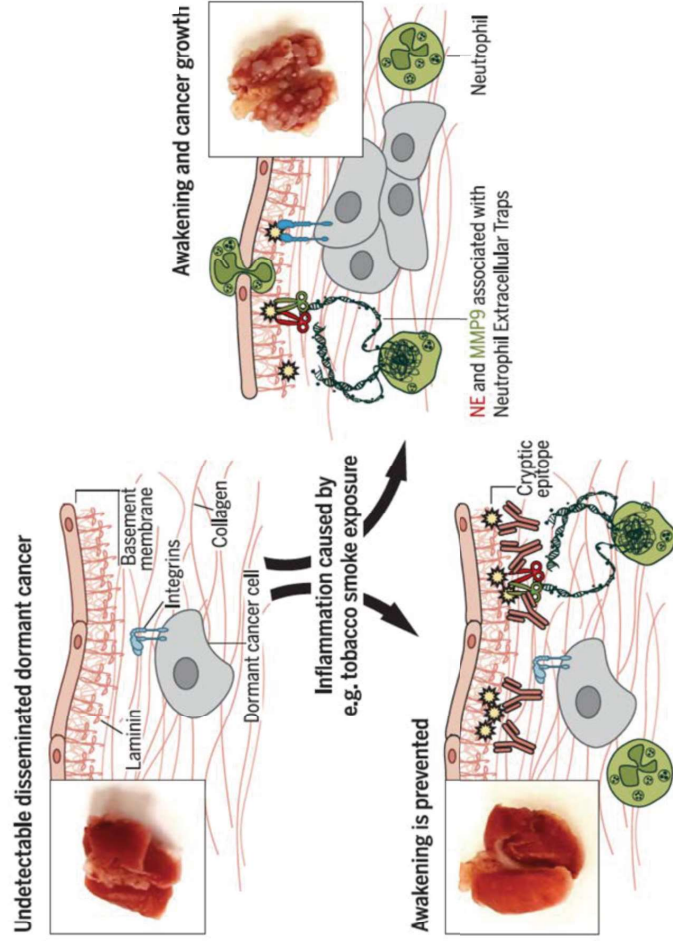


CANCER

Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice

Jean Albrengues, Mario A. Shields, David Ng, Chun Gwon Park, Alexandra Ambrico, Morgan E. Poindexter, Priya Upadhyay, Dale L. Uyeminami, Arnaud Pommier, Victoria Küttner, Emilis Bružas, Laura Maiorino, Carmelita Bautista, Ellese M. Carmona, Phyllis A. Gimotty, Douglas T. Fearon, Kenneth Chang, Scott K. Lyons, Kent E. Pinkerton, Lloyd C. Trotman, Michael S. Goldberg, Johannes T.-H. Yeh, Mikala Egeblad*



- Lung inflammation and the accompanying formation of Neutrophil Extracellular Traps (NETs) could convert dormant cancer cells to aggressive lung metastases;
- Could it be prevented by an antibody against the remodeled version of a matrix protein 'laminin-111' ?

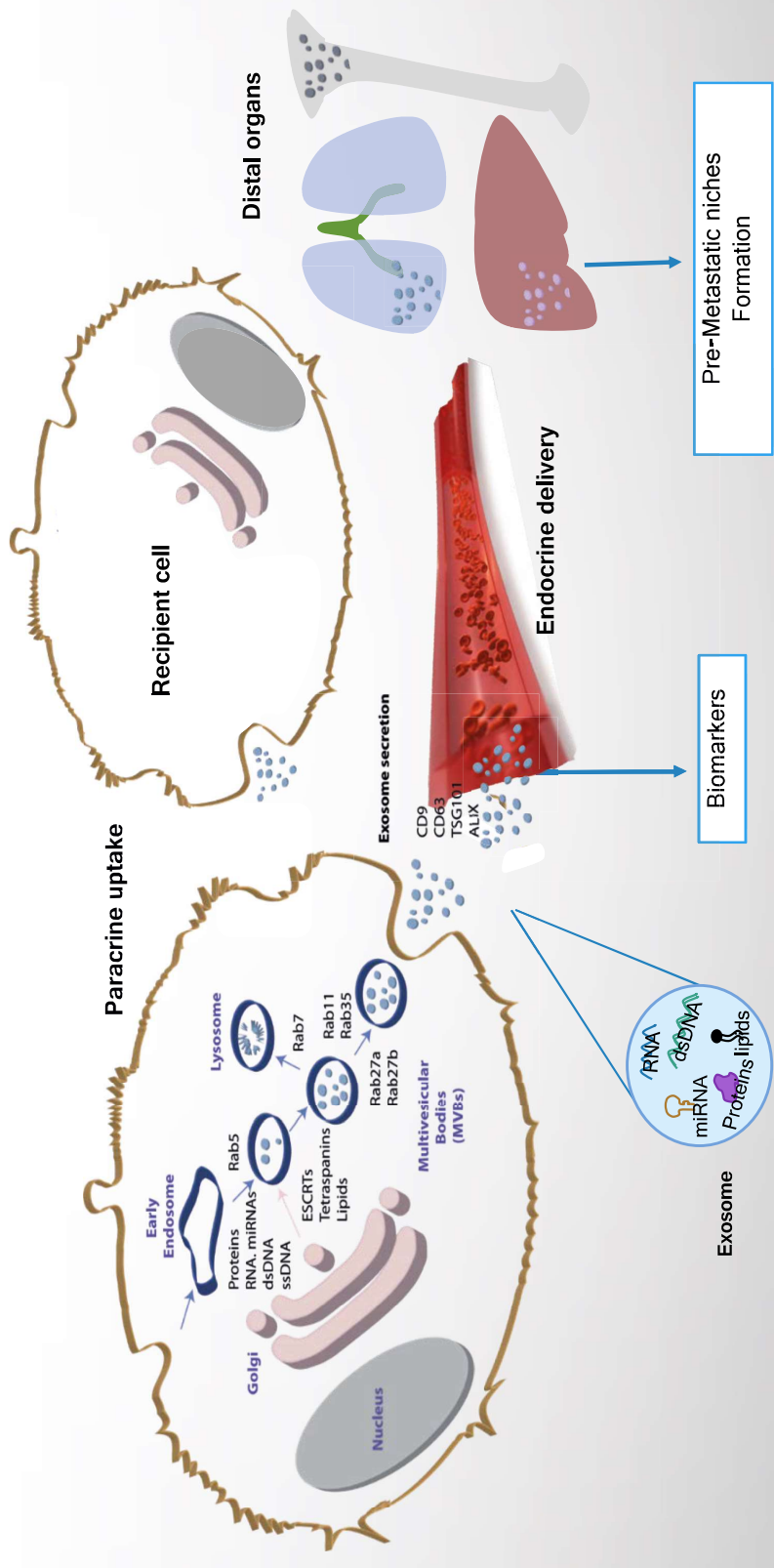
Tumour exosome integrins determine organotropic metastasis

