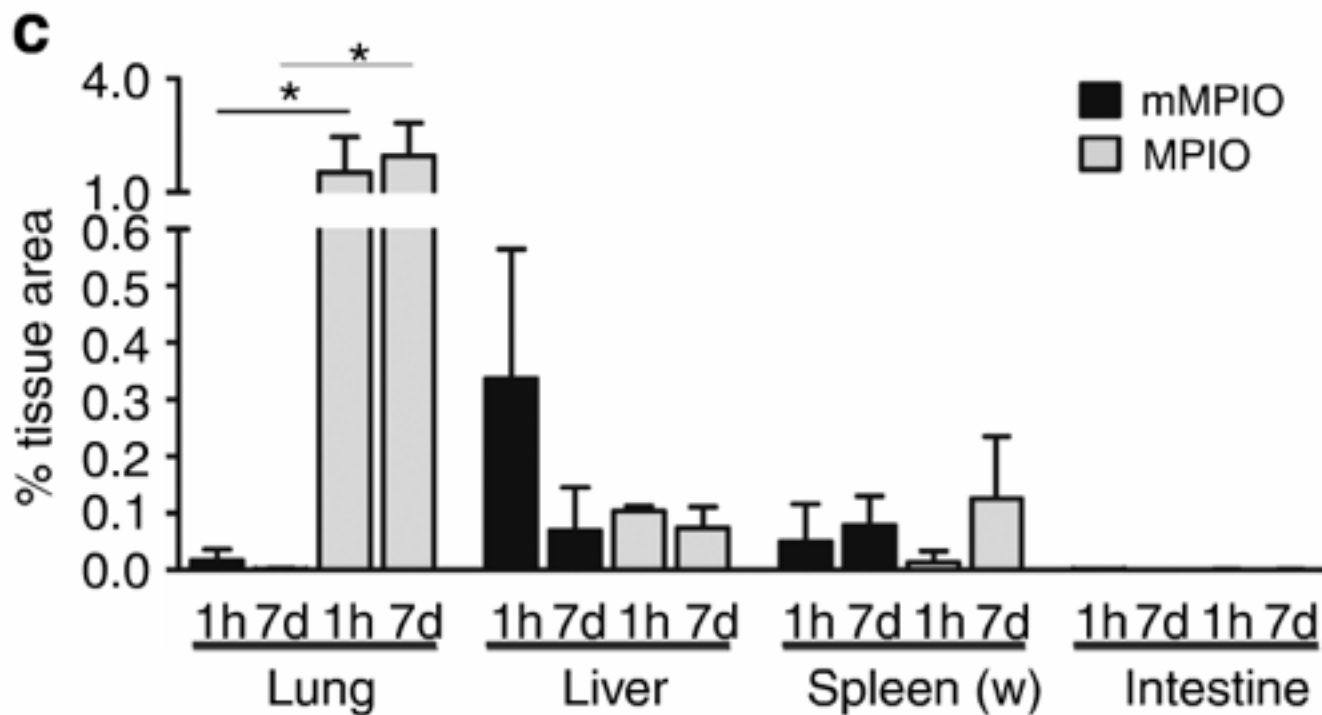
Glass capillaries pre-coated with mouse ALCAM protein



