

A microscopic image showing several cells with bright, glowing outlines, likely representing metastatic breast cancer stem cells. The cells are irregular in shape and have a textured, granular appearance. The background is a light, hazy blue.

Metastatic breast cancer stem cells

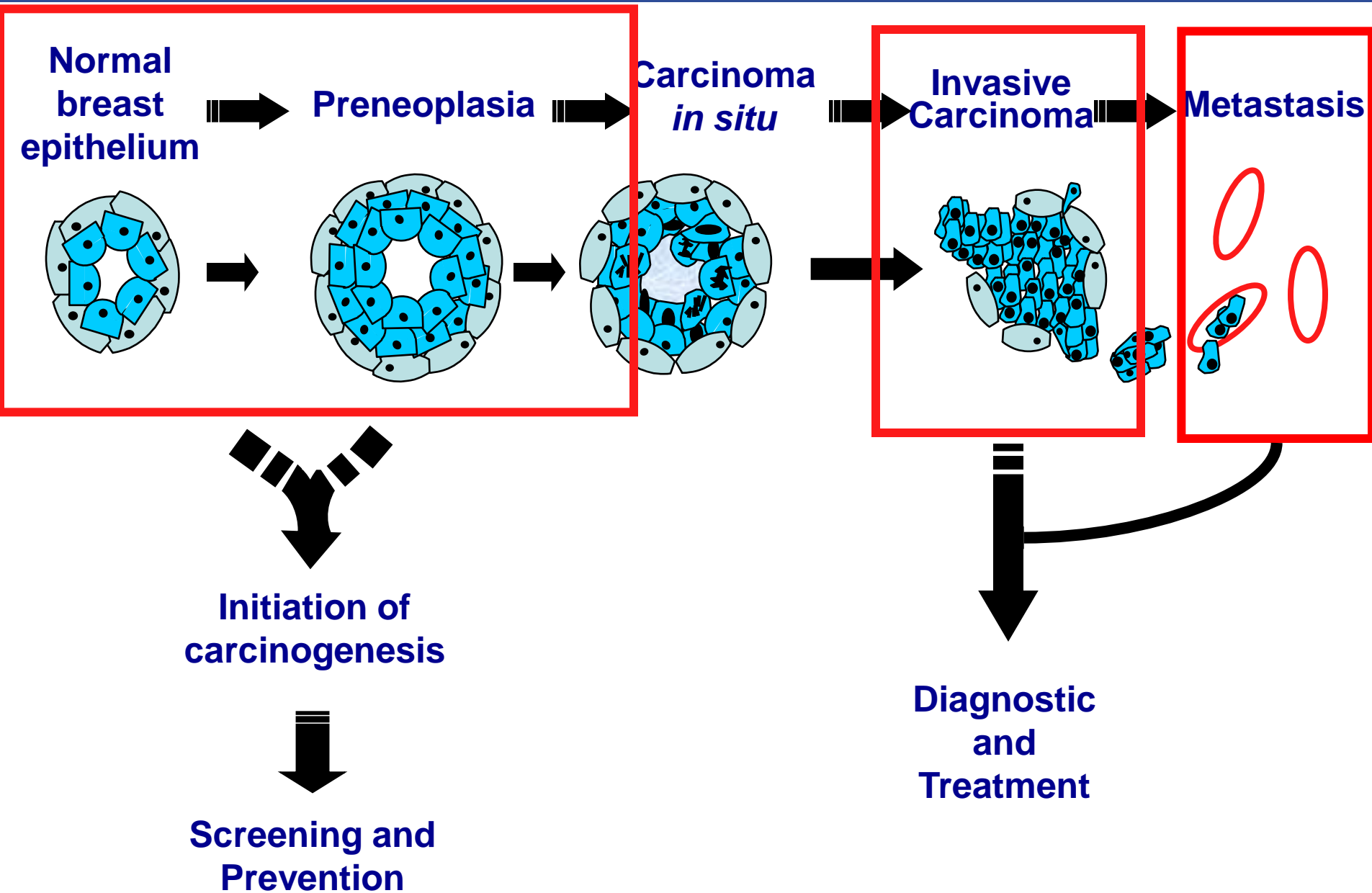
Christophe GINESTIER, PhD

**Centre de Recherche en Cancérologie de Marseille
Laboratoire d'Oncologie Moléculaire
Breast Stem Cell Group
U1068/Inserm/Institut Paoli-Calmettes
Marseille**

CRCM

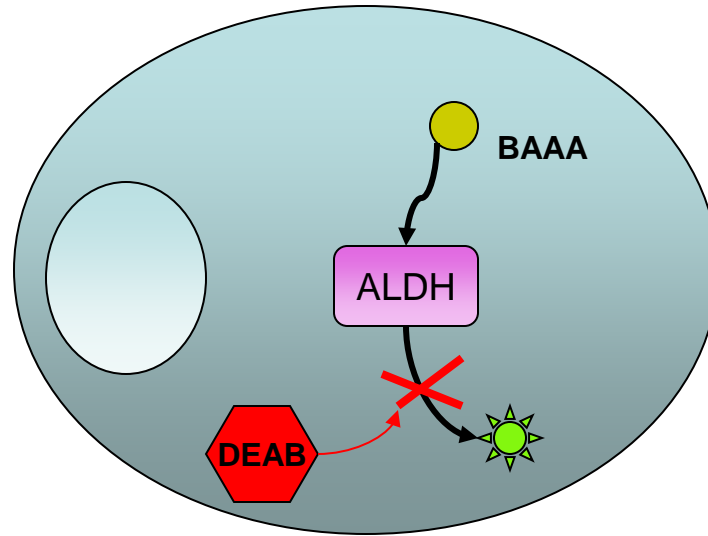
Centre de Recherche
en Cancérologie de Marseille

Different step of the breast carcinogenesis

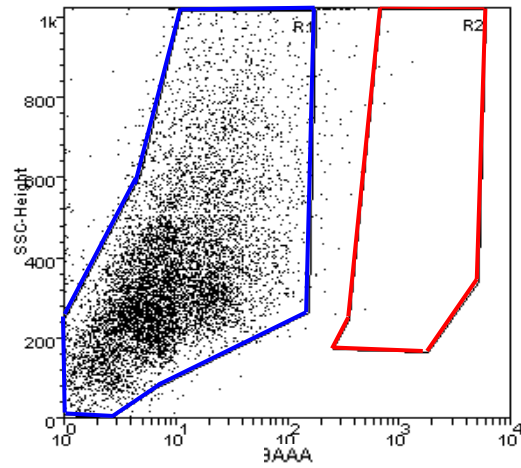


"BRCA1 regulates human mammary stem/progenitor cell fate"
(Liu, Ginestier et al. PNAS, 2008)