Ayuko Hoshino^{1*}, Bruno Costa-Silva^{1*}, Tang-Long Shen^{1,2*}, Goncalo Rodrigues^{1,3}, Ayako Hashimoto^{1,4}, Milica Tesic Mark⁵, Henrik Molina⁵, Shinji Kohsaka⁶, Angela Di Giannatale¹, Sophia Ceder⁷, Swarnima Singh¹, Caitlin Williams¹, Nadine Soplop⁸, Kunihiko Uryu⁸, Lindsay Pharmed⁹, Tari King⁹, Linda Bojmar^{1,10}, Alexander E. Davies¹¹, Yonathan Ararso¹, Tuo Zhang^{1,12}, 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 Sandstrom¹⁰, Knut Jørgen Labori¹⁸, Elin H. Kure¹⁹, Paul M. Grandgenett²⁰, Michael A. Hollingsworth²⁰, Maria de Sousa^{1,3}, Sukhwinder Kaur²¹, Manesh Jain²¹, Kavita Mallya²¹, Surinder K. Batra²¹, William R. Jarnagin¹³, Mary S. Brady^{1,22}, Oystein Fodstad^{23,24}, Volkmar Muller²⁵, Klaus Pantel²⁶, Andy J. Minn²⁷, Mina J. Bissell¹¹, Benjamin A. Garcia²⁸, Yibin Kang^{29,30}, Vinagolu K. Rajasekhar³¹, Cyrus M. Ghajar³², Irina Matei¹, Hector Peinado^{1,33}, Jacqueline Bromberg^{34,35} & David Lyden^{1,14}

Ever since Stephen Paget's 1889 hypothesis, metastatic organotropism has remained one of cancer's greatest mysteries. Here we demonstrate that exosomes from mouse and human lung-, liver- and brain-tropic tumour cells fuse preferentially with resident cells at their predicted destination, namely lung fibroblasts and epithelial cells, liver Kupffer cells and brain endothelial cells. We show that tumour-derived exosomes uptaken by organ-specific cells prepare the pre-metastatic niche. Treatment with exosomes from lung-tropic models redirected the metastasis of bone-tropic tumour cells. Exosome proteomics revealed distinct integrin expression patterns, in which the exosomal integrins $\alpha_6\beta_4$ and $\alpha_6\beta_1$ were associated with lung metastasis, while exosomal integrin $\alpha_v\beta_5$ was linked to liver metastasis. Targeting the integrins $\alpha_6\beta_4$ and $\alpha_v\beta_5$ decreased exosome uptake, as well as lung and liver metastasis, respectively. We demonstrate that exosome integrin uptake by resident cells activates Src phosphorylation and pro-inflammatory *S100* gene expression. Finally, our clinical data indicate that exosomal integrins could be used to predict organ-specific metastasis.