Schematic representation of the synthesis of multimeric MPIO

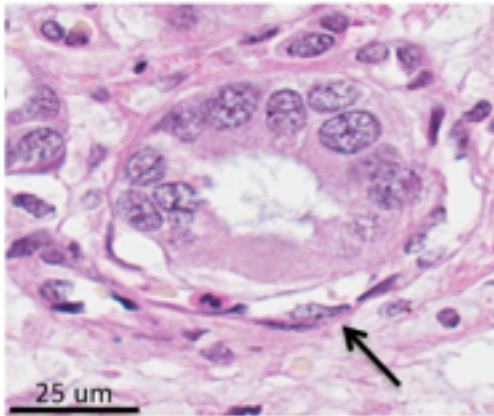


Bio distribution of MPIO and mMPIO

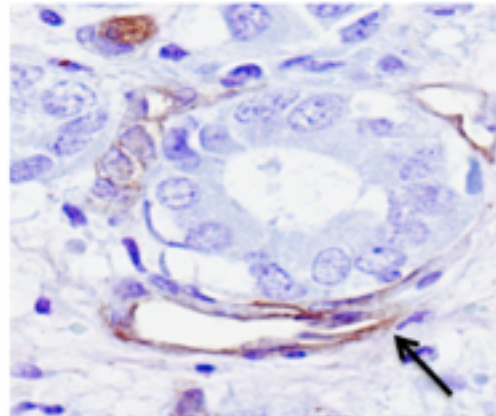


Lung adenocarcinoma

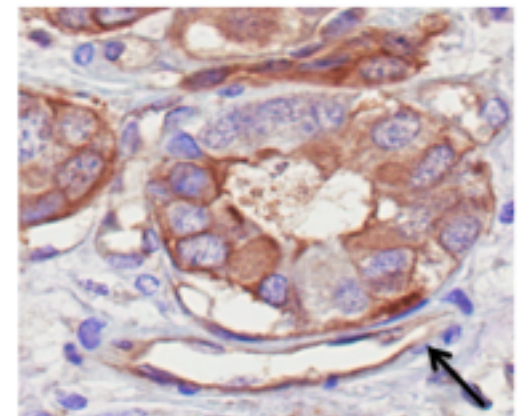
H&E



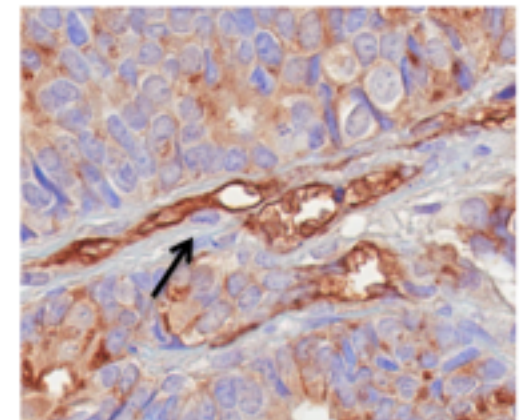
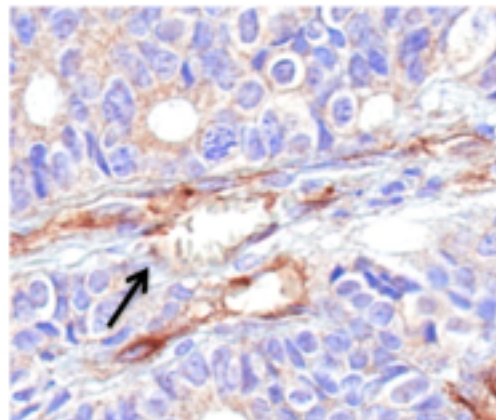
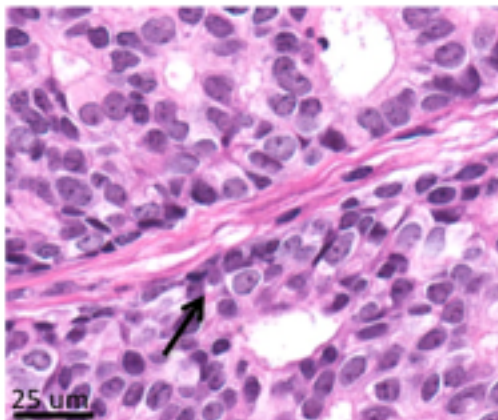
CD34