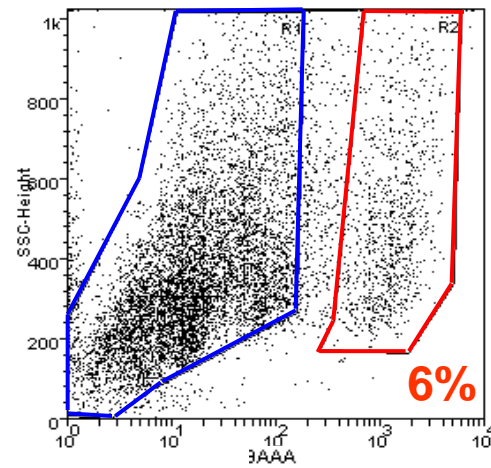
ALDEFLUOR + cells



With DEAB

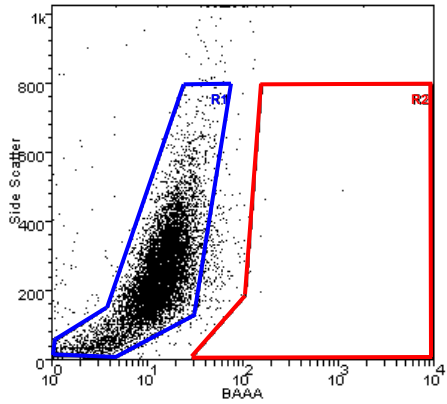


Without DEAB

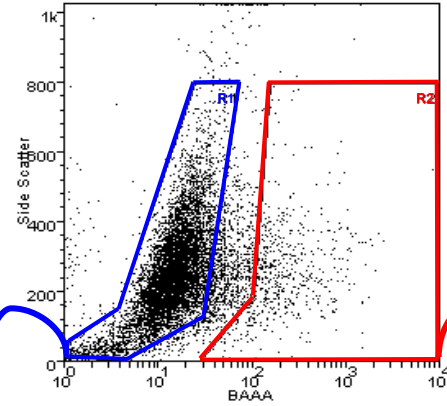


ALDEFLUOR+ population and tumorigenicity

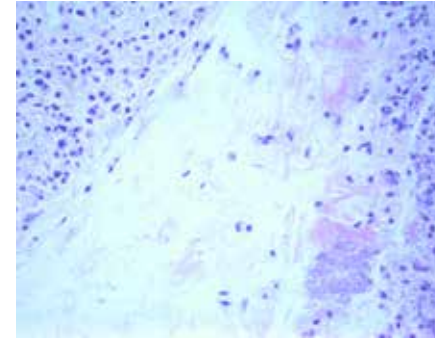
With DEAB



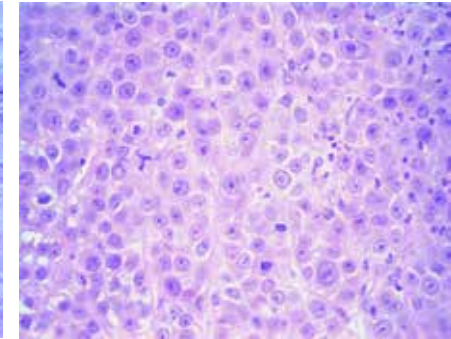
Without DEAB



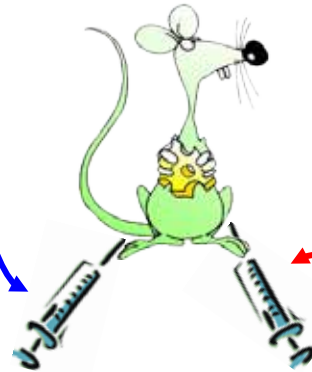
ALDEFLUOR-



ALDEFLUOR+

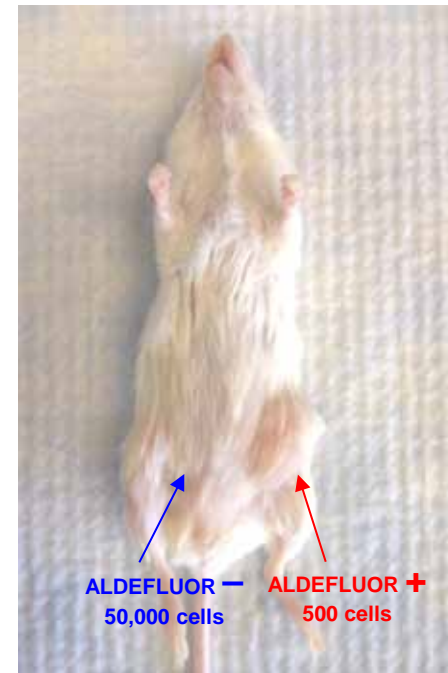


5% to 10% of ALDEFLUOR + population in Breast tumors



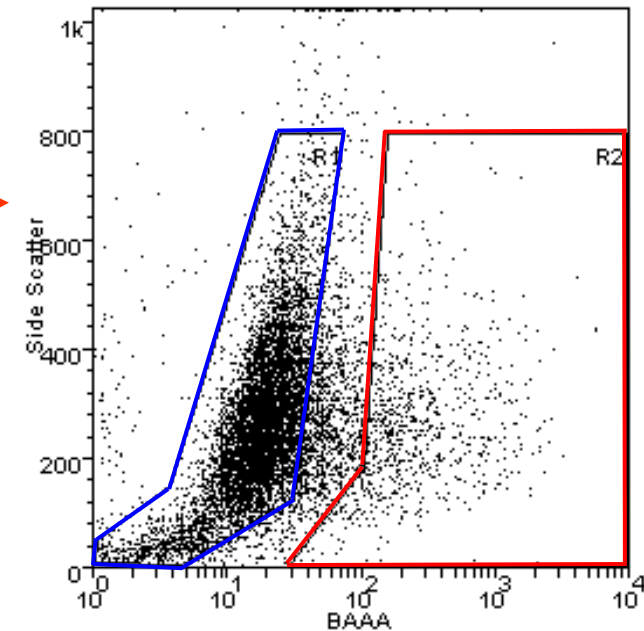
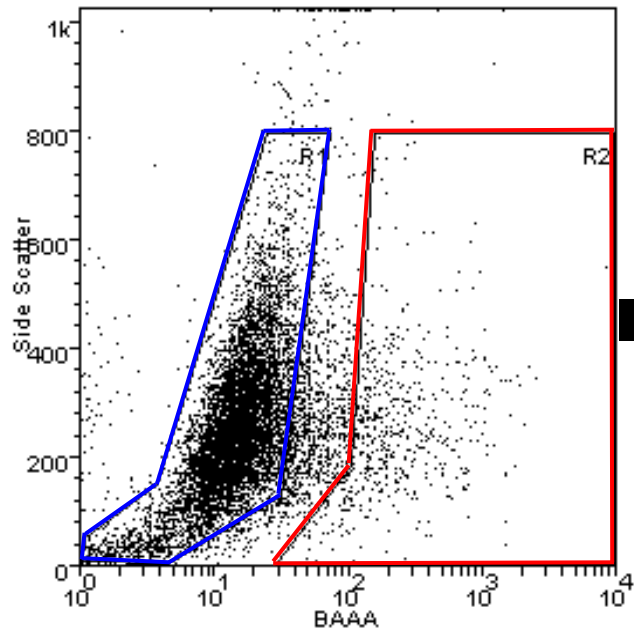
ALDEFLUOR-
50,000 cells
5000 cells
500 cells

ALDEFLUOR+
50,000 cells
5000 cells
500 cells



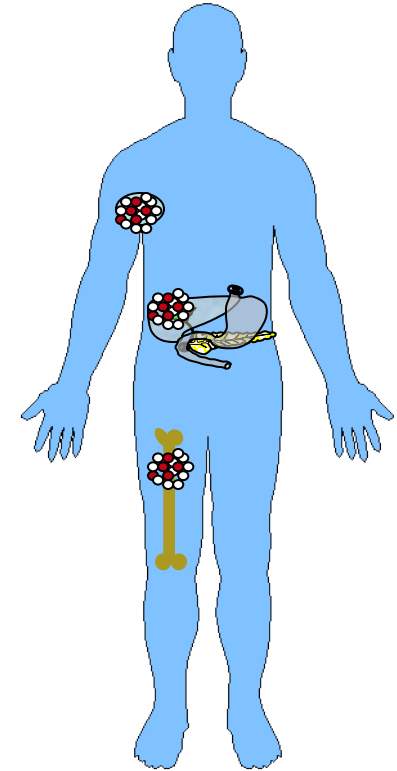
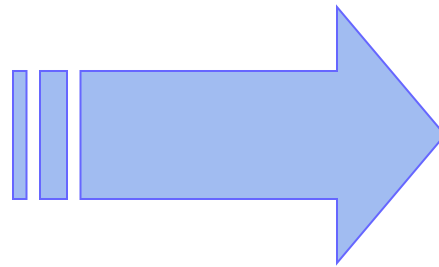
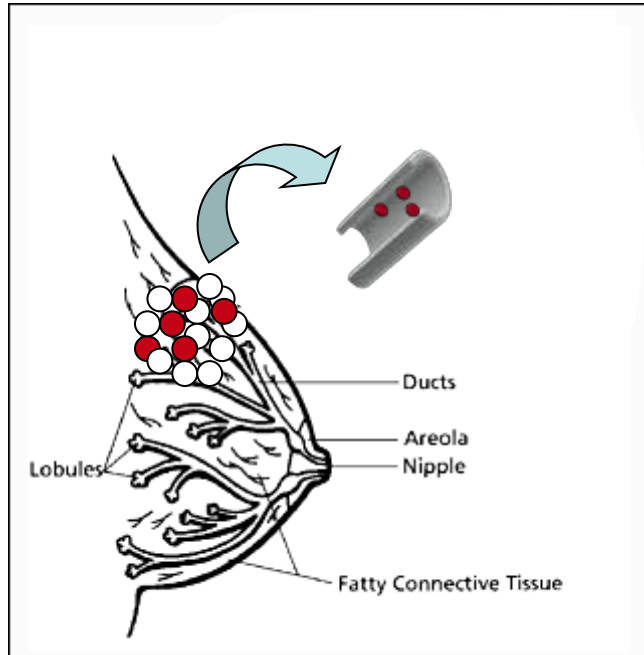
Ginestier et al. Cell stem cell, 2007