Exosomes: their role in the metastatic cascade

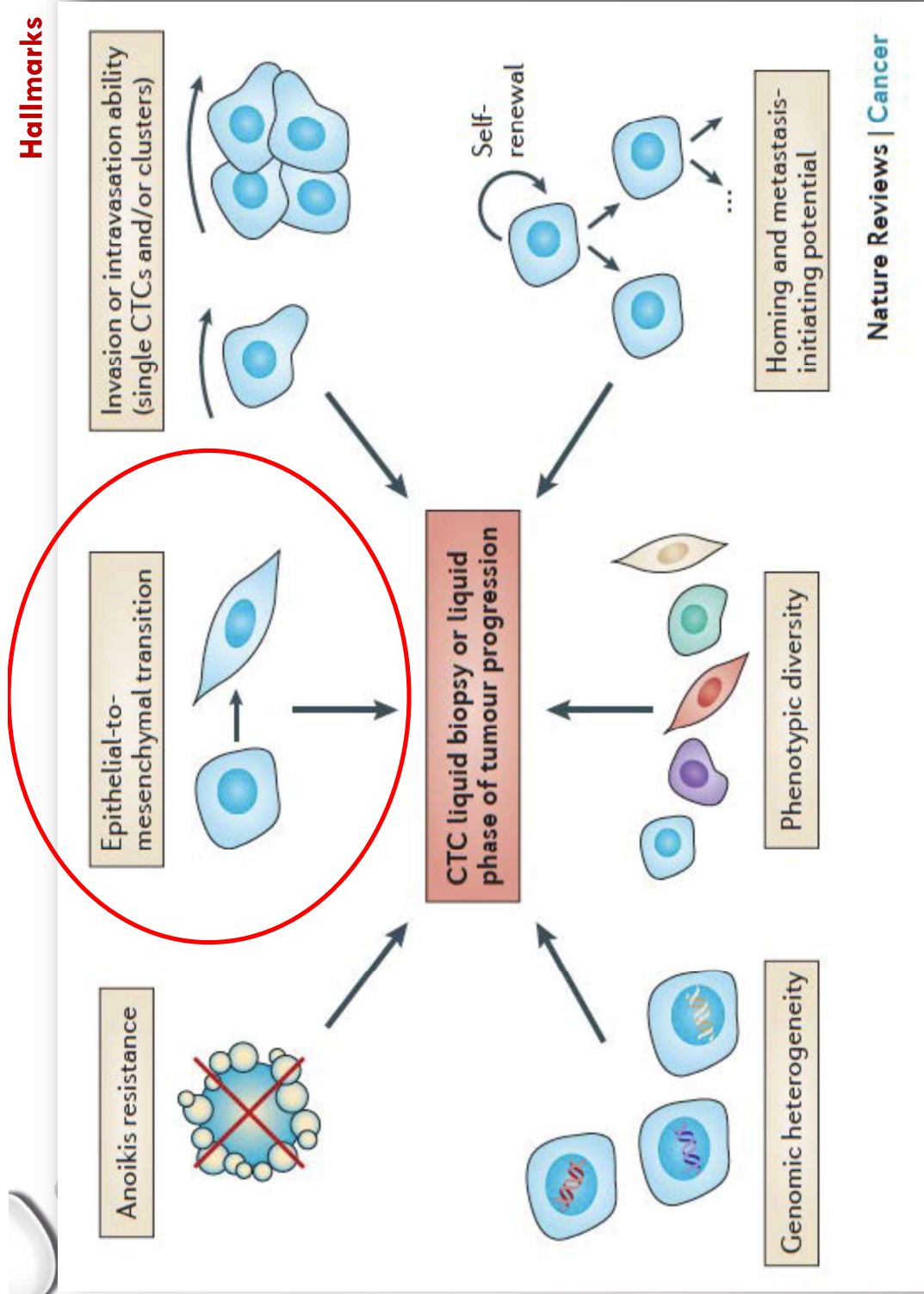
Exosomes as potential biomarkers in *liquid biopsy*



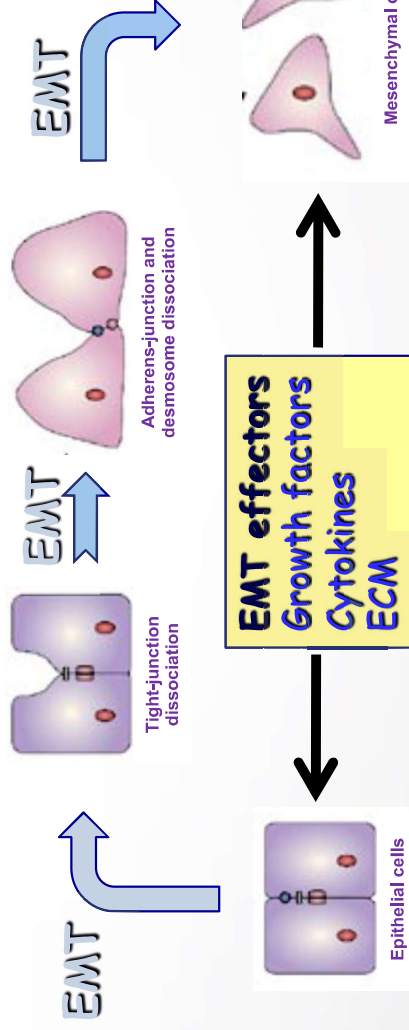
Hoshino, Pantel, Lyden et al. Nature 2015: Exosomes guide organ-specific metastasis