ALCAM

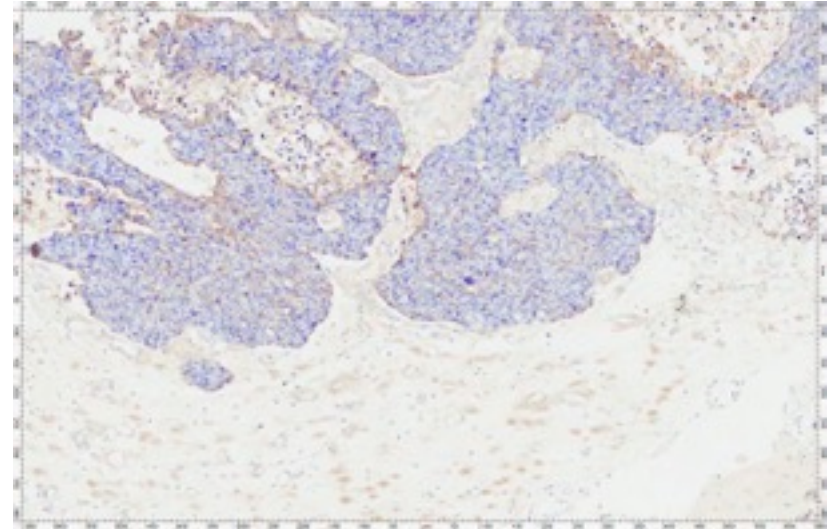


Breast carcinoma

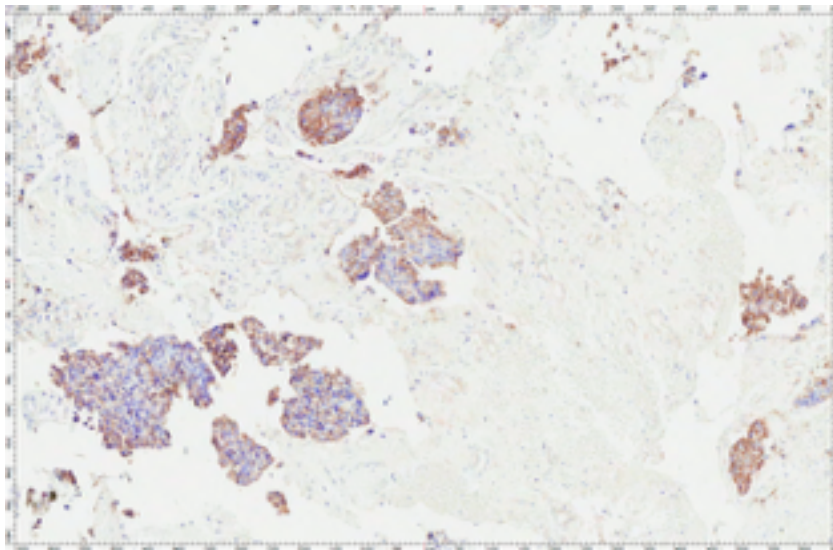


ALCAM upregulation on human brain metastases biopsies

Lung origin

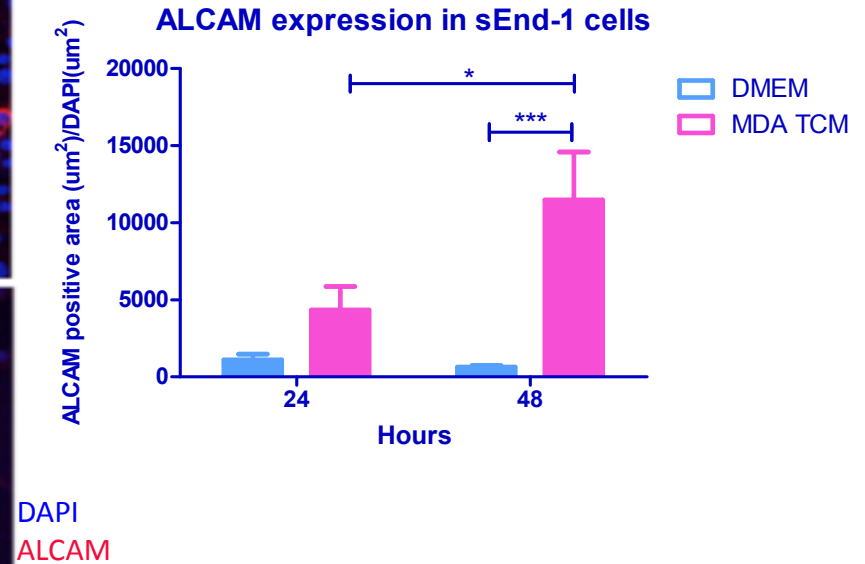
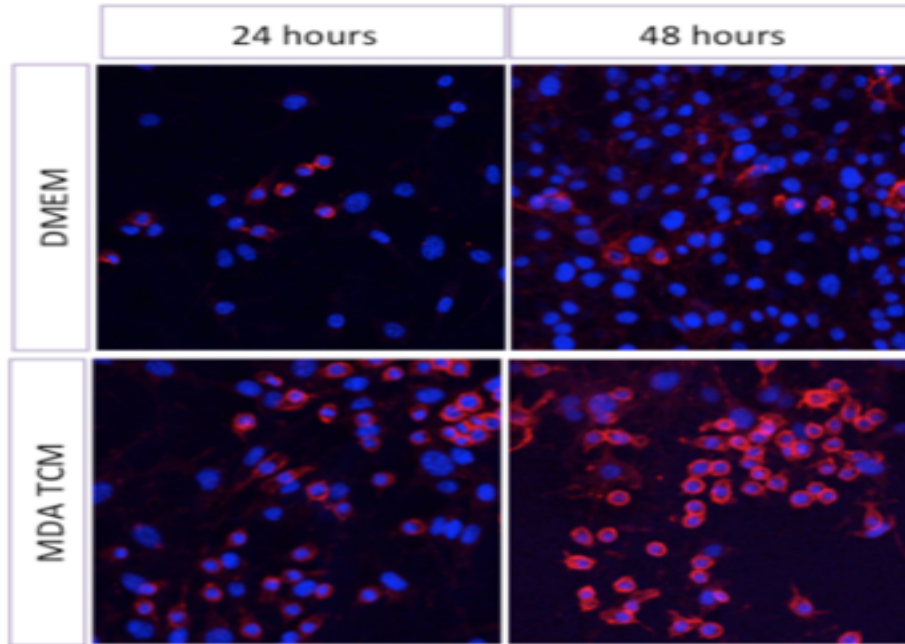


Breast origin