ALDEFLUOR+ population and tumorigenicity

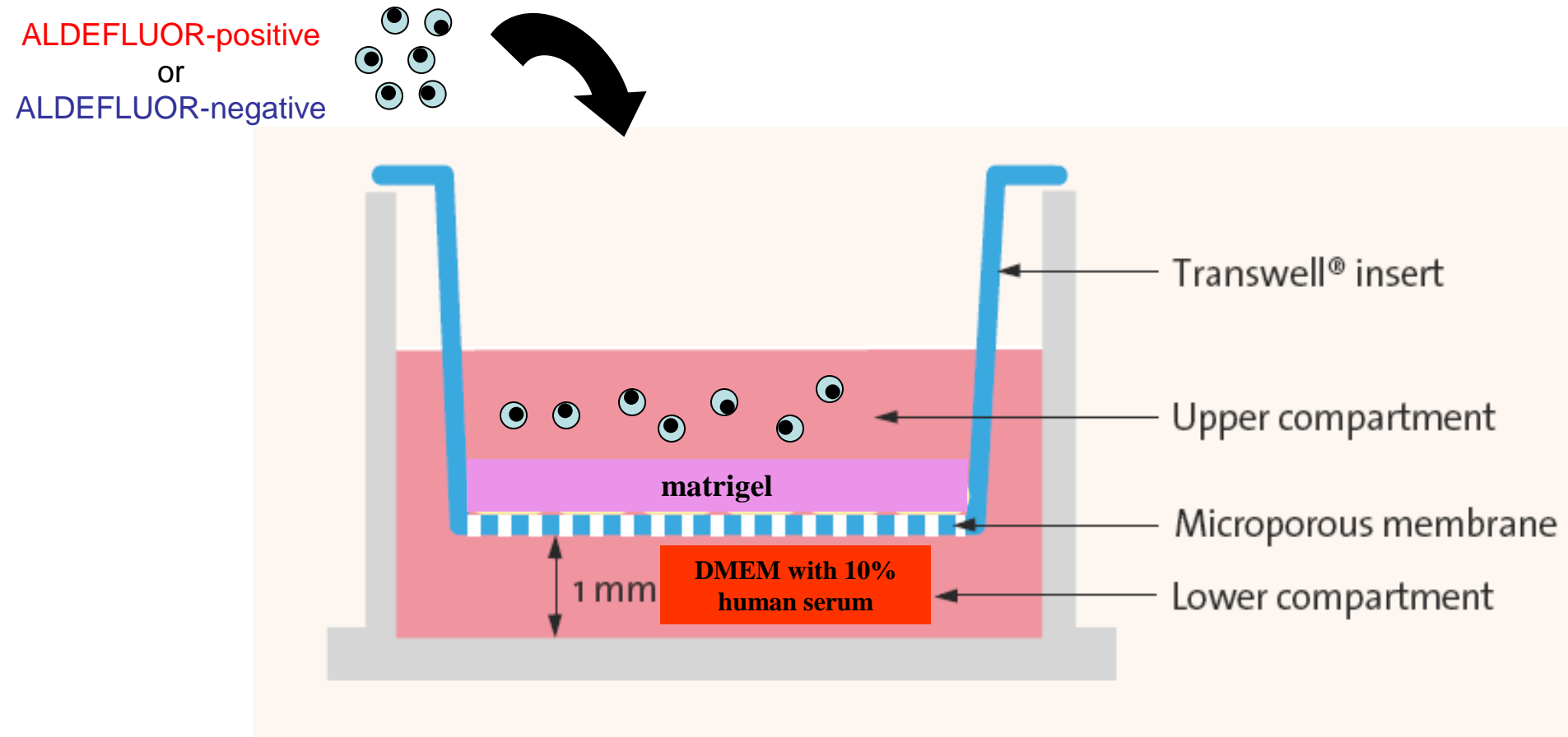


ALDEFLUOR+ population regenerates heterogeneity of the initial tumor

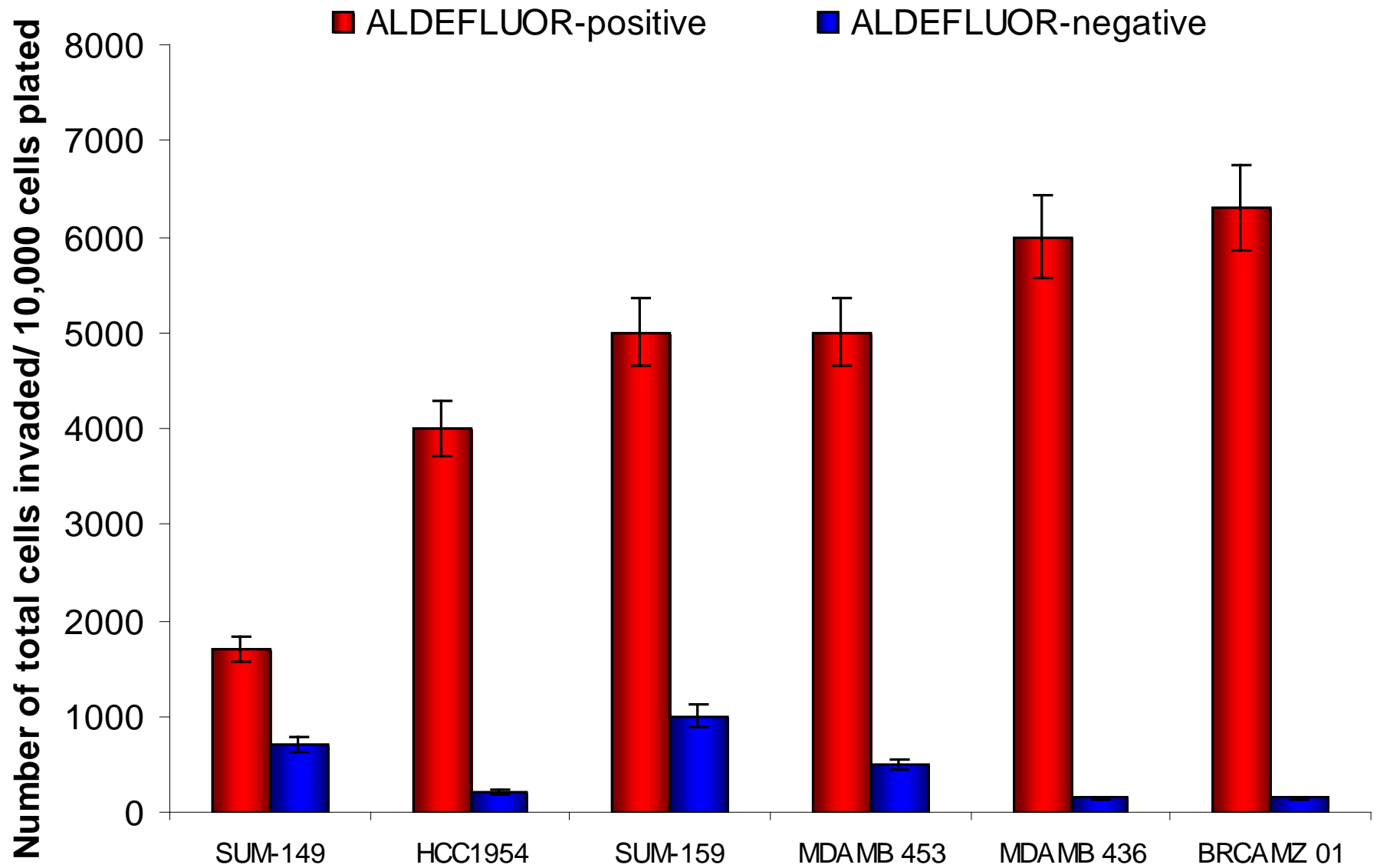
Cancer stem cells and metastasis



Cell invasion assay

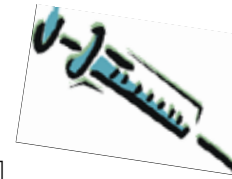
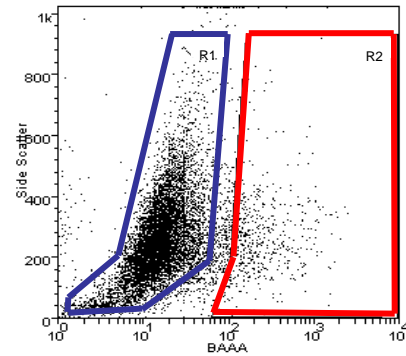


Cell invasion assay

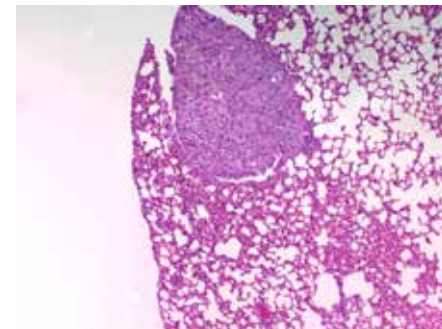
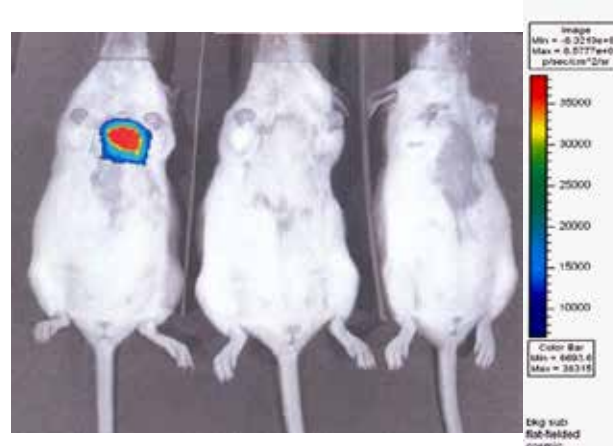
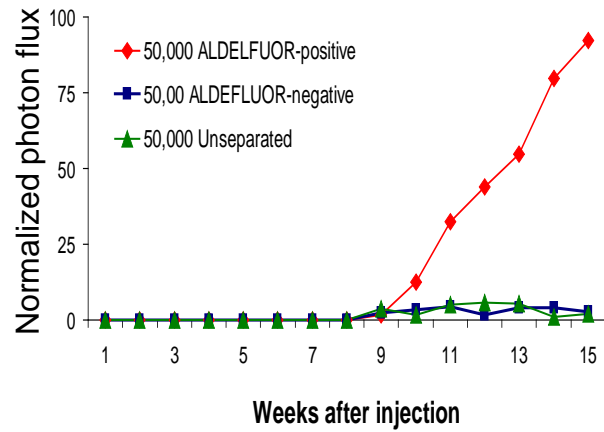
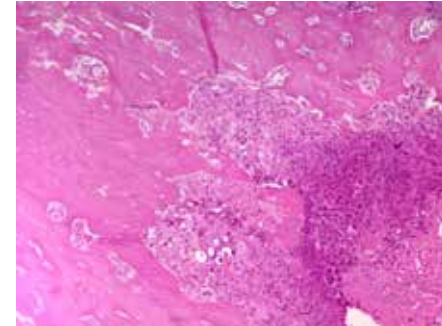
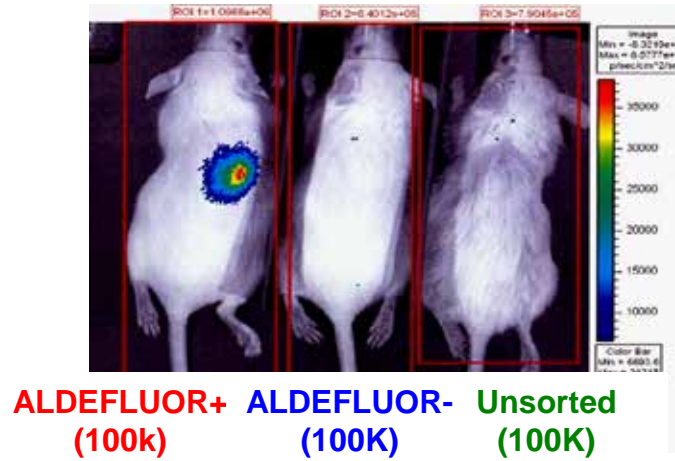
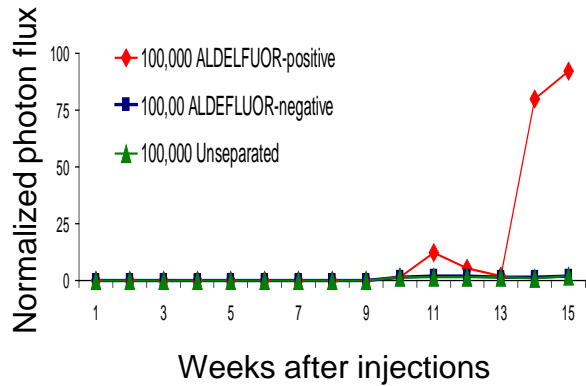