CTC BIOLOGY

Hallmarks



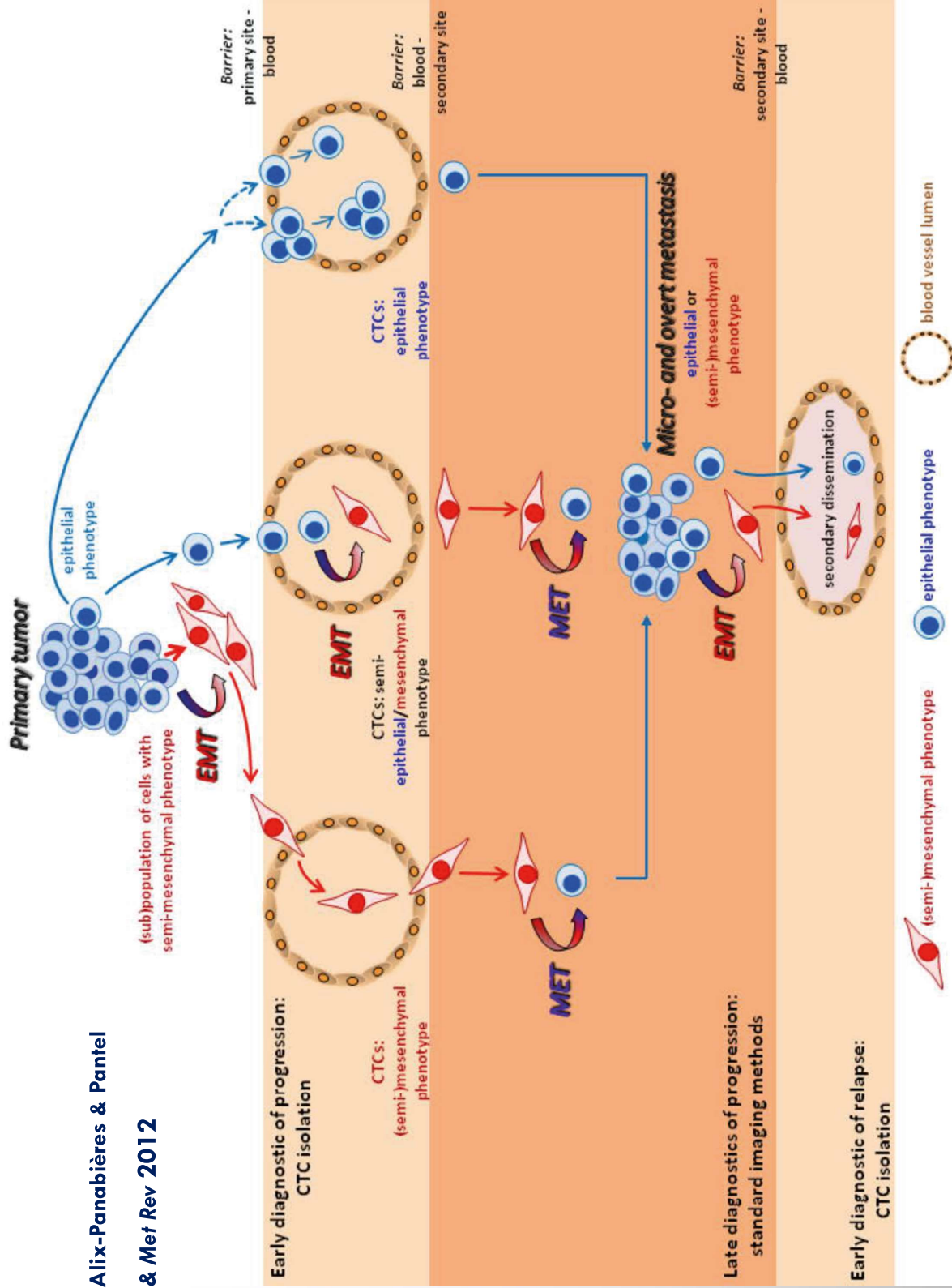
Epithelial-to-mesenchymal transition (EMT)



- Epithelial markers
- E-cadherin
 - Claudins
 - Occludins
 - Desmoplakin
 - Cytokeratin-8, -9, -18
 - Mucin-1

- Mesenchymal markers
- Fibronectin
 - Vitronectin
 - FSP1
 - Vimentin
 - Smooth-muscle actin
 - FGFR2 IIIb & IIIc variants

Bednarz-Knoll, Alix-Panabières & Pantel
Cancer & Met Rev 2012

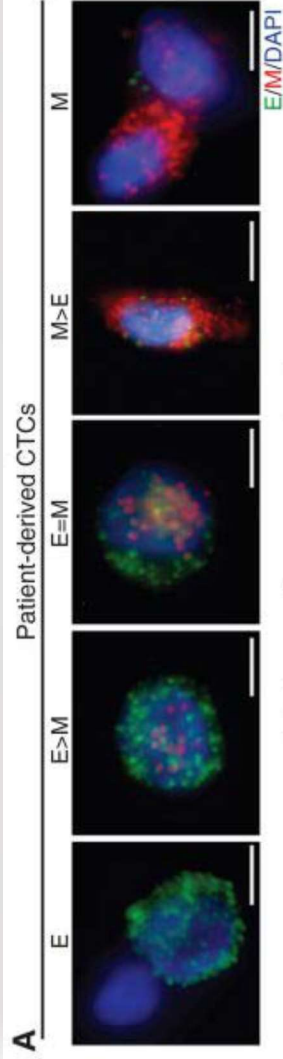


Science, 2013 Feb 1;339(6119):580-4. doi: 10.1126/science.1228522.