ALCAM up-regulation in vitro

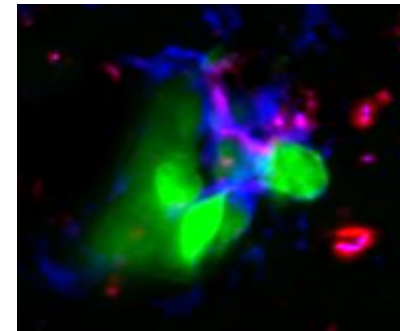
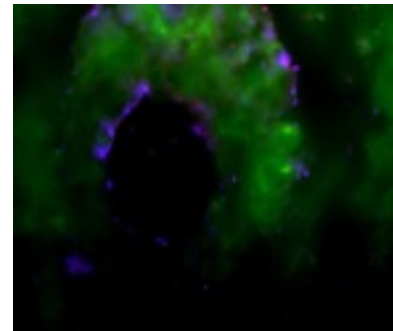
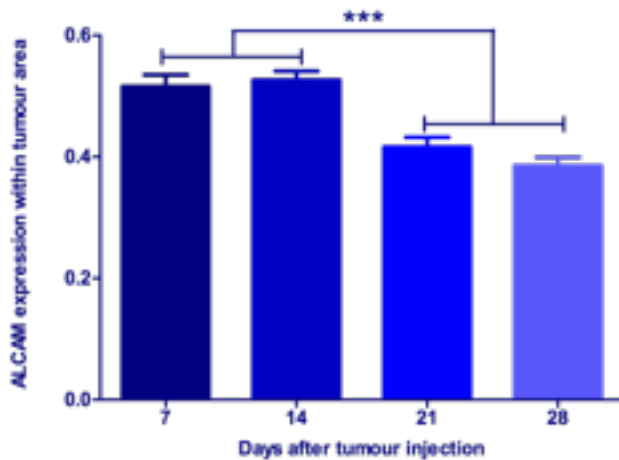
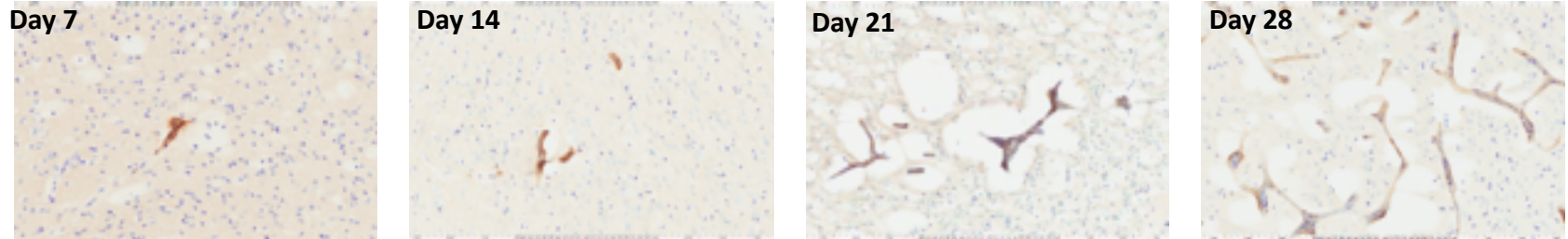
- **Mouse endothelial cells** treated with MDA-MB-231-Br tumour conditioned media (TCM)