Intracardiac injections

Lentivirus expressing Luciferase



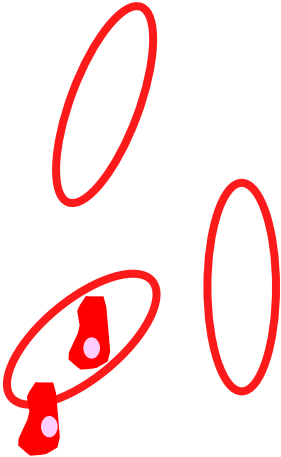
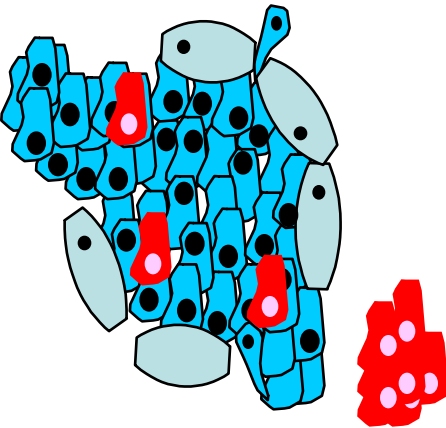
Intracardiac injections



**Invasive
Carcinoma**



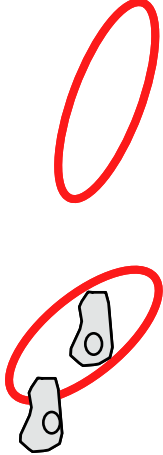
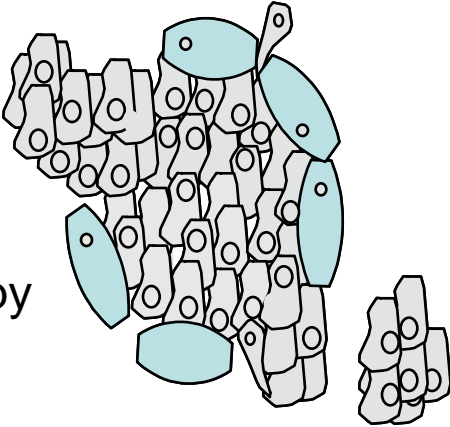
Metastasis



Anti-CSC therapy

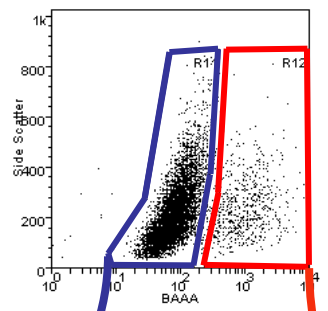


Conventional therapy



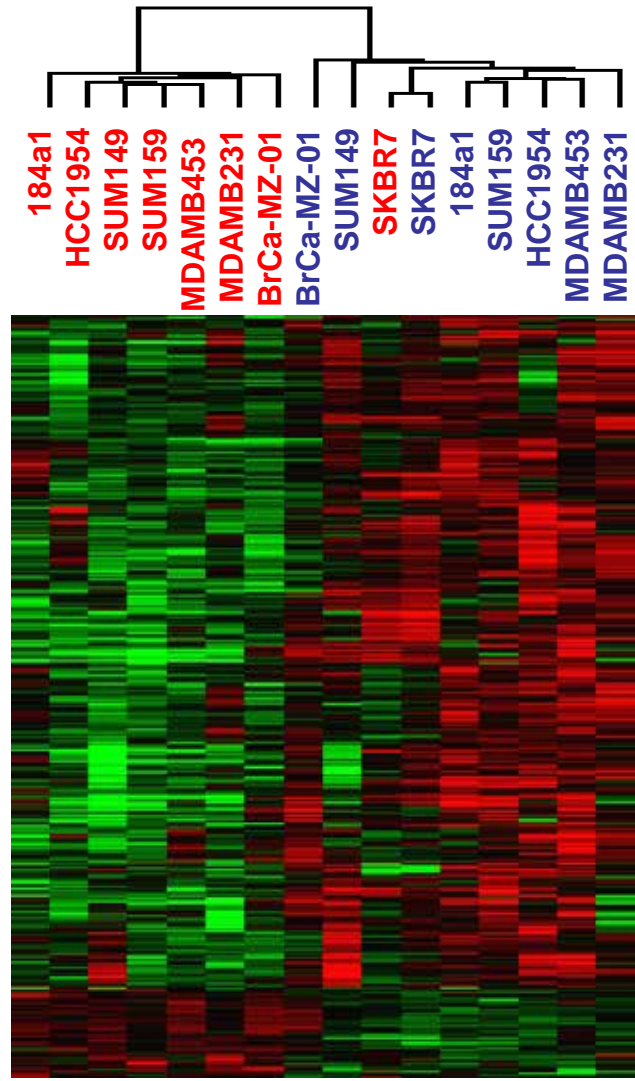
Breast Cancer Stem Cell Gene Expression Signature

8 Breast cell lines



- 184a1
- HCC1954
- SUM149
- SUM159
- MDAMB453
- MDAMB231
- BrCaMZ01
- SKBR7

- 184a1
- HCC1954
- SUM149
- SUM159
- MDAMB453
- MDAMB231
- BrCaMZ01
- SKBR7



413 genes
breast cancer stem cell signature

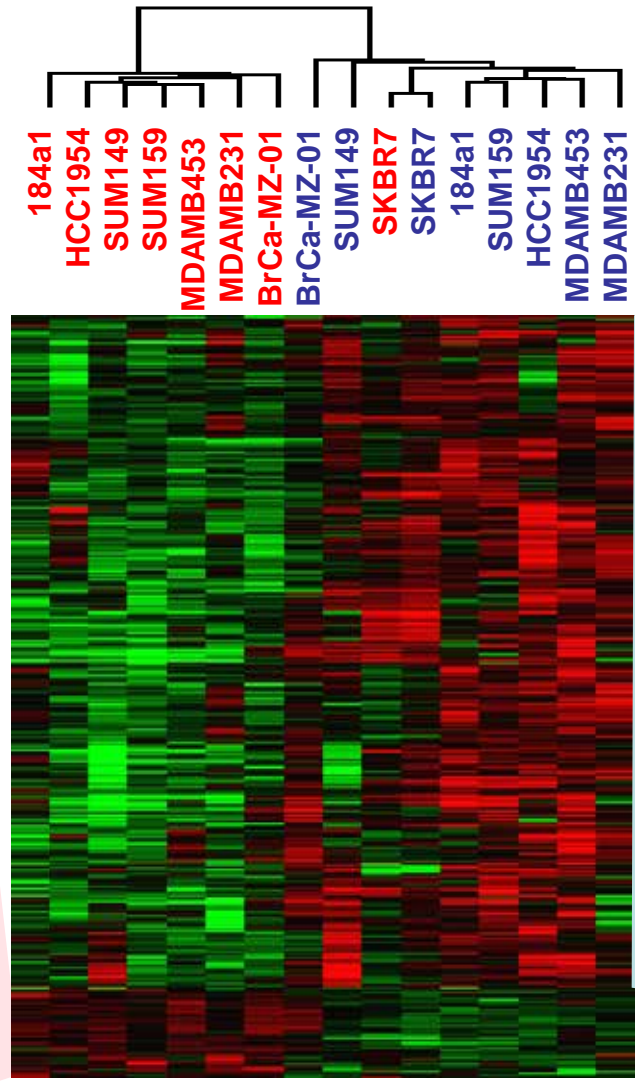
33 genes overexpressed in the
ALDEFLUOR-positive populations

380 genes overexpressed in the
ALDEFLUOR-negative populations

Breast Cancer Stem Cell Gene Expression Signature

Genes up-regulated in **ALDEFLUOR-positive** populations

Genes up-regulated in **ALDEFLUOR-negative** populations

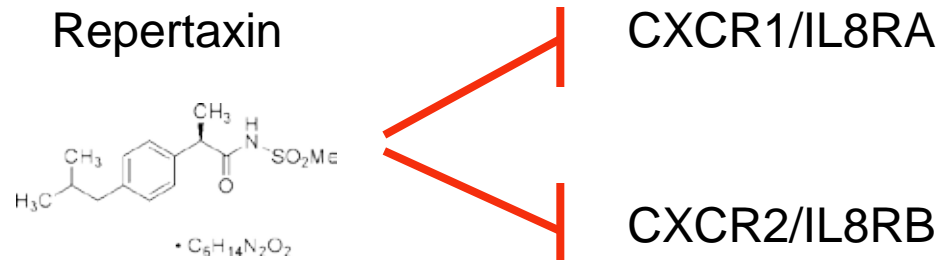


- Role in stem cell biology
 - NOTCH2
 - NFYA
 - TPRXL
 - RBM15
 - PCNX
- Cell Signaling
 - FBXO21
 - CAMK2B
 - ADRBK1
 - UGCCL1
- Membrane protein
 - CXCR1** ←
 - CD300LB
 - GIPC3
 - TAS2R14
- DNA repair/
Chromatin remodeling
 - RAD51
 - ARID1B
- Unknown
 - ZFP41
 - FAM49B
 - PSORS1C2