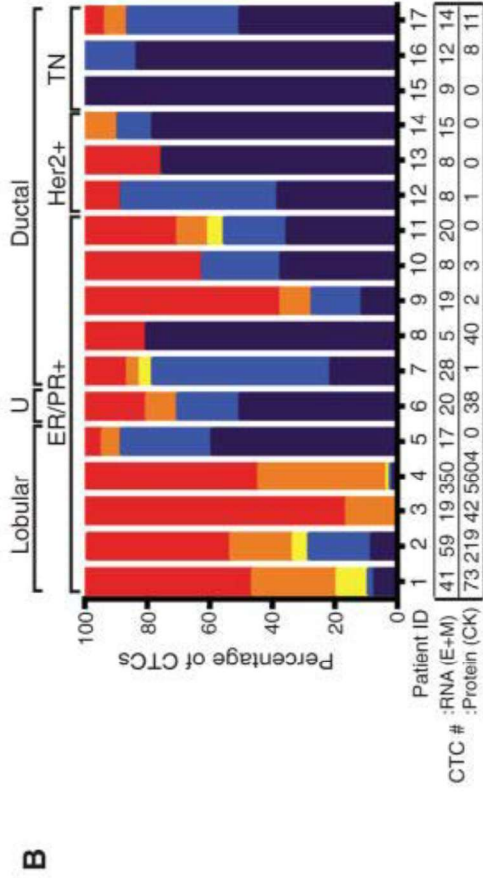
Circulating breast tumor cells exhibit dynamic changes in epithelial and mesenchymal composition.

Yu M, Bardia A, Wittner BS, Stott SL, Smas ME, Ting DT, Isakoff SJ, Ciciliano JC, Wells MN, Shah AM, Concannon KF, Donaldson MC, Sequist LV, Brachtel E, Sgroi D, Baselga J, Ramaswamy S, Toner M, Haber DA, Maheswaran S.
 Massachusetts General Hospital Cancer Center, Harvard Medical School, Charlestown, MA 02129, USA.

CK



VIM

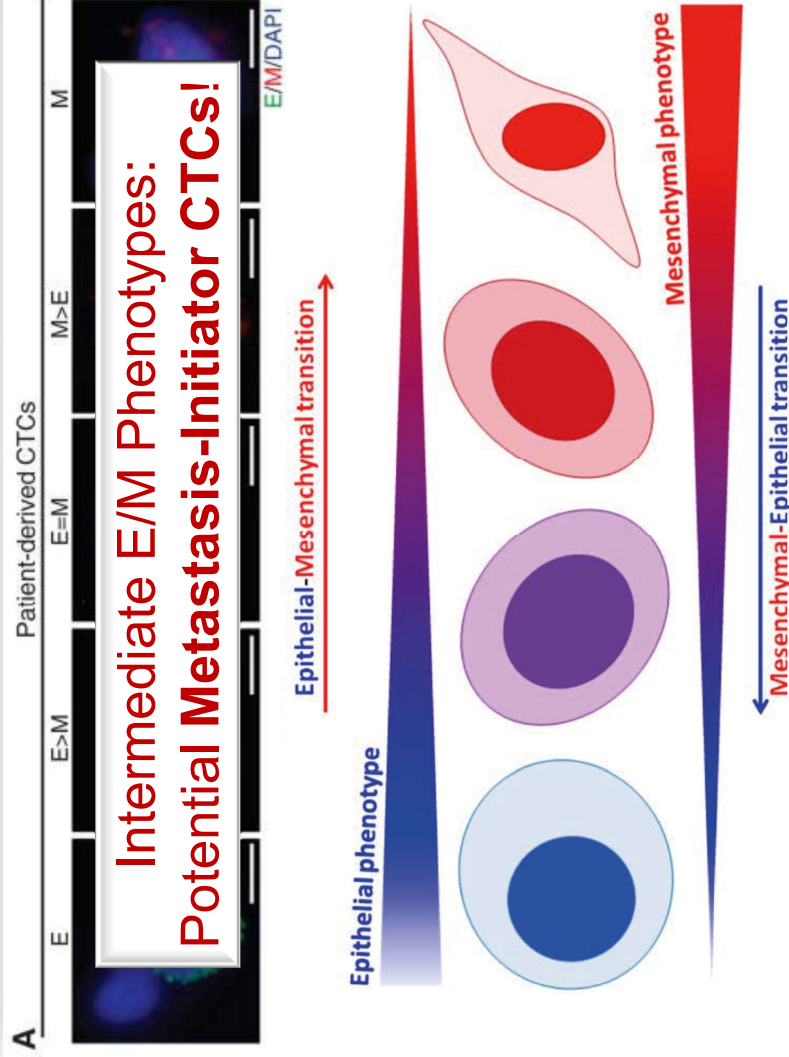


Science, 2013 Feb 1;339(6119):580-4. doi: 10.1126/science.1228522.