ALCAM up-regulation in vivo

Brain metastases models:

MDA-MB-231-Br (Human brain tropic breast cancer)



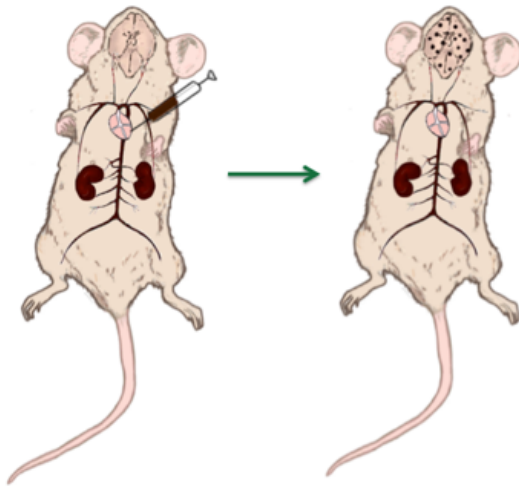
ALCAM
CD-31
Tumour

Co-localisation of MDA, ALCAM and CD-31

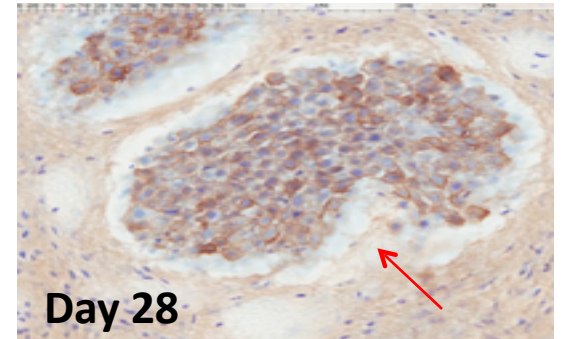
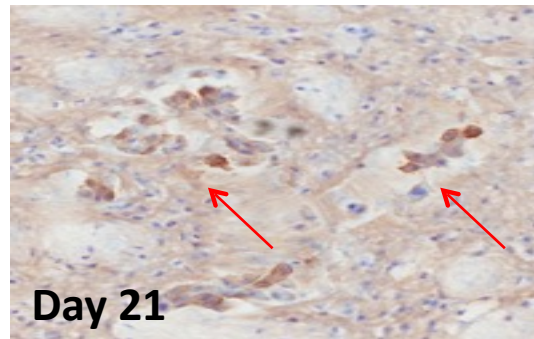
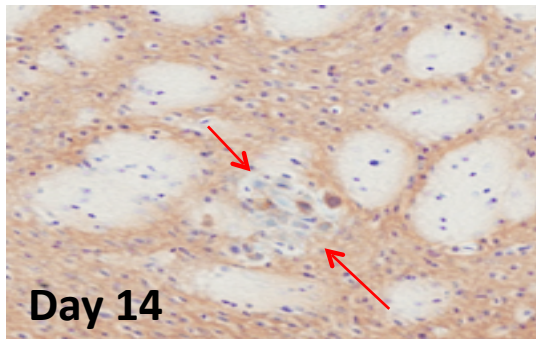
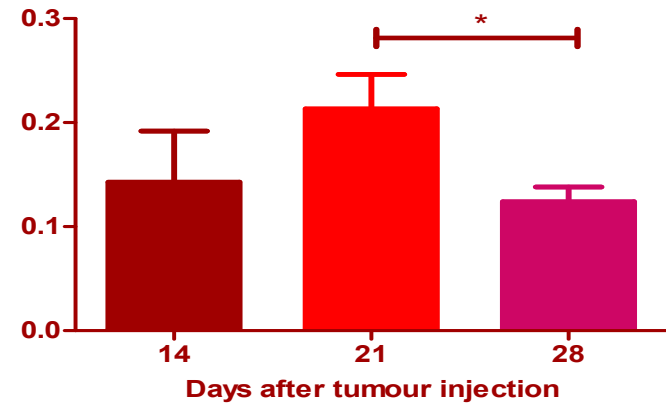
ALCAM up-regulation in vivo