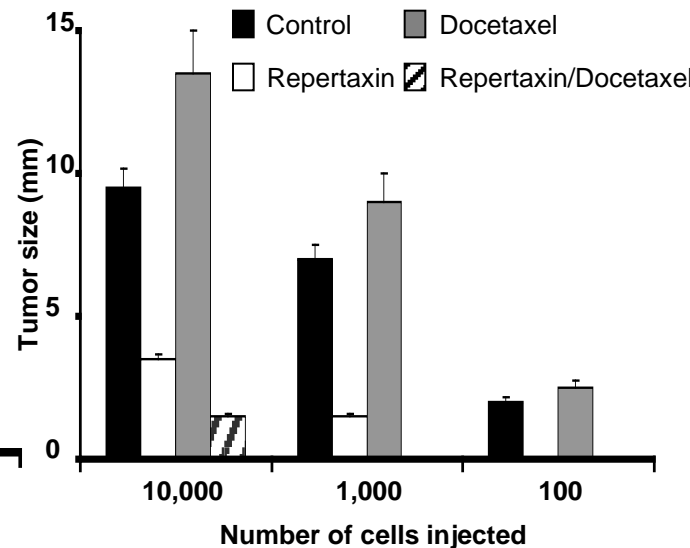
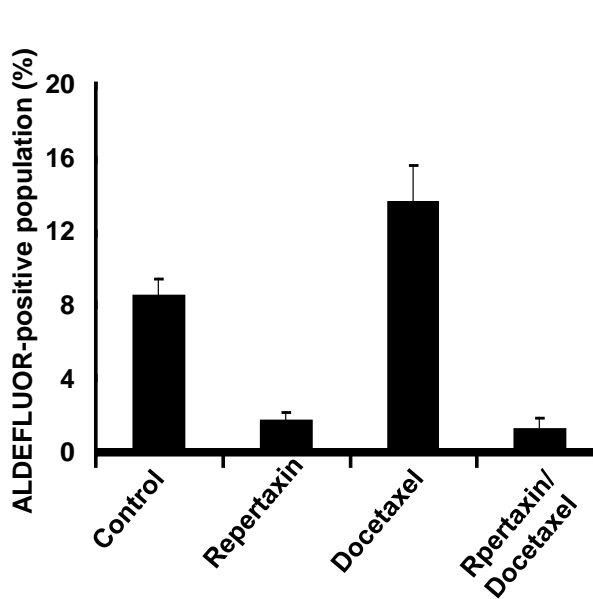
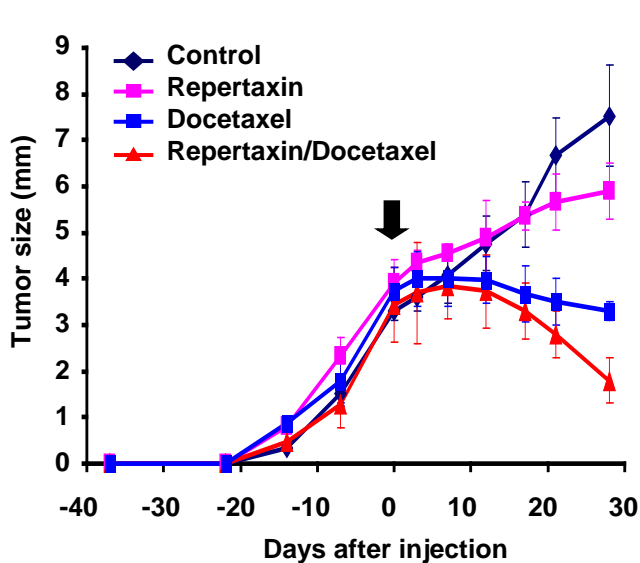
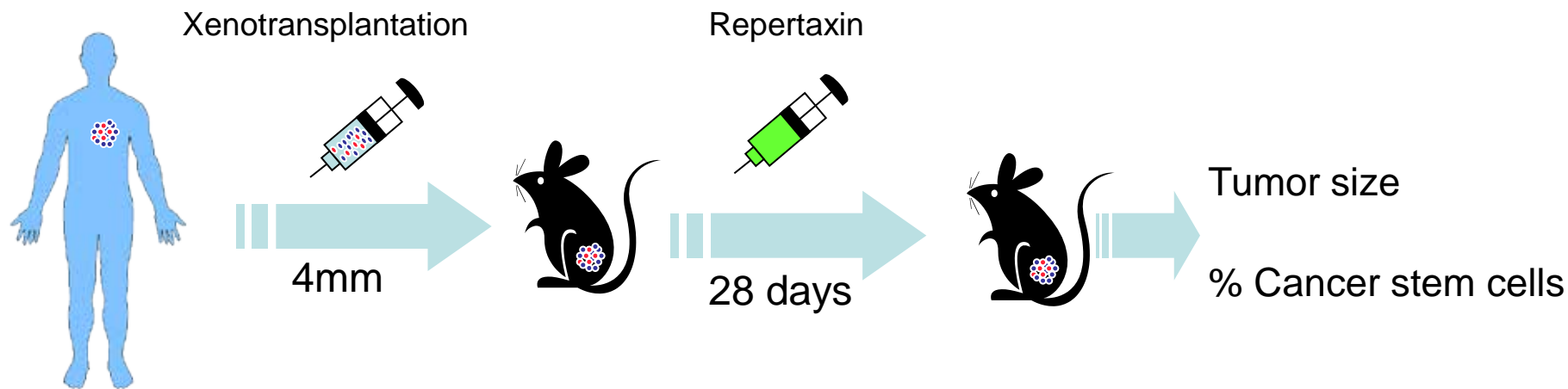
- Cell Signaling
 - ALG5
 - HBLD2
 - GART
 - DC2
 - COMMD6
 - UBL5
- Apoptosis
 - MRPL41
 - PDCD10
 - PDCD5
- Differentiation
 - NACA
- Oxidative phosphorylation
 - ATP5S
 - NDUFA2
 - ATP5J2
 - IMMP1L
- RNA splicing
 - CCNL1
 - PRPF39
 - LSM3
 - SFRS7
 - PRPF4B

CXCR1/IL8RA

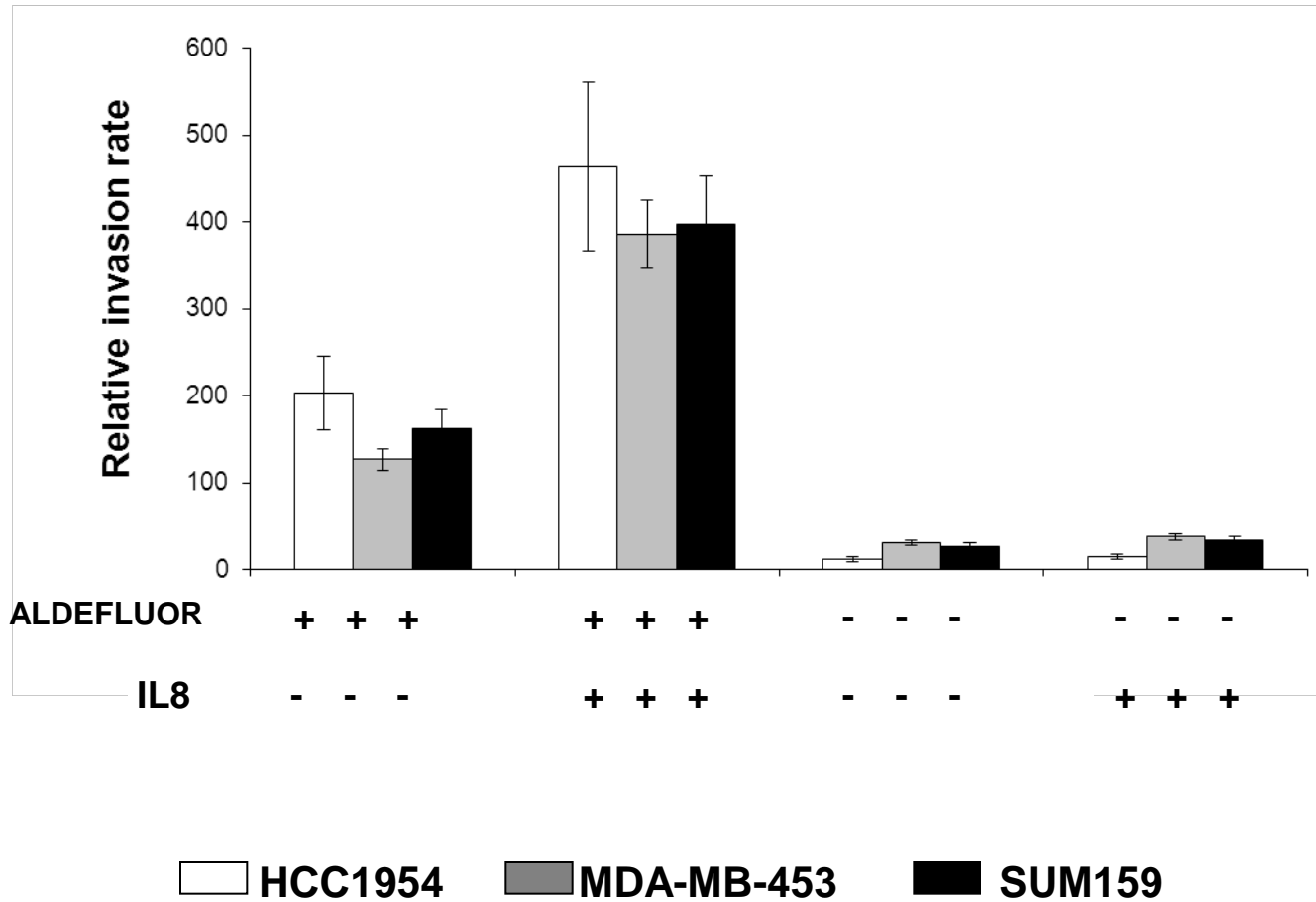
- ★ CXCR1 is a receptor for Interleukin-8 involves in the recruitment of leukocytes to sites of inflammation
- ★ CXCR1 is increased in variety of cancers including breast cancer
- ★ CXCR1/IL-8 promotes:
 - ➔ Tumor cells motility/metastasis
 - ➔ Tumor cells proliferation
- ★ Repertaxin a small molecule inhibitor of IL8 signaling



