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ESMO Preceptorship Programme

Breast Cancer

Multidisciplinary management, standards of care, therapeutic targets and future perspectives

Lisbon, Portugal

16-17 September 2016

THE INTERNATIONAL ACADEMY OF CYTOLOGY 1957

LNS LUXEMBOURG

LOCALLY ADVANCED BREAST CANCER

Definition and biology

Prof. Fernando Schmitt
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Laboratoire National de Santé, Luxembourg
General-Secretary of the International Academy of Cytology

Management of locally advanced breast cancer—perspectives and future directions

Konstantinos Tryfonidis, Elzbieta Senkus, Maria J. Cardoso and Fatima Cardoso

Abstract | Locally advanced breast cancer (LABC) constitutes a heterogeneous entity that includes advanced-stage primary tumours, cancers with extensive nodal involvement and inflammatory breast carcinomas. Although the definition of LABC can be broadened to include some large operable breast tumours, we use this term to strictly refer to inoperable cancers that are included in the above-mentioned categories. The prognosis of such tumours is often unfavourable; despite aggressive treatment, many patients eventually develop distant metastases and die from the disease. Advances in systemic therapy, including radiation treatment, surgical techniques and the development of new targeted agents have significantly improved clinical outcomes for patients with this disease. Notwithstanding these advances, LABC remains an important clinical problem, particularly in developing countries and those without widely adapted breast cancer awareness programmes. The optimal management of LABC requires a multidisciplinary approach, a well-coordinated treatment schedule and close cooperation between medical, surgical and radiation oncologists. In this Review, we discuss the current state of the art and possible future treatment strategies for patients with LABC.

Tryfonidis, K. *et al. Nat. Rev. Clin. Oncol*. advance online publication 10 February 2015; doi:10.1038/nrclinonc.2015.13

LOCALIZED ADVANCED BREAST CANCER (LABC) DEFINITION

- T0-T3 primary tumours with clinically detectable axillary, ipsilateral infraclavicular, supraclavicular or internal mammary lymph nodes (N2-N3) or tumour extension to the chest wall or skin (T4) regardless of nodal status.

- Inflammatory breast carcinoma (IBC)

LOCALIZED ADVANCED BREAST CANCER (LABC) DEFINITION

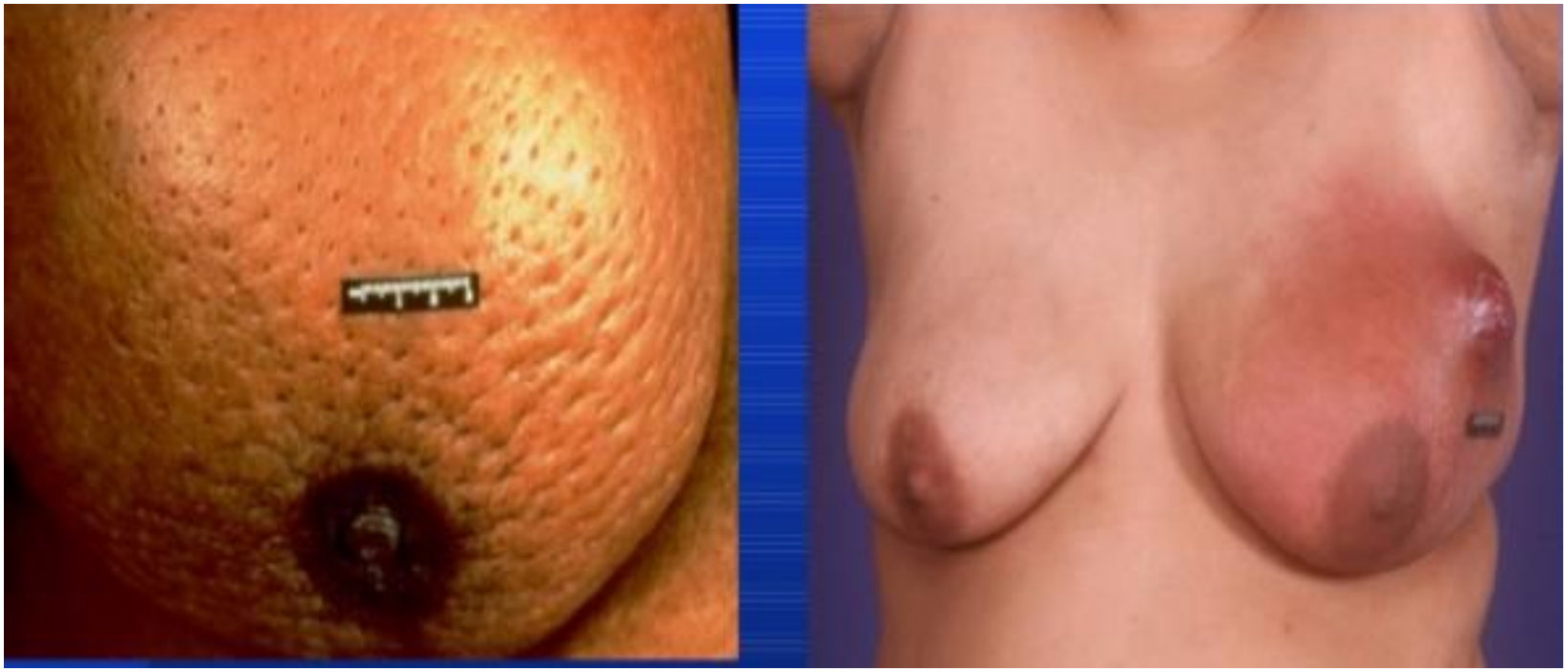
- Tumours more than 5 cm in size with regional lymphadenopathy (N1–3)
- Tumours of any size with direct extension to the chest wall or skin, or both (including ulcer or satellite nodules), regardless of regional lymphadenopathy
- Presence of regional lymphadenopathy (clinically fixed or matted axillary lymph nodes, or any of infraclavicular, supraclavicular, or internal mammary lymphadenopathy) regardless of tumour stage

National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer.* Ver. 2.2015. Fort Washington, PA: NCCN; 2015. [Current ver-

LOCALIZED ADVANCED BREAST CANCER (LABC) DEFINITION

- **“INOPERABLE CASES WITH INFLAMMATORY AND/OR EXTENSIVE SKIN INVOLVEMENT, FIXED OR VERY BULKY AXILLARY NODAL DISEASE AND/OR SUPRACLAVICULAR OR INTERNAL MAMMARY NODAL INVOLVEMENT”.**

LOCALIZED ADVANCED BREAST CANCER (LABC) DEFINITION



LOCALIZED ADVANCED BREAST CANCER (LABC) EPIDEMIOLOGY AND RISK FACTORS

- 8.5% of American and 4% of European patients, however can reach as high as 60% in low-resources countries.
- This percentage decrease in populations undergoing regular screening programmes.
- Risk factors (IBC): race (black and Hispanic), obesity, young age at first delivery, rural residence and longer cumulative duration of breastfeeding.