Circulating breast tumor cells exhibit dynamic changes in epithelial and mesenchymal composition.

Yu M, Bardia A, Wittner BS, Stott SL, Smas ME, Ting DT, Isakoff SJ, Ciciliano JC, Wells MN, Shah AM, Concannon KF, Donaldson MC, Sequist LV, Brachtel E, Sgroi D, Baselga J, Ramaswamy S, Toner M, Haber DA, Maheswaran S.

Massachusetts General Hospital Cancer Center, Harvard Medical School, Charlestown, MA 02129, USA.



Bednarz-Knoll, Alix-Panabières & Pantel Cancer & Met Rev 2012

Epithelial-mesenchymal plasticity in circulating tumor cells

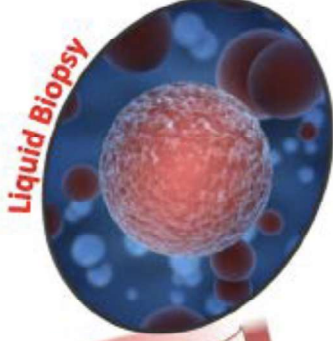
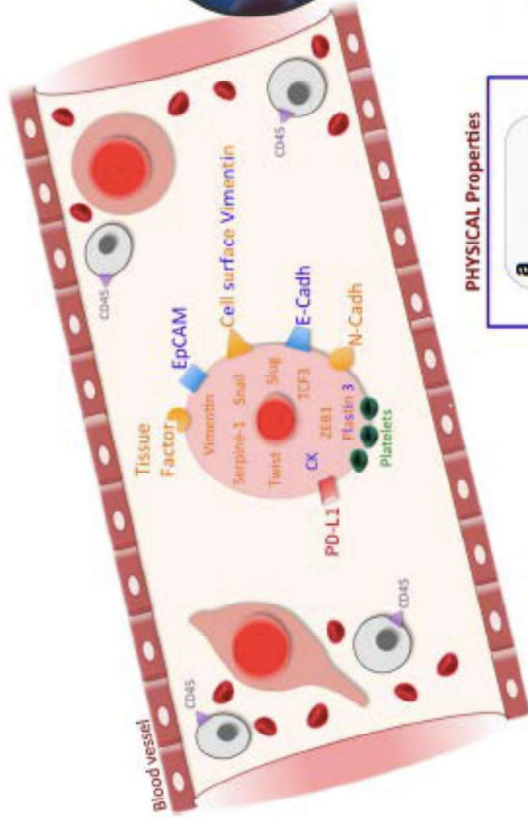
Catherine Alix-Panabières^{1,2} · Sonja Mader³ · Klaus Pantel³

Biology of CTCs and their epithelial-to-mesenchymal plasticity

Technologies for enrichment and detection of CTCs with high epithelial-mesenchymal plasticity

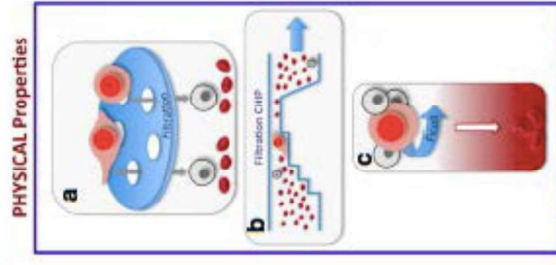
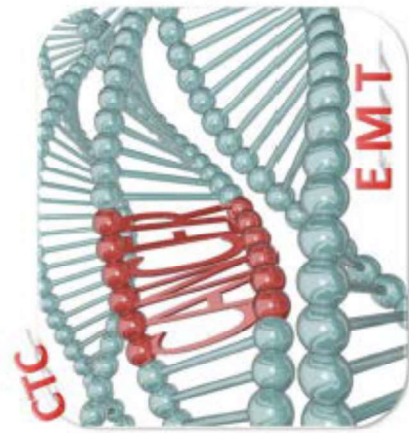
Clinical studies on the relevance of CTCs with high epithelial-mesenchymal plasticity

Epithelial-to-Mesenchymal Plasticity & CTCs

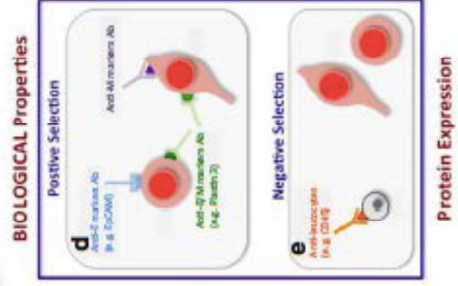


2017

Alix-Panabières... Pantel et al.