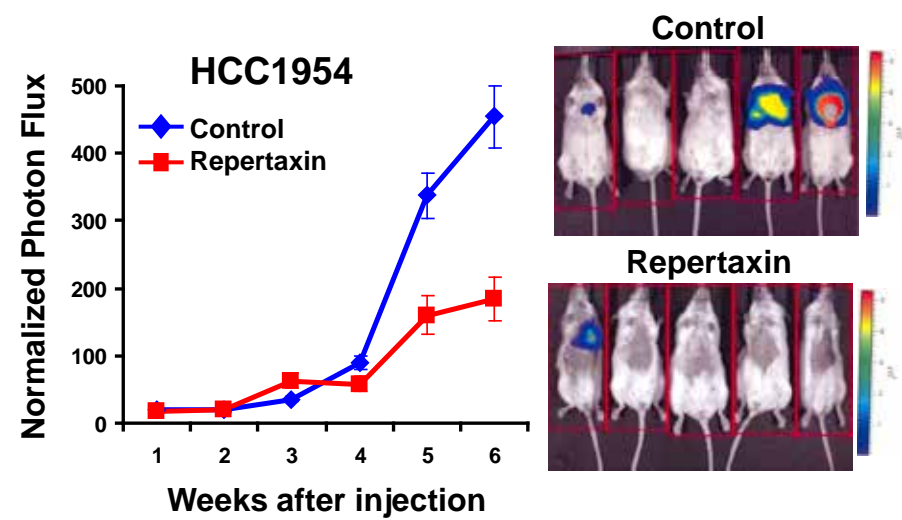
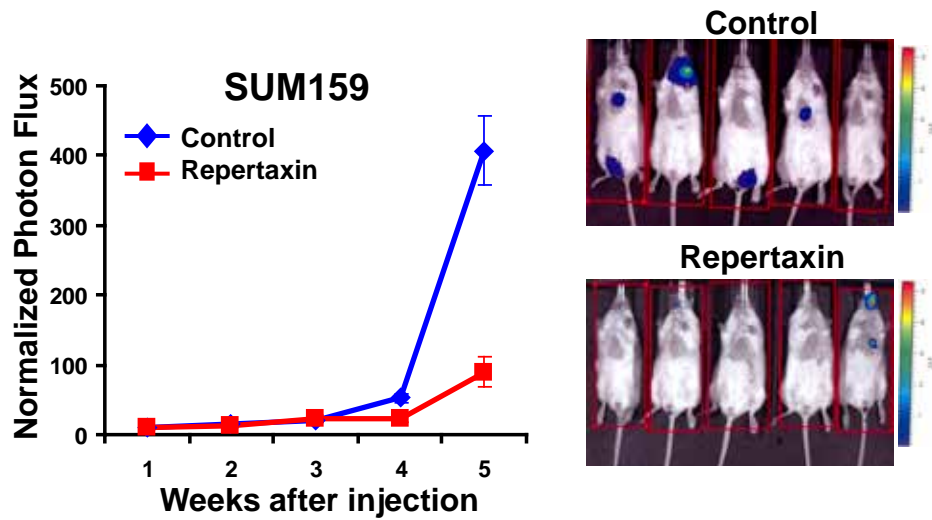
Effect of Repertaxin treatment on cancer cells survival



IL-8 induces invasion of breast CSC

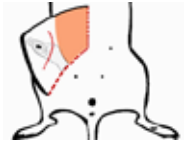
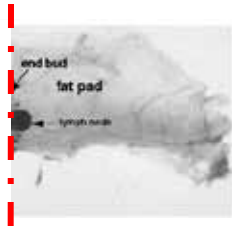


Effect of CXCR1 blockade on metastasis formation

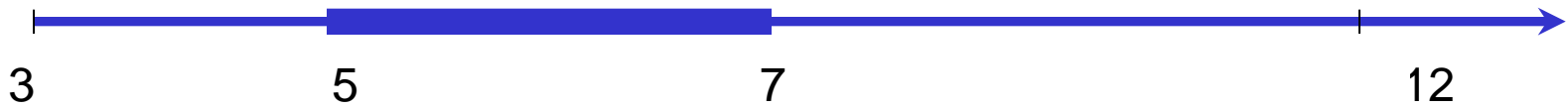


Patient-derived xenograft (PDX)

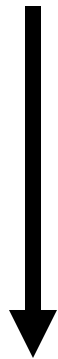
«Clearing»



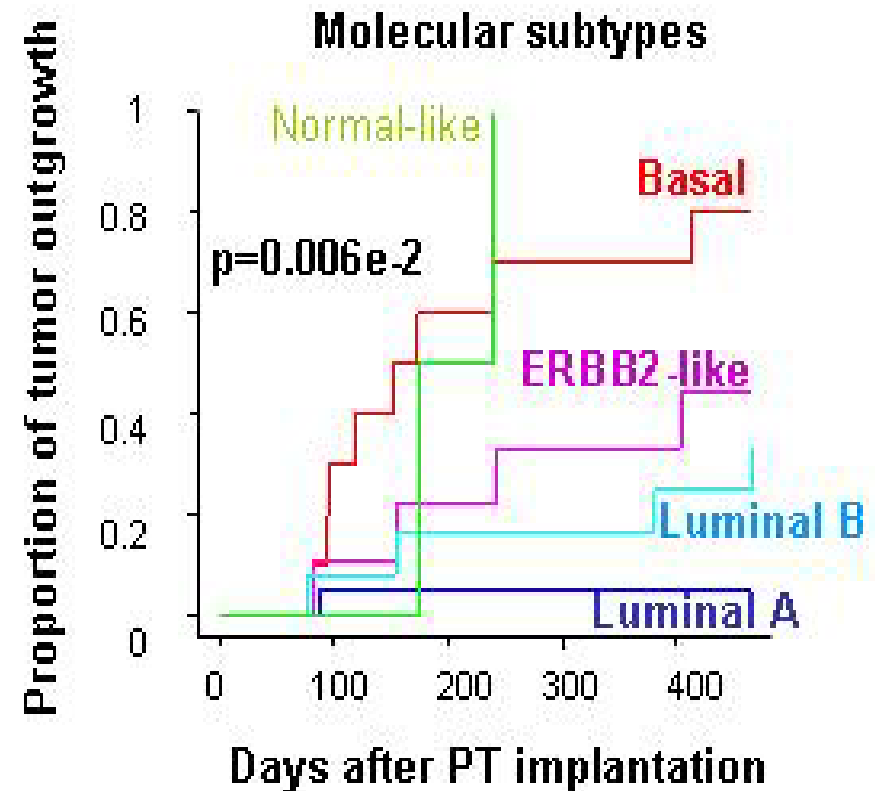
Time from birth
(weeks)



> 200 Primary tumor injections

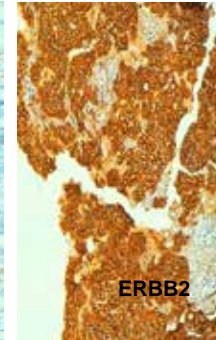
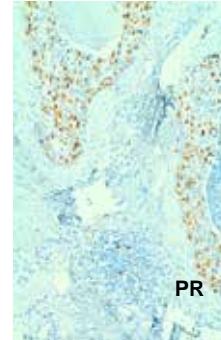
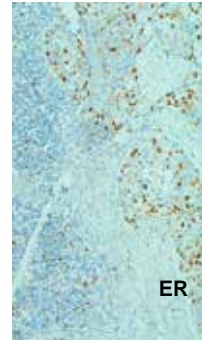
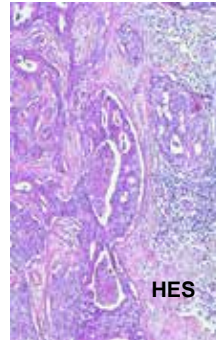


> 50 established PDXs

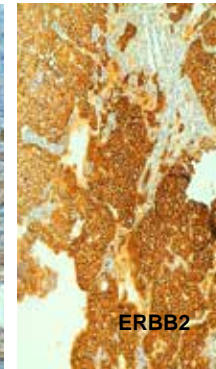
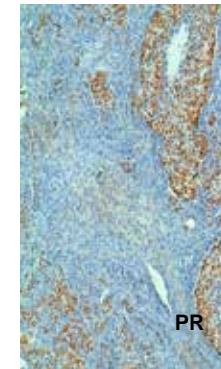
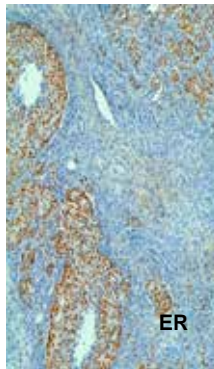
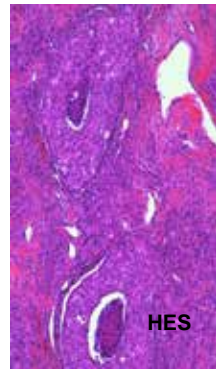