LOCALIZED ADVANCED BREAST CANCER (LABC) PROGNOSIS

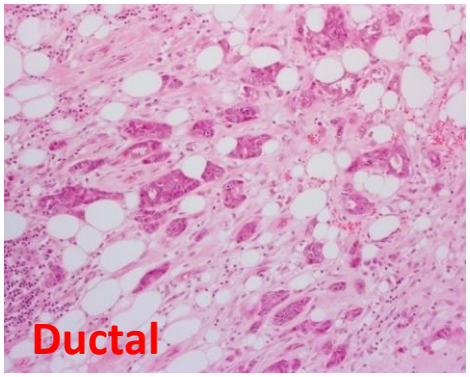
5-YEAR SURVIVAL IN BREAST CANCER, ACCORDING TO STAGE

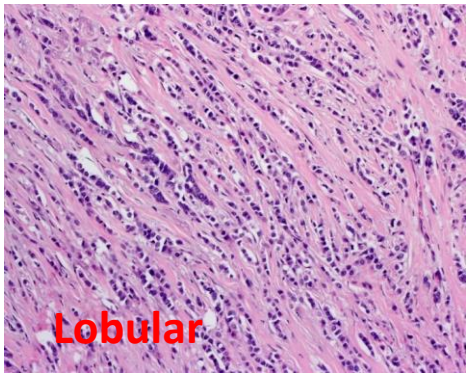
STAGE	5-YEAR SURVIVAL (%)
IIA	85 %
IIB	70 %
IIIA	52 %
IIIB	48 %
IV	18 %

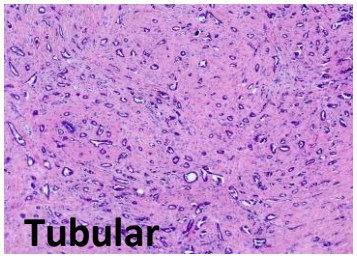
LABC

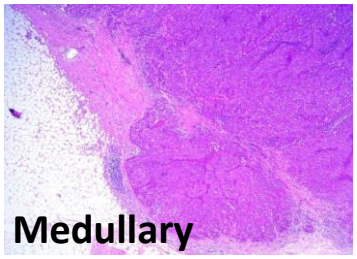
For primary IBC the 5-Y survival range from 25% to 48% and it is worst than non-inflammatory LABC

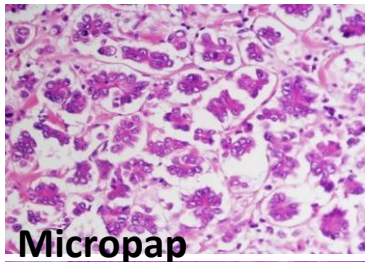
LOCALIZED ADVANCED BREAST CANCER (LABC)
HISTOLOGICAL TYPE

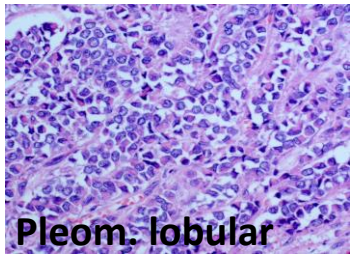


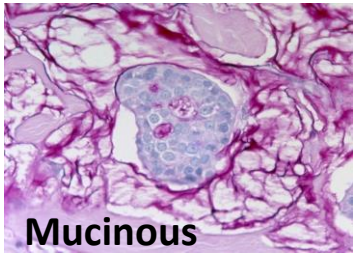


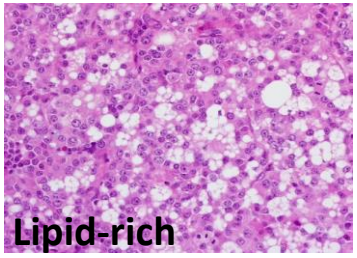


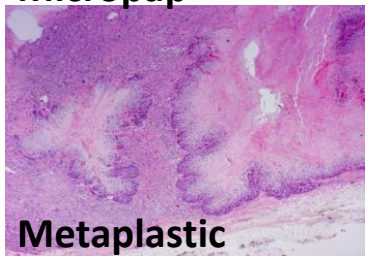


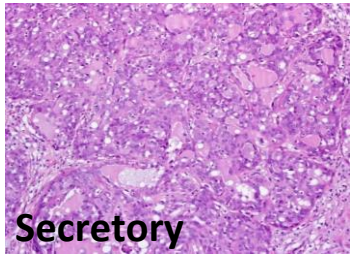












LOCALIZED ADVANCED BREAST CANCER (LABC) MOLECULAR SUBTYPE

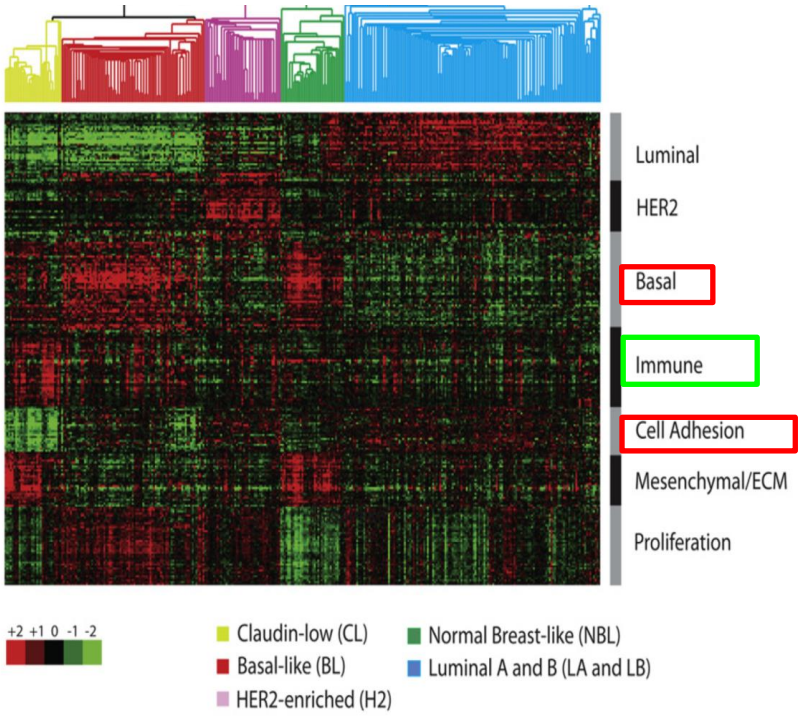
Prat et al. Breast Cancer Research 2010, 12:R68
http://breast-cancer-research.com/content/12/5/R68

Breast Cancer RESEARCH

RESEARCH ARTICLE Open Access

Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer

Aleix Prat[1,2,3], Joel S Parker[1,2†], Olga Karginova[1,2,3†], Cheng Fan[1], Chad Livasy[1,3], Jason I Herschkowitz[4], Xiaping He[1,2,3], Charles M Perou[1,2,3*]