Size - Deformability - Density



Protein Expression



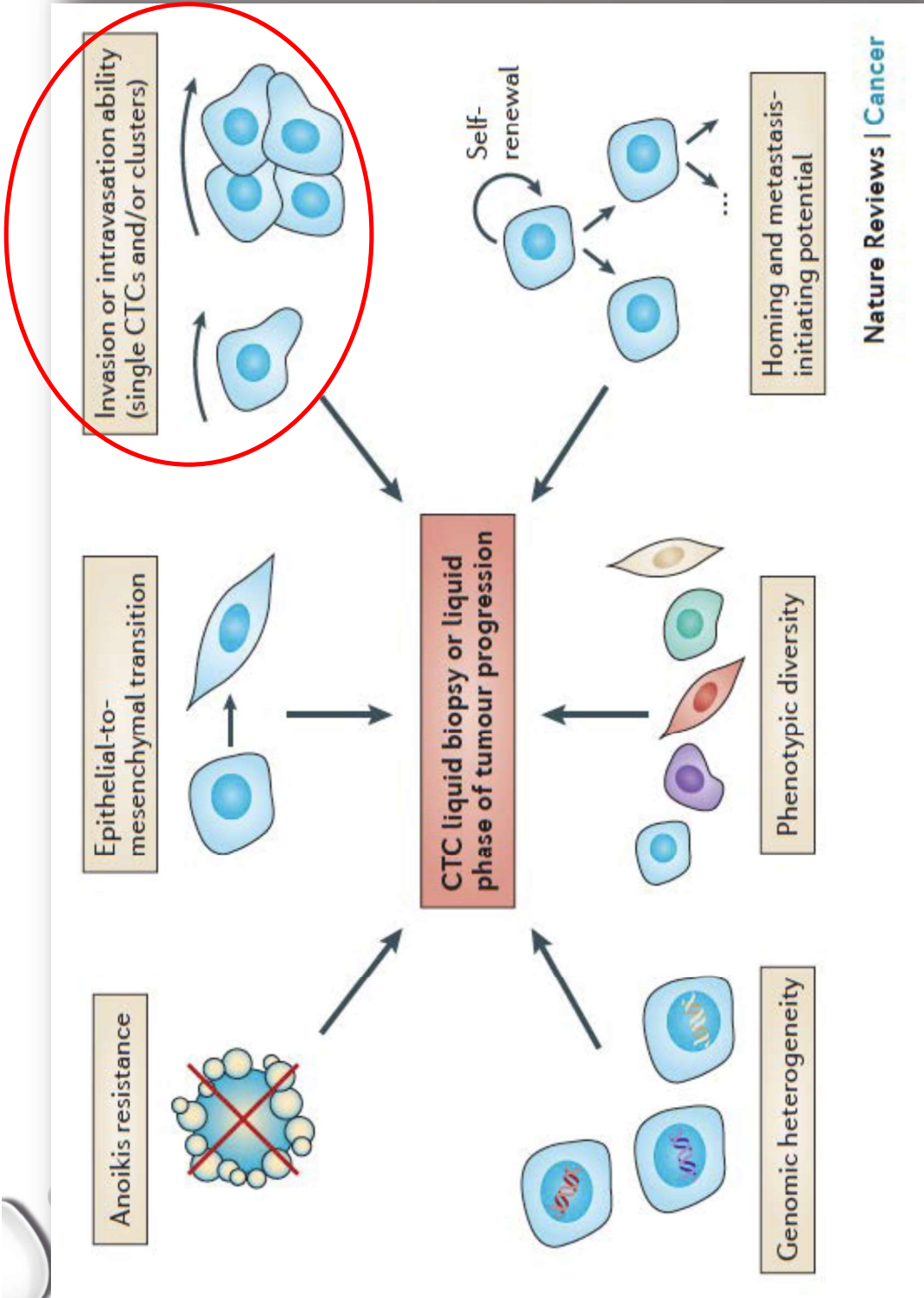
Plastin3 Is a Novel Marker for Circulating Tumor Cells Undergoing the Epithelial–Mesenchymal Transition and Is Associated with Colorectal Cancer Prognosis

Takehiko Yokobori^{1,2}, Hisae Iinuma³, Teppei Shimamura⁴, Seiya Imoto⁴, Keishi Sugimachi¹, Hideshi Ishii¹, Masaaki Iwatsuki¹, Daisuke Ota¹, Masahisa Ohkuma¹, Takeshi Iwaya¹, Naohiro Nishida¹, Ryunosuke Kogo¹, Tomoya Sudo¹, Fumiaki Tanaka¹, Kohei Shibata¹, Hiroyuki Toh⁷, Tetsuya Sato⁷, Graham F. Barnard¹⁰, Takeo Fukagawa⁵, Seiichiro Yamamoto⁶, Hayao Nakanishi⁸, Shin Sasaki⁷, Satoru Miyano⁴, Toshiaki Watanabe³, Hiroyuki Kuwano², Koshi Mimori¹, Klaus Pantel¹¹, and Masaki Mori⁹

PLS3 : specific, novel marker for the detection of CTCs, including EMT-induced tumor cells with a putative stem cell phenotype.