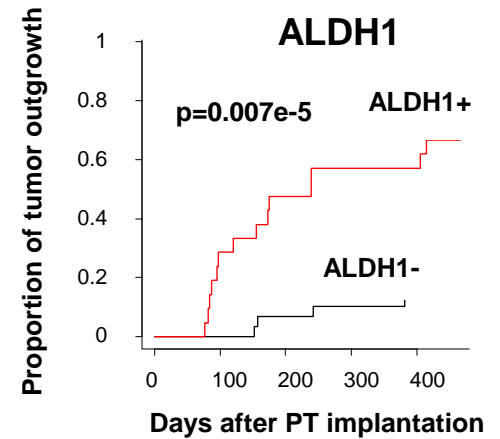
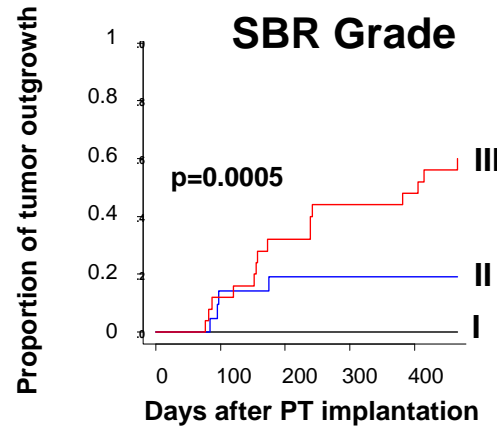
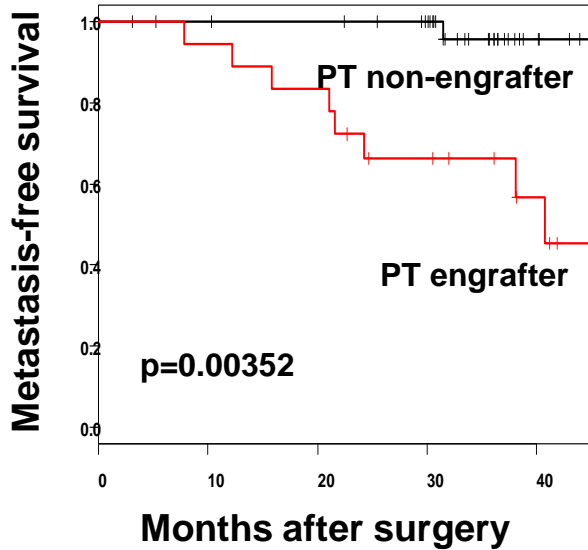
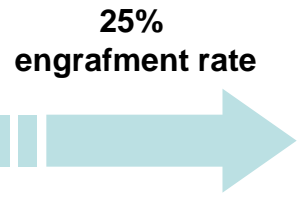
PDX retains histological/molecular features of corresponding primary tumors