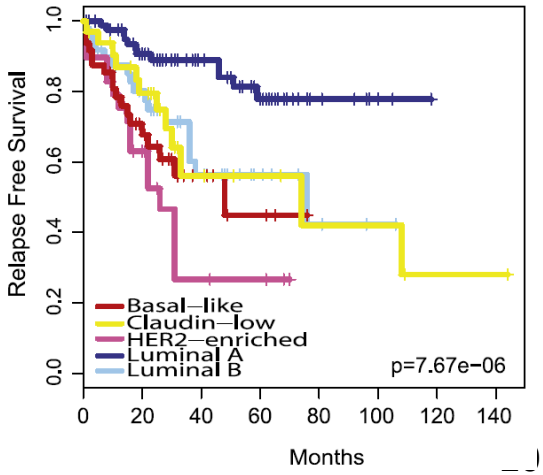
LUMINAL A: ER+/PgR+/HER2-

LUMINAL B: ER+/PgR+/HER2+and or Ki67+

HER-OE: ER-/PgR-/HER2+

BASAL-LIKE:ER-/PgR-/HER2-/Basal Markers

CLAUDIN-LOW:ER-/Pg-/HER2-/Claudin^{low}



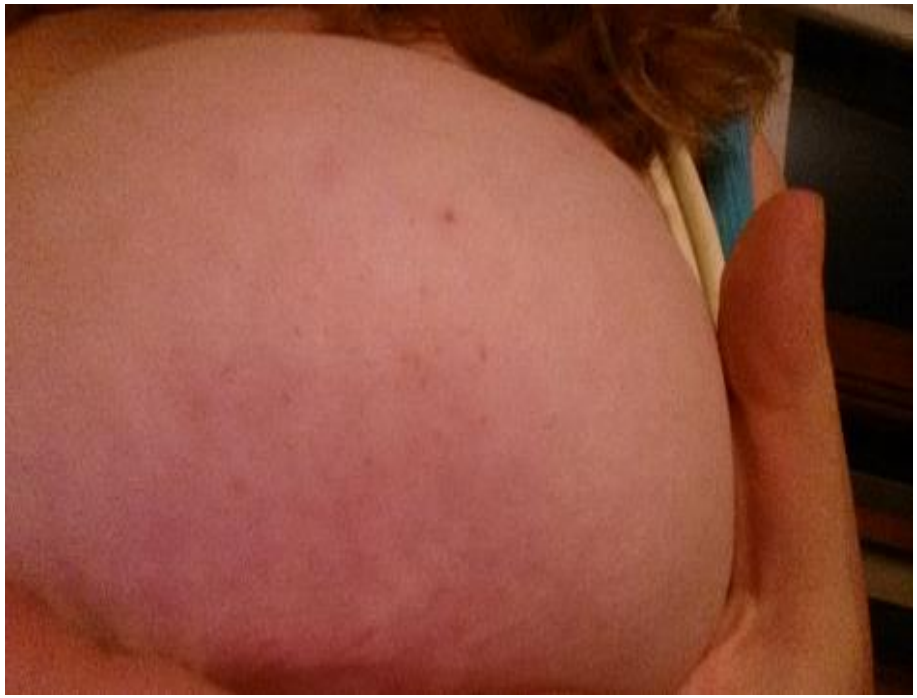
INFLAMMATORY BREAST CARCINOMA (IBC) DEFINITION

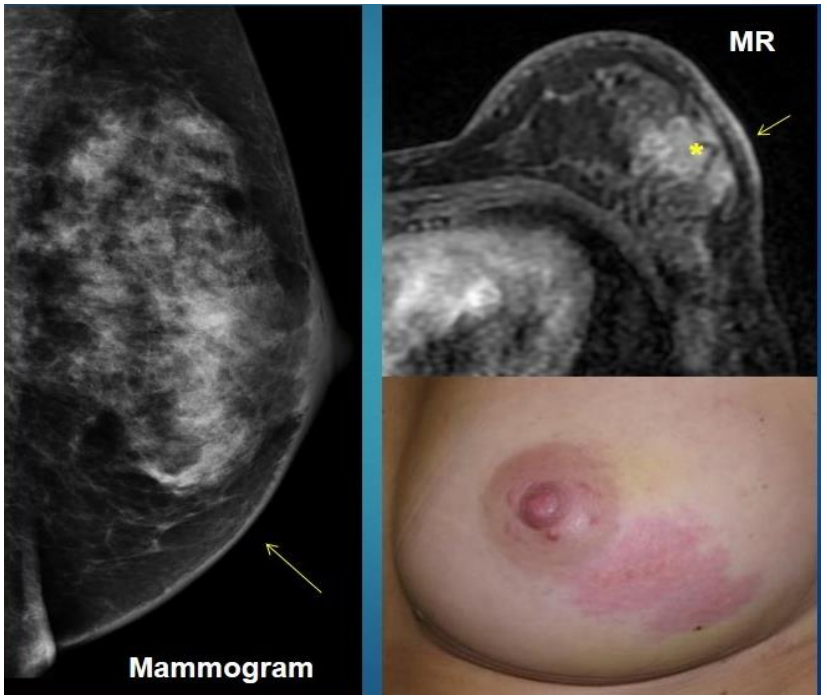
- “When a purple colour is on the skin over the tumour it is a very unpropitious beginning”. Charles Bell, 1807

- 1924: Lee and Tannenbaum proposed the currently used term *inflammatory carcinoma*.

- « A clinical and pathological entity characterized by erythema and oedema involving a third or more of the skin of the breast » - AJCC definition.

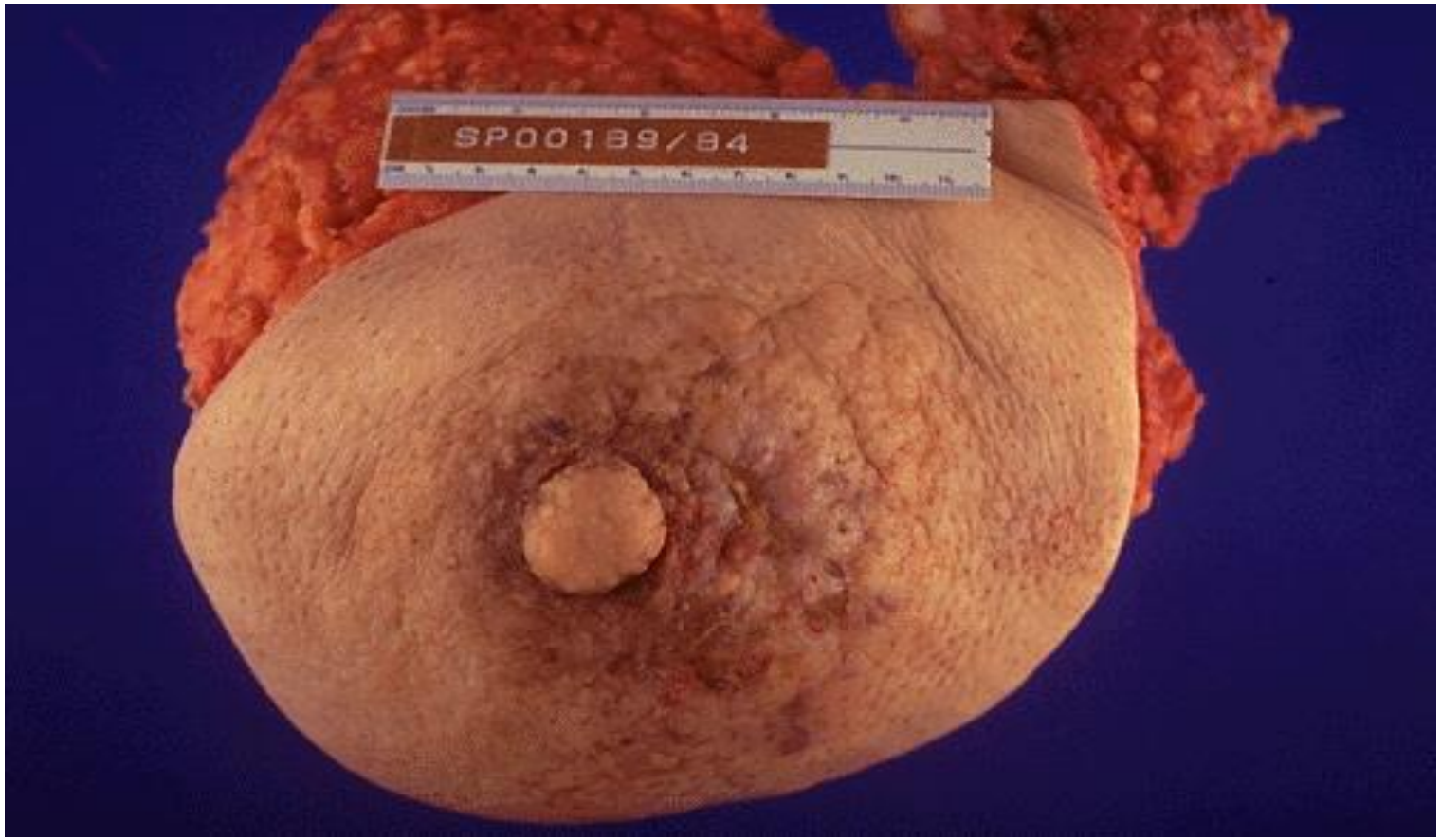
INFLAMMATORY BREAST CARCINOMA (IBC)