Brain metastases models:

H1-DL2 (Human brain tropic melanoma)

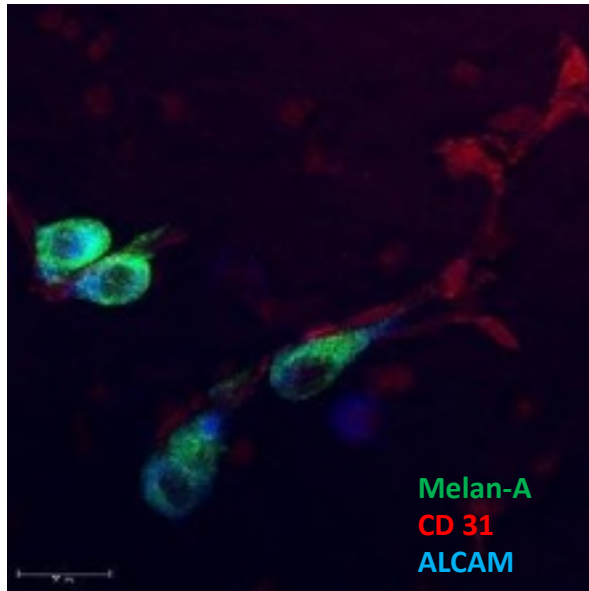


ALCAM expression within tumour area

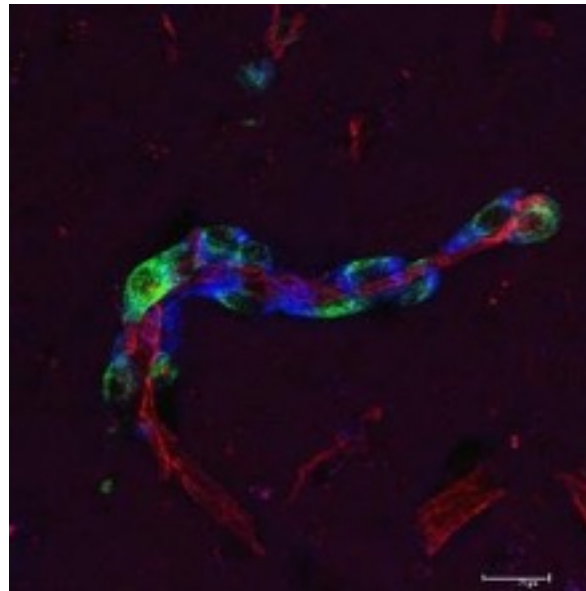


ALCAM and endothelial colocalization in H1-DL2 model

D14



D21



D28