CRCM 224 PT



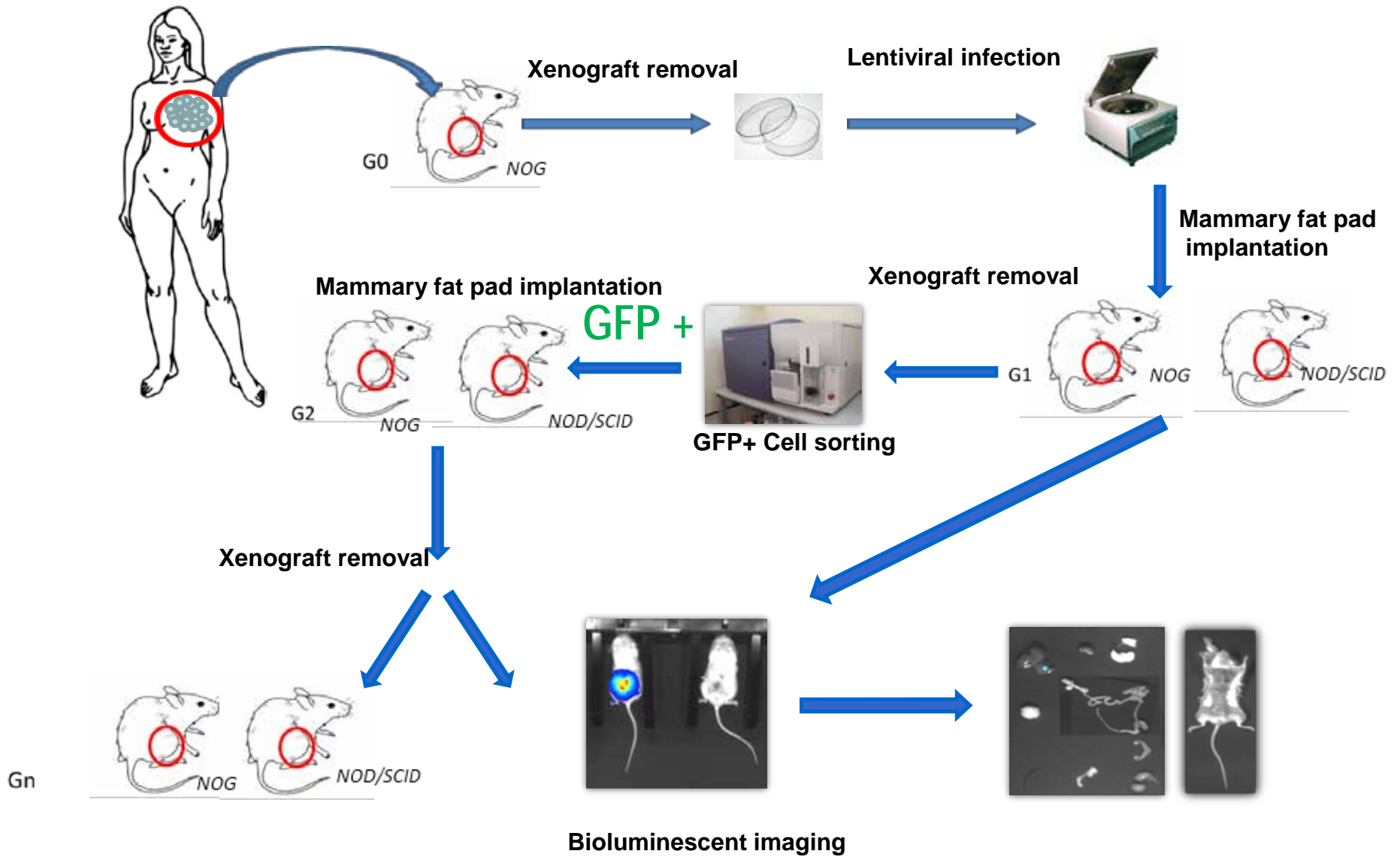
CRCM 224X



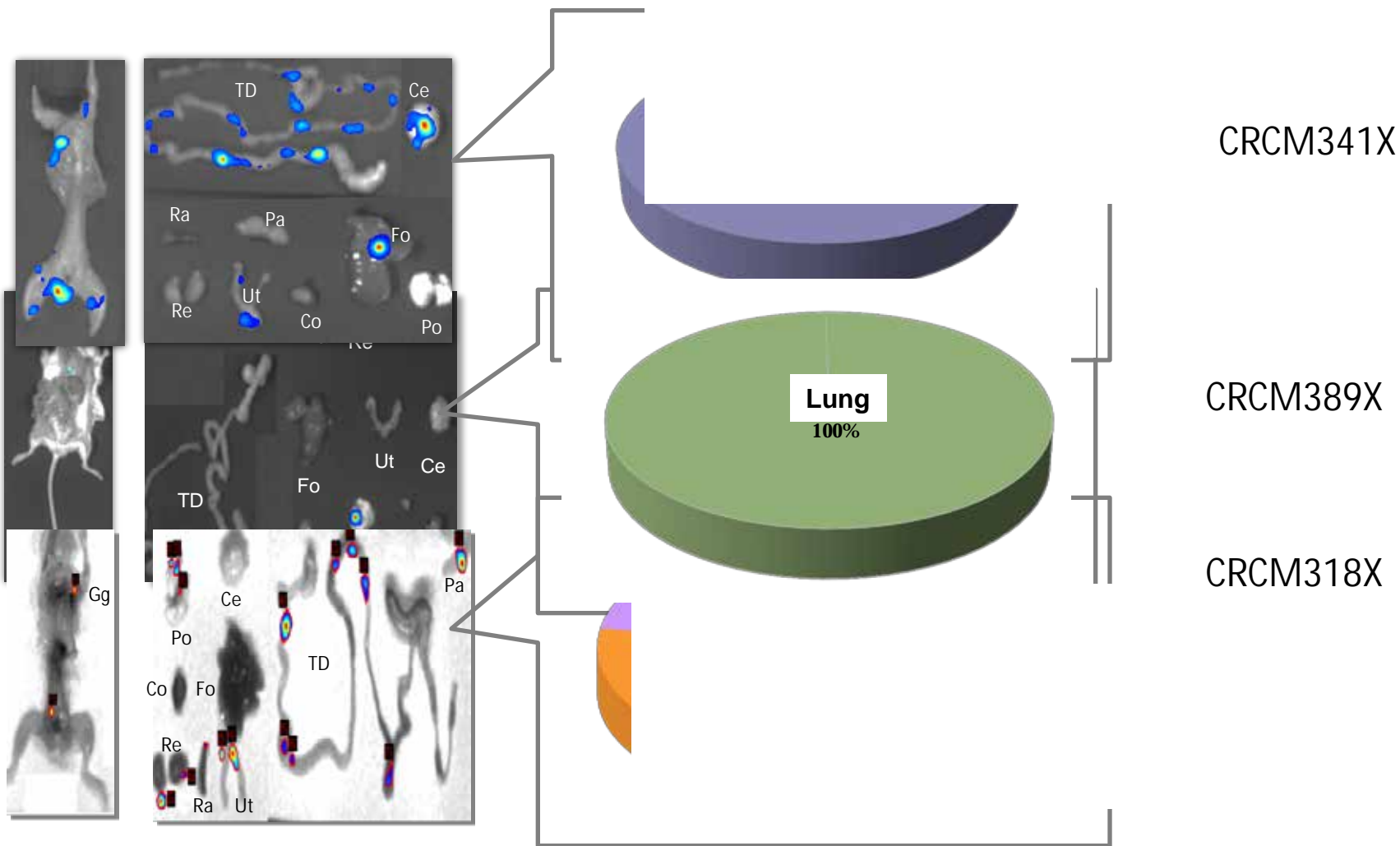


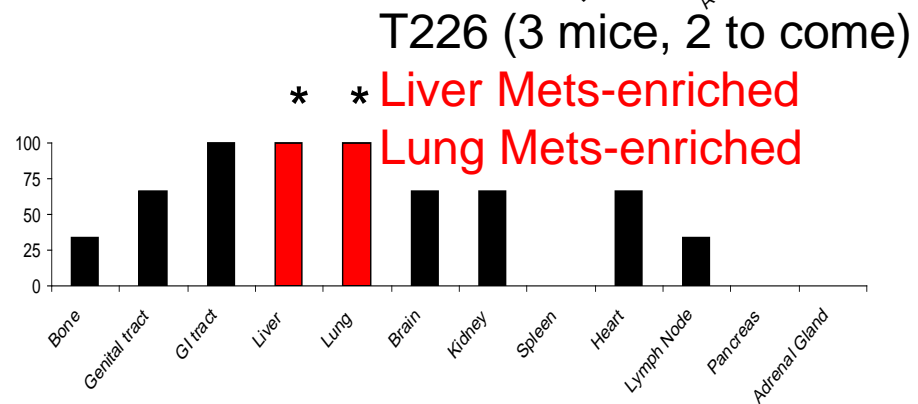
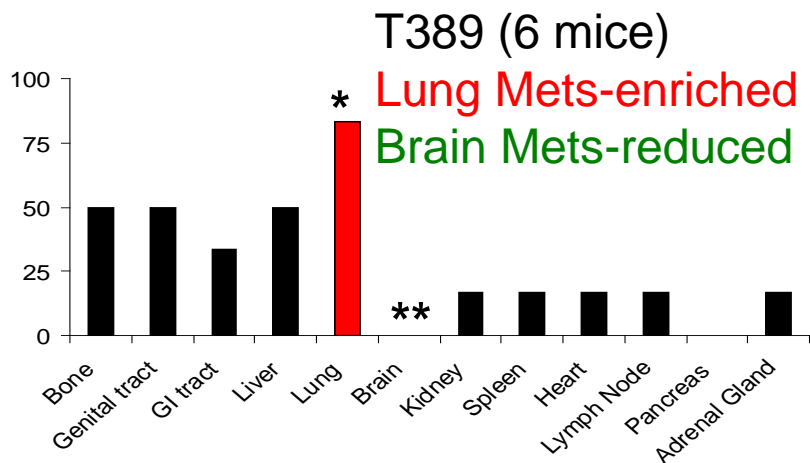
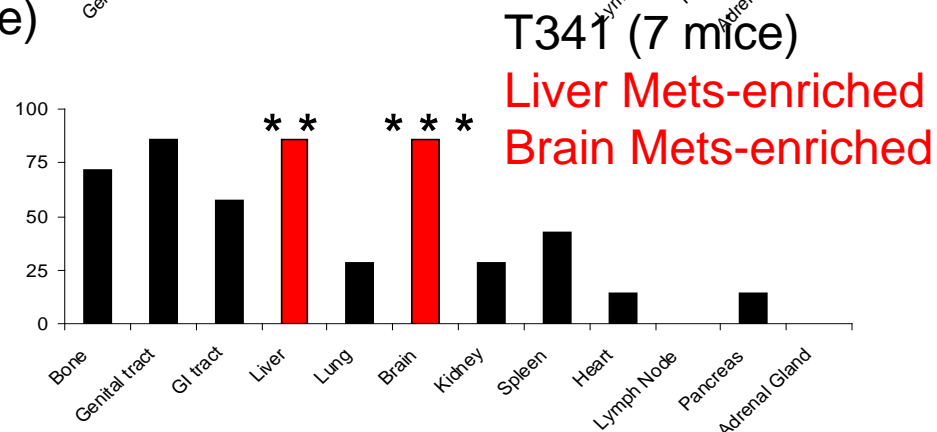
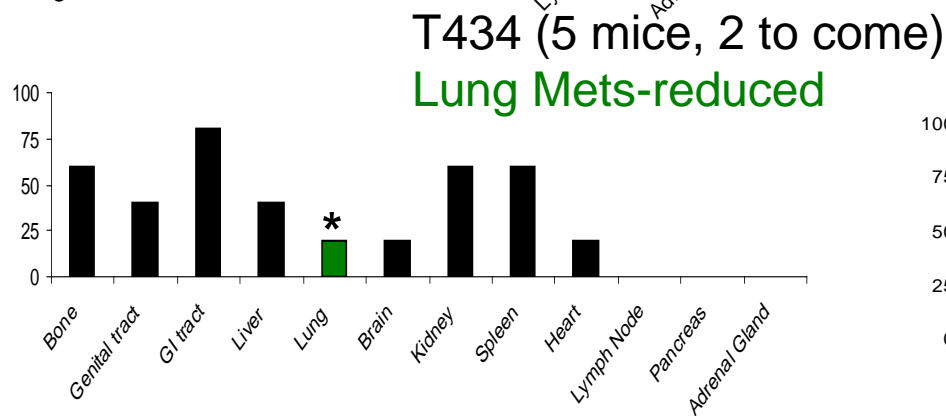
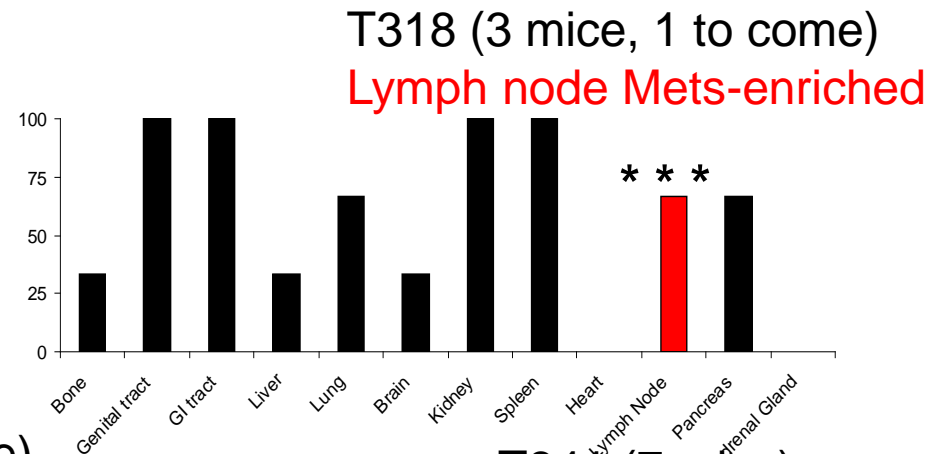
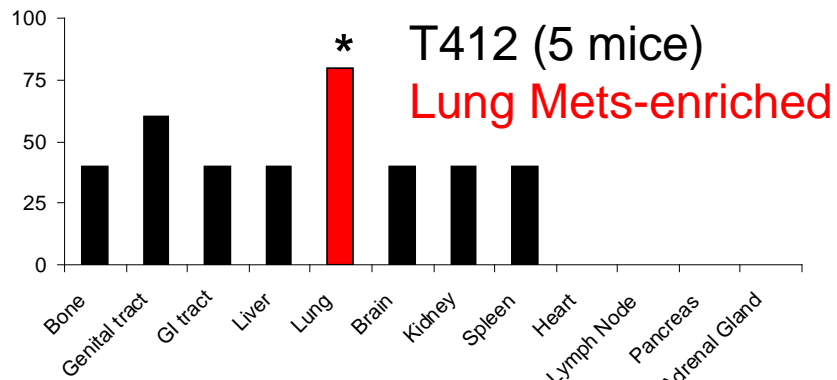
Variable	Hazard ratio (95% CI)	p-value
ER	0.78 [0.27-2.31]	0,66
PR	0.67 [0.23-1.92]	0,45
SBR Grade	2.94 [1.02-8.44]	4,60E-02
KI67	1.32 [0.46-3.82]	0,61
ALDH1	3.61 [1.12-11.65]	3,20E-02

PDX model for metastasis study



Metastatic patterns







Centre de Recherche en Cancérologie de Marseille



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Marion SALVADOR

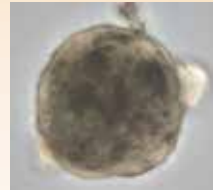
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Rita EL HELOU

Julien WICINSKI

Olivier CABAUD

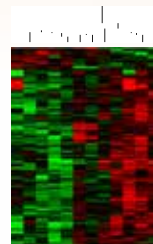
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J-F Saunière



University of Michigan

Max WICHA

Gabriela DONTU

Suling LIU

Hasan KORKAYA

Marc DIEBEL



Mofitt Cancer center

Said Sebti



IRIS

Stephane Depil

Helene Lelièvre

Laurence Kraus-Berthier