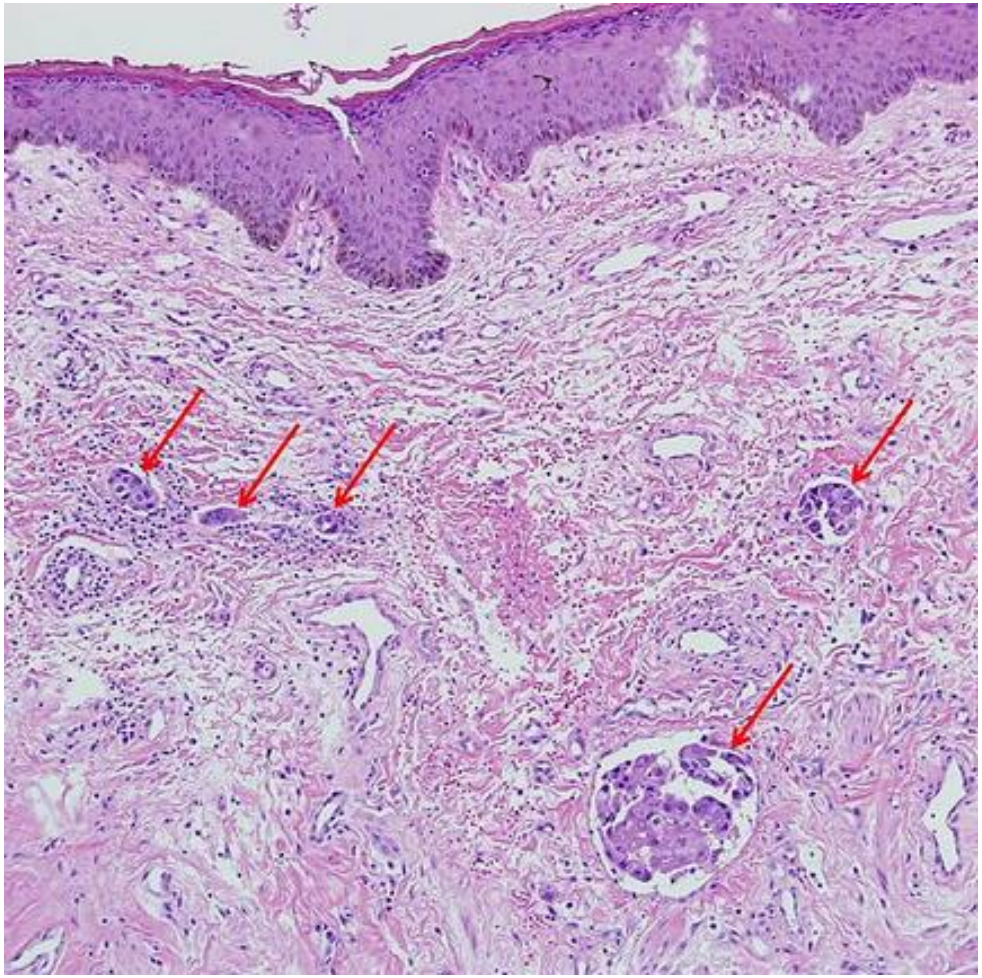


- 1-5% of invasive breast carcinomas
- 8.5% of LABC

INFLAMMATORY BREAST CARCINOMA (IBC) PATHOLOGY



INFLAMMATORY BREAST CARCINOMA (IBC) PATHOLOGY



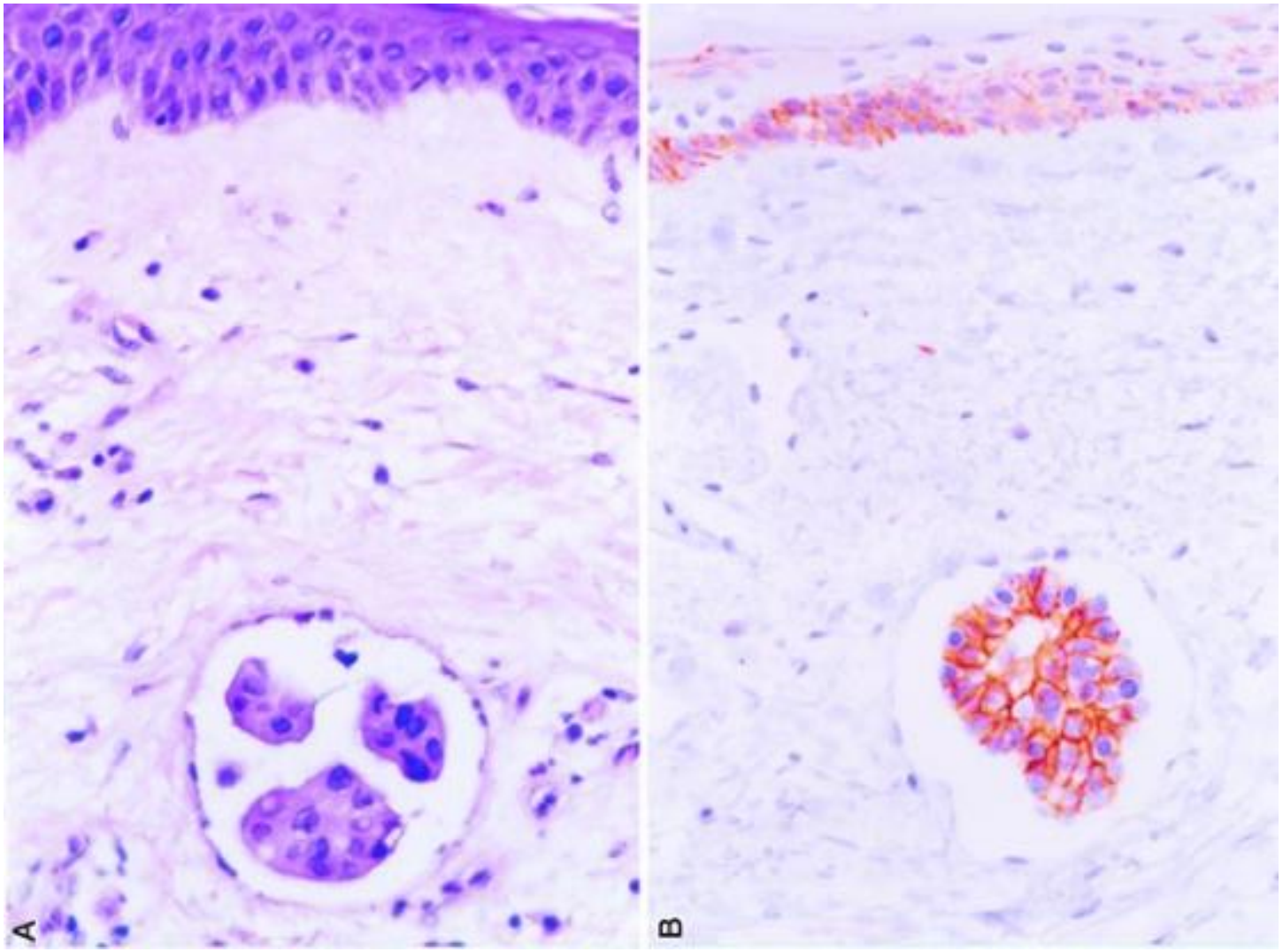
INFLAMMATORY BREAST CARCINOMA (IBC) PATHOLOGY

- Macroscopically the tumours are frequently indistinct, present throughout the breast.
- Histologically are IDC, grade 3, frequently present in lymphatic spaces in dermis.
- Cutaneous ulceration and Paget disease are rare.

INFLAMMATORY BREAST CARCINOMA (IBC) IMMUNOHISTOCHEMICAL PROFILE

- More frequently ER and PR negative.
- HER2 more frequently positive (41%) than non IBC.
- P53 positive in up to 84% of the cases.
- High KI 67 index
- E-cadherin positive
- High angiogenic index

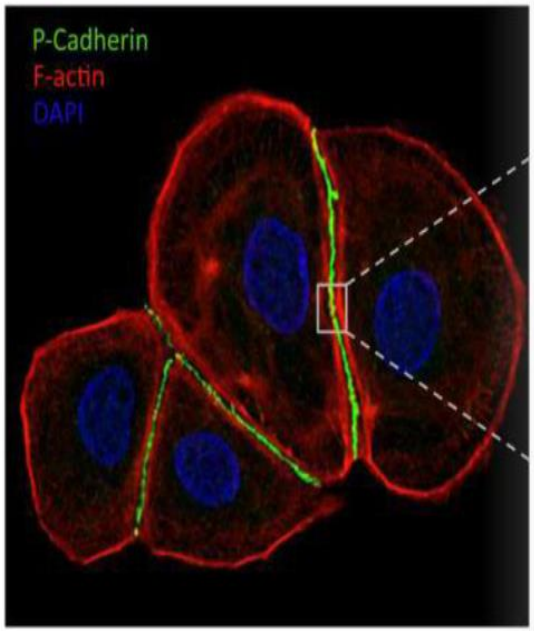
INFLAMMATORY BREAST CARCINOMA (IBC)
E-CADHERIN EXPRESSION

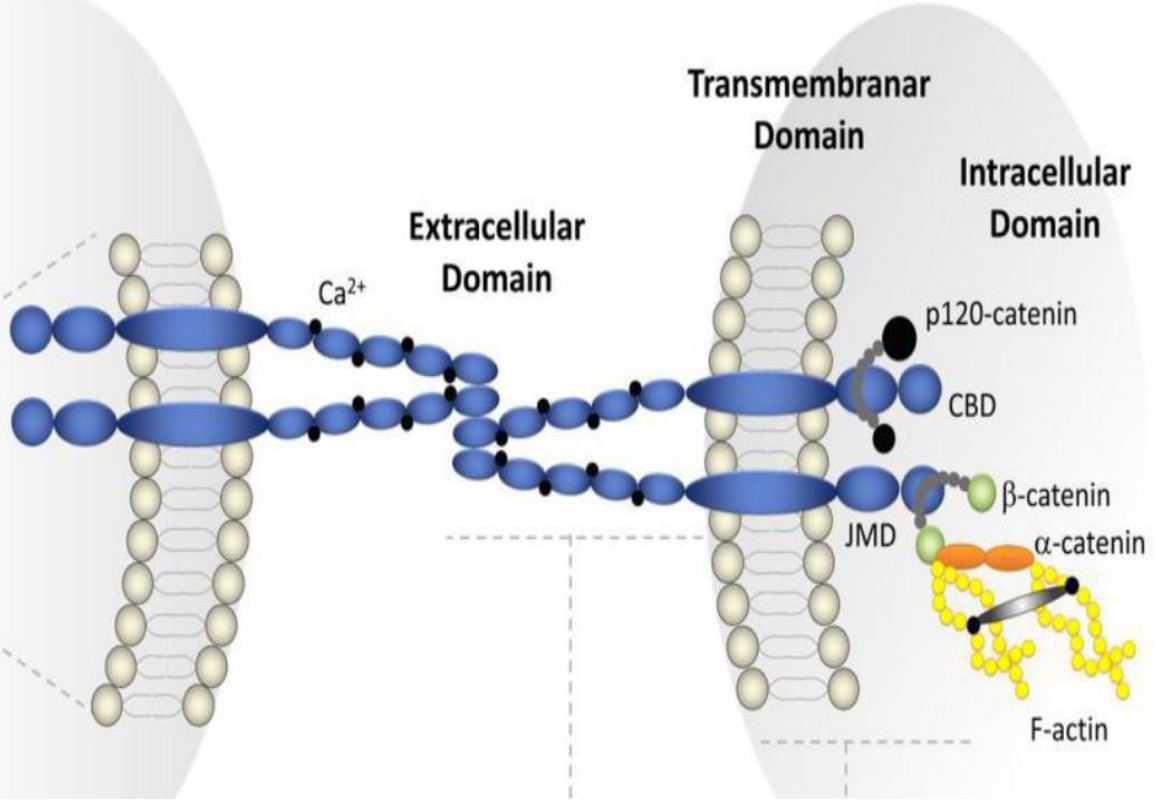


Classical Cadherin family

Epithelial cadherin – E-cadherin

Placental cadherin – P-cadherin





Cadherin/catenin complexes

- **Cell Shape and polarity**
- **Cytoskeleton Organization**
- **Differentiation**
- **Cell Motility**
- **Signaling pathway**

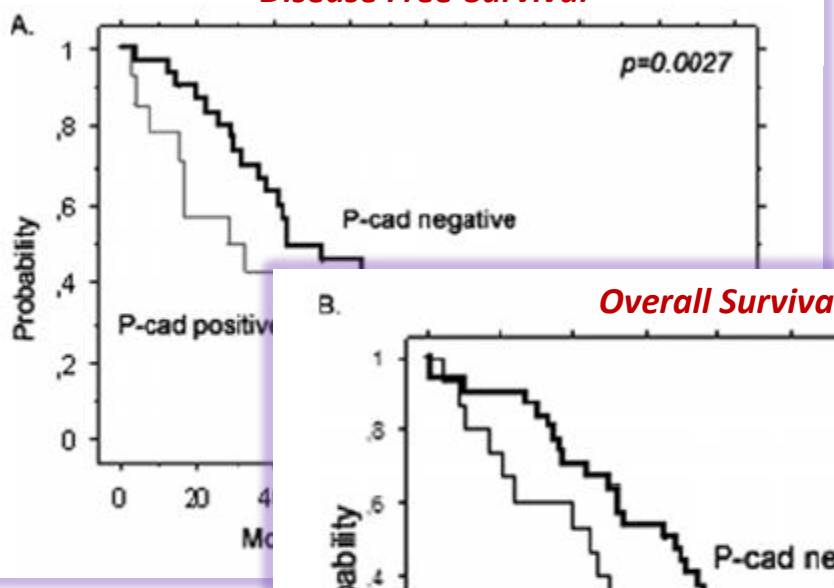
Albergaria A et al. Int J Dev Biol, 2011

P-Cadherin Overexpression Is an Indicator of Clinical Outcome in Invasive Breast Carcinomas and Is Associated with *CDH3* Promoter Hypomethylation

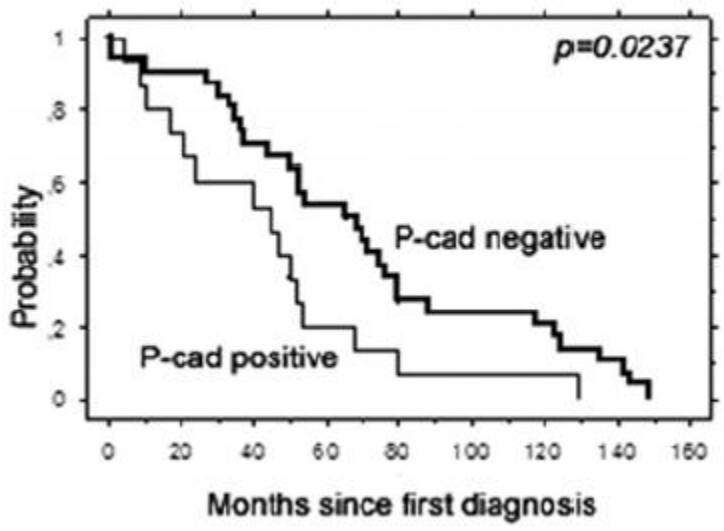
Joana Paredes,[1] André Albergaria,[1] João T. Oliveira,[1] Carmen Jerónimo,[2,3] Fernanda Milanezi,[1,5] and Fernando C. Schmitt[1,4]

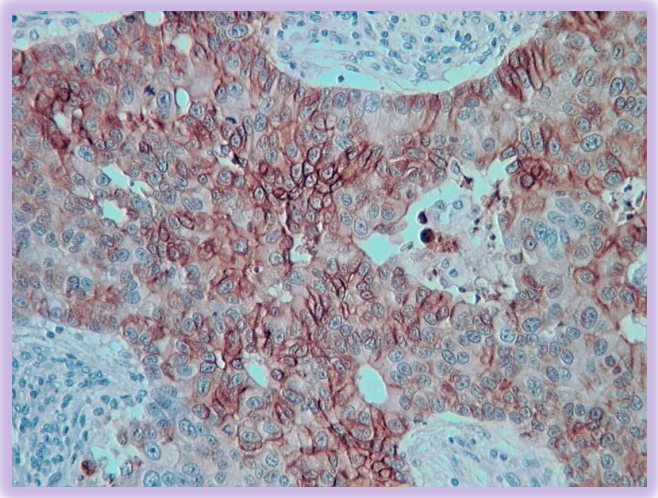
Clin Cancer Res 2005;11 (16) August 15, 2005

Disease Free-Survival



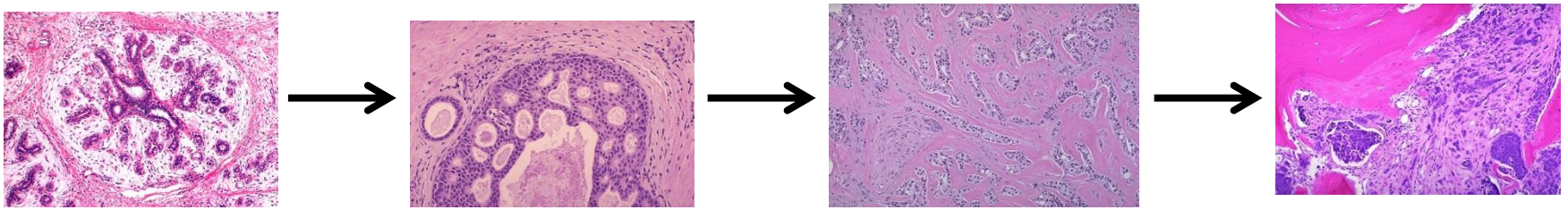
Overall Survival

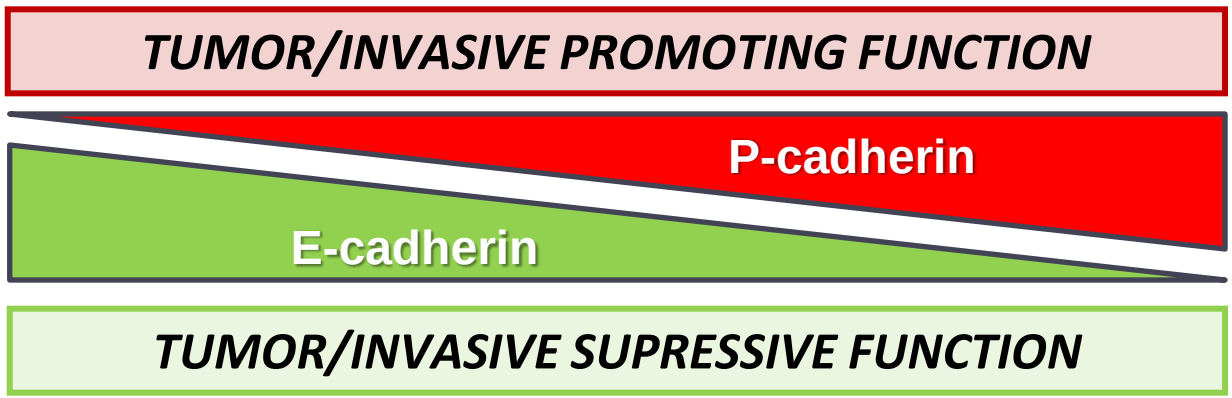




P-cadherin expression is significantly associated with decreased survival in a short-term follow-up (≈ 5 years after diagnosis)

E- and P-cadherin role in cancer progression





Mechanisms involved in the process of progression and expression:

- promoter hypomethylation
- inactivation of P-cadherin transcription repressors (BRCA1, ER-α)
- induction of P-cadherin transcription activators (cEBP-β, p63 and β-ctn)

Mechanisms involved in the process of progression and expression inactivation or downregulation:

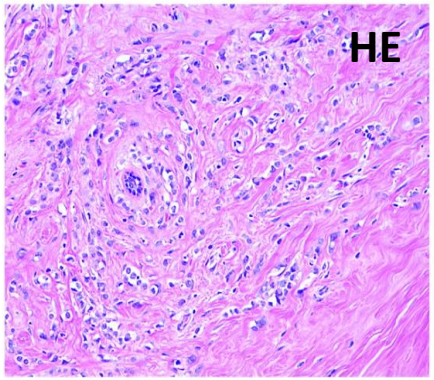
- gene mutations
- loss of heterozygozity
- promoter hypermethylation
- expression of E-cadherin repressors

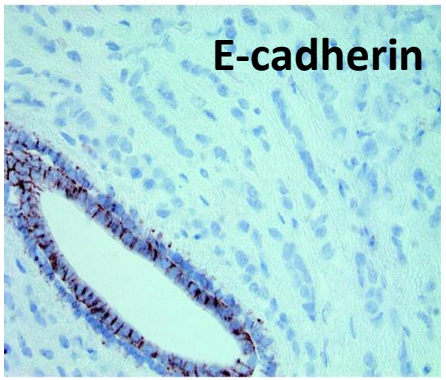
E- and P-cadherin in Breast Cancer

Invasive Lobular Carcinoma

• Represent about 10 -15% of all invasive breast carcinomas

• Loss of cell-cell adhesion (E-cadherin negative)



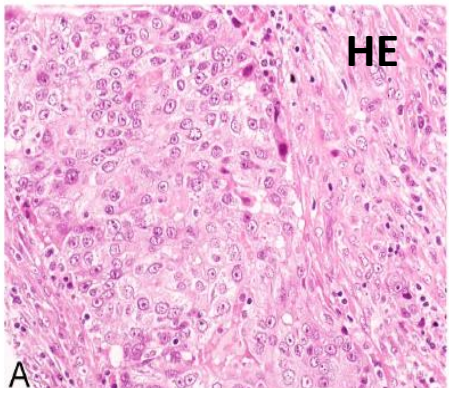


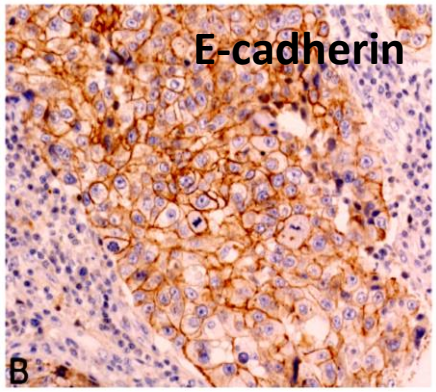
Invasive Ductal Carcinoma

• Most common type of breast cancer

• Represent 85 – 90% of all breast cancers

• Maintenance of cell-cell adhesion (E-cad positive)





E-cadherin expression is retained:

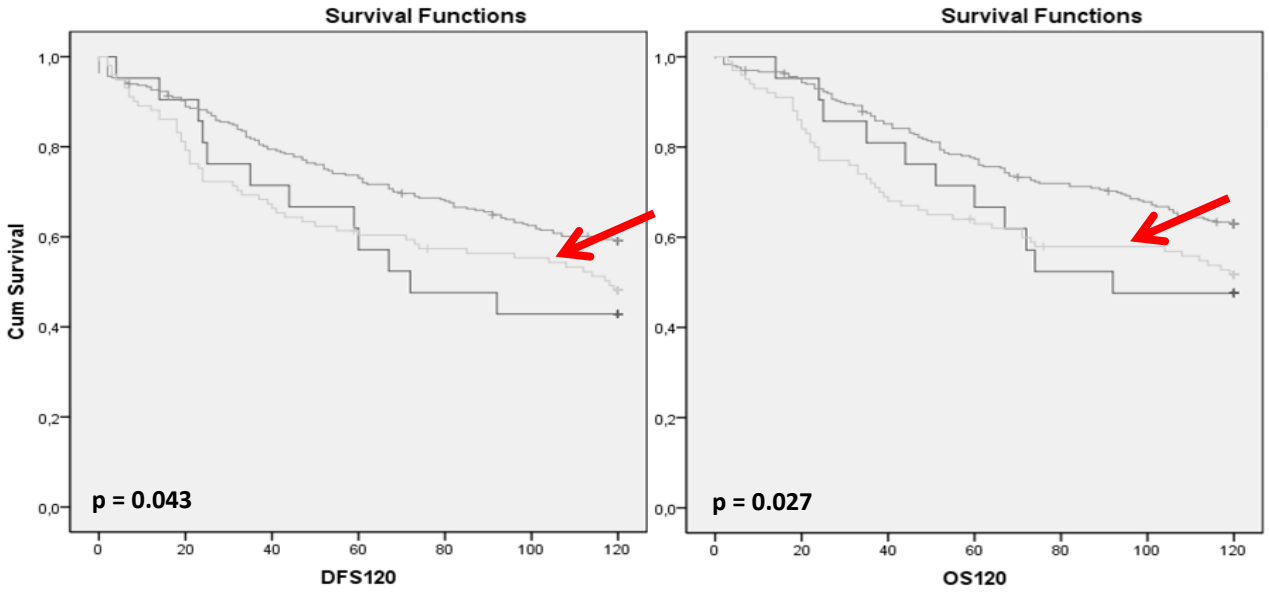
• mouse 4T1 highly metastatic breast cancer cell model

• inflammatory breast cancer

• derivative metastases

Masciari S et al. J Med Genet, 2007

Prognosis of E- and P-Cadherin co-expression in Breast Cancer



Ecad+/Pcad- (n=298)

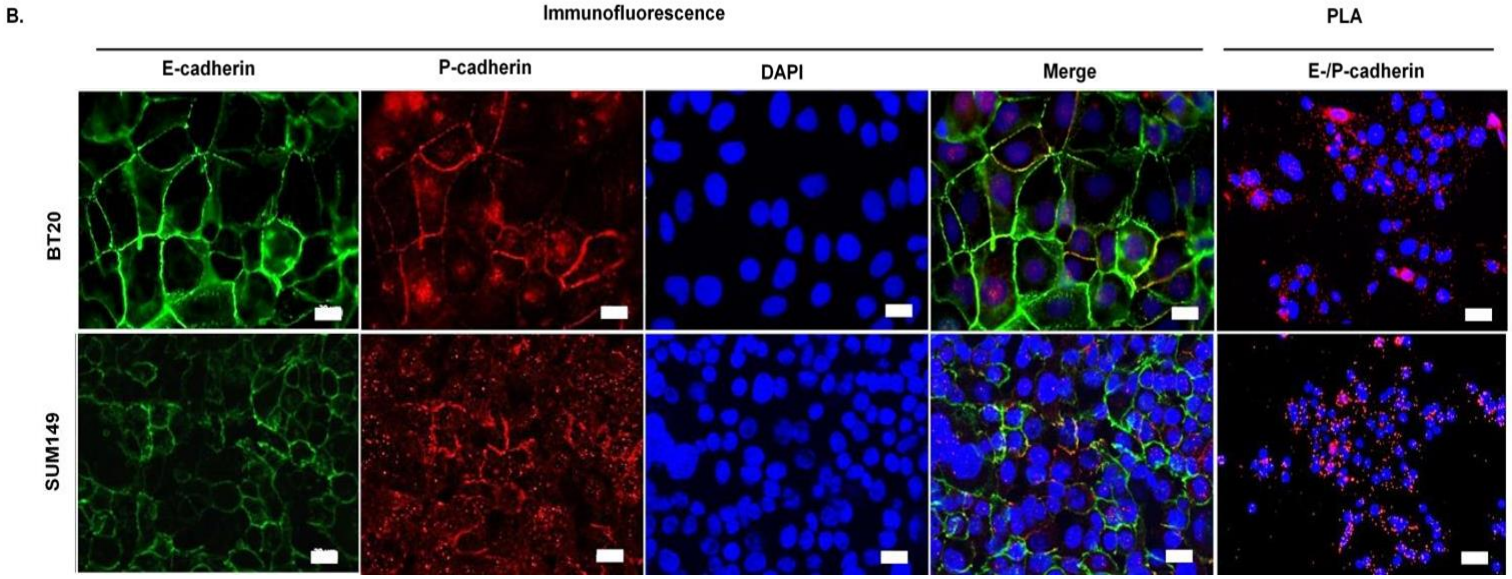
Ecad+/Pcad+ (n=100)

Ecad-/Pcad- (n=21)

		Univar ate Cox Proportional hazard analysis				Multivariate Cox Proportional hazard analysis			
		Disease free-survival		Overall survival		Disease free-survival		Overall survival	
Variable	Evaluation	HR (95% confidence interval)	P value	HR (95% confidence interval)	P value	HR (95% confidence interval)	P value	HR (95% confidence interval)	P value
E-/P-cadherin expression	Positive/Negative	1		1		1		1	
	Negative/Negative	1.59 (0.88 to 2.88)	0.124	1.58 (0.85 to 2.93)	0.149	1.06 (0.46 to 2.46)	0.88	0.8 (0.32 to 1.99)	0.627
	Positive/Positive	1.44 (1.04 to 1.99)	0.029	1.53 (1.09 to 2.15)	0.014	1.35 (0.94 to 1.95)	0.109	1.51 (1.03 to 2.22)	0.036

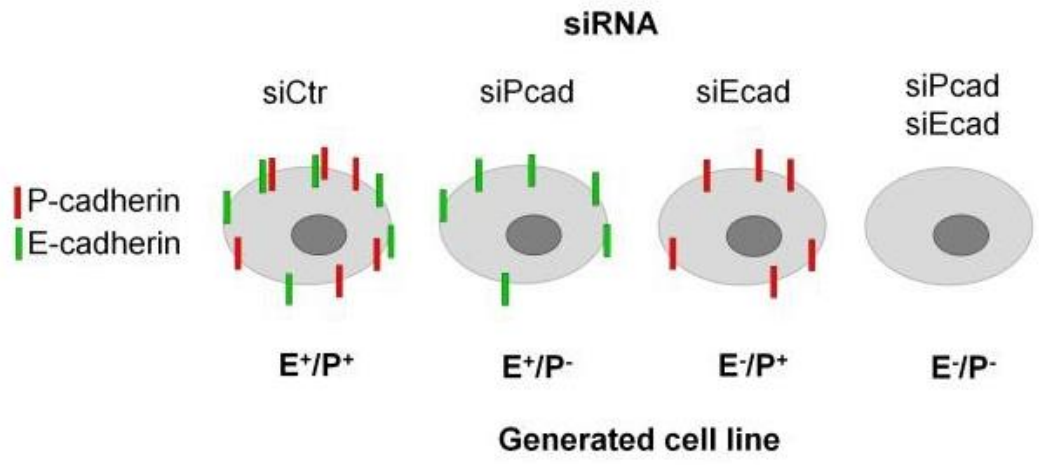
E- and P-Cadherin co-expression in breast tumors is associated with a decreased survival time and is a significant poor prognostic predictor for breast cancer patients

IN VITRO BREAST CANCER CELL MODELS

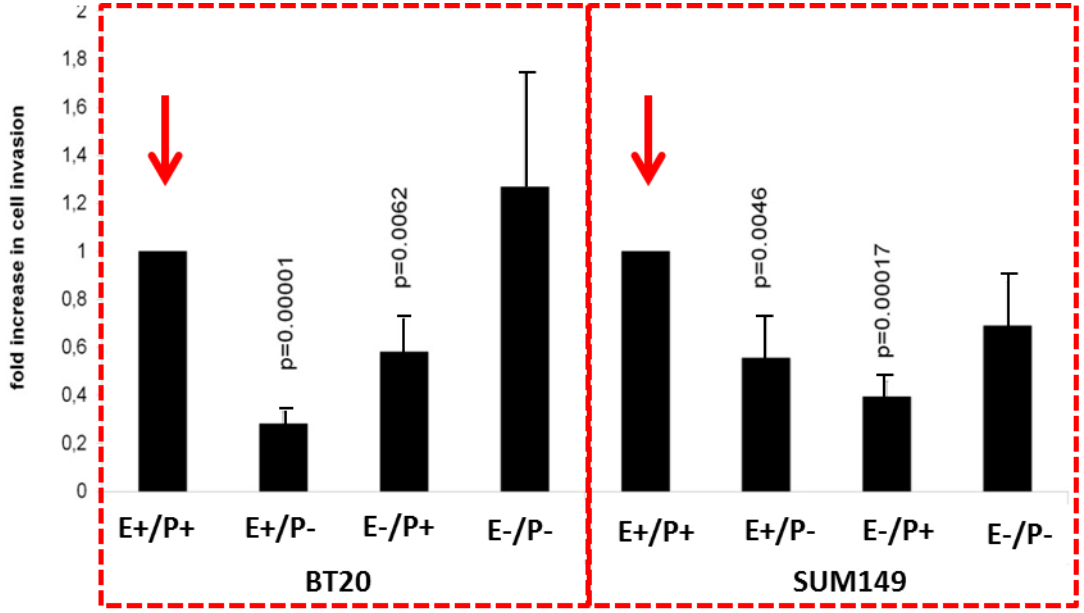


Breast Carcinoma

Primary Inflammatory Breast cancer

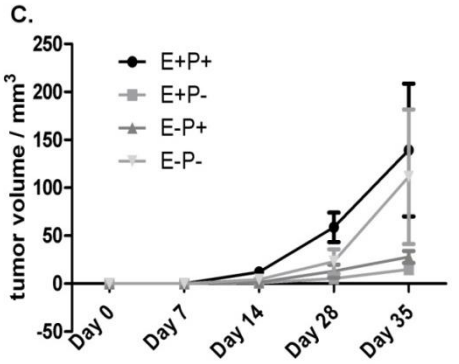


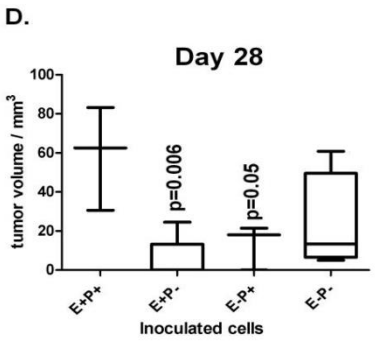
E and P-Cadherin co-expression: invasion and growth

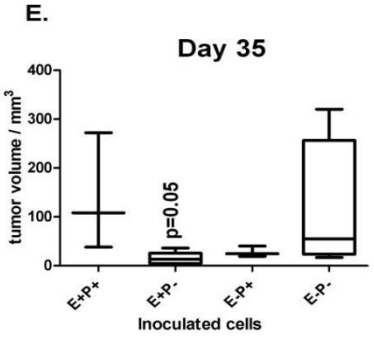


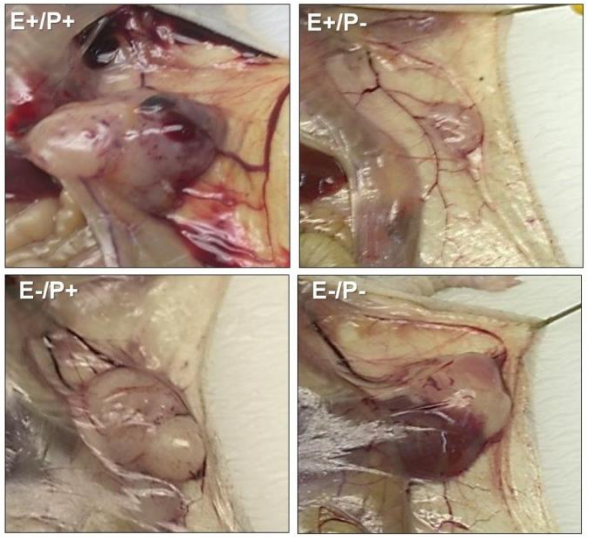
P-cad expression in a E-cad wt backgroud, promotes cell invasion

E- and P-cad co-expressing or none cadherin expressing cells show similar invasive behaviour