→ potentially overcomes the limitations of current epithelial markers (cytokeratins or EpcAM)

CTC BIOLOGY



Événement	Cadre	DAPI/CK-PE	CK-PE	DAPI	CD45-APC	<UDA>
1647	60					
683	37					
649	32					
1899	66					
2250	62					
1165	49					
2523	85					
3016	99					
2197	78					
1233	51					
97	88					

CTC

Large

Median

Small

M₁ COLON
CANCER

1 CTC
1 Leucocyte



IMPRIMER REVUE DE LA RECHERCHE

ID échantillon : 099132551656 ID cartouche : 01197136 Date d'impression : 20.09.2013 11:54
 Evénement Cadre DAPI/CK-PE DAPI CK-PE CD45-APC <UDA>

Evénement	Cadre	DAPI/CK-PE	DAPI	CK-PE	CD45-APC	<UDA>
188	10					
189	10					
2805	94					
2109	76					

Clusters

M1 COLON
CANCER



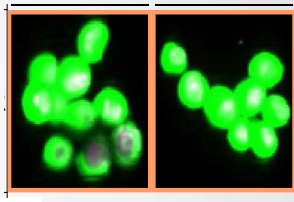
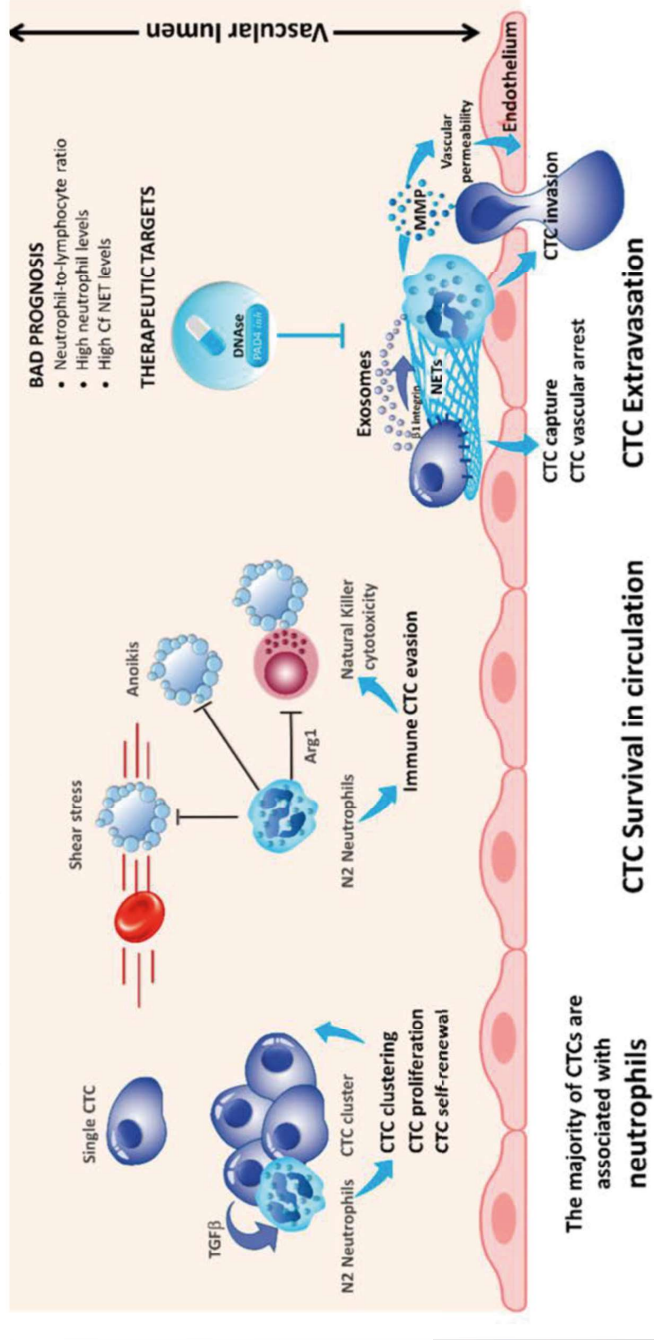
cells



Review

Never Travel Alone: The Crosstalk of Circulating Tumor Cells and the Blood Microenvironment

Simon Heeke ^{1,2}, Baharia Mograbi ^{1,2}, Catherine Alix-Panabières ³ and Paul Hofman ^{1,2,4,*}



Neutrophils escort circulating tumour cells to enable cell cycle progression

Barbara Maria Szczerba¹, Francesc Castro-Giner^{1,2}, Marcus Vetter^{3,4}, Ilona Krol¹, Sofia Gkoutela¹, Julia Landin⁴, Manuel C. Scheidmann¹, Cinzia Donato¹, Ramona Scherrer¹, Jochen Singer^{2,5}, Christian Beisel⁵, Christian Kurzeder^{3,6}, Viola Heinzelmann-Schwarz³, Christoph Rochlitz⁴, Walter Paul Weber⁶, Niko Beerenwinkel^{2,5} & Nicola Aceto^{1,*}

Cell



Article

Circulating Tumor Cell Clustering Shapes DNA Methylation to Enable Metastasis Seeding

Sofia Gkoutela,¹ Francesc Castro-Giner,^{1,2} Barbara Maria Szczerba,¹ Marcus Vetter,^{3,4} Julia Landin,^{4,5} Ramona Scherrer,¹ Ilona Krol,¹ Manuel C. Scheidmann,¹ Christian Beisel,⁶ Christian U. Stirmmann,⁷ Christian Kurzeder,^{3,5} Viola Heinzelmann-Schwarz,³ Christoph Rochlitz,⁴ Walter Paul Weber,⁵ and Nicola Aceto^{1,8,*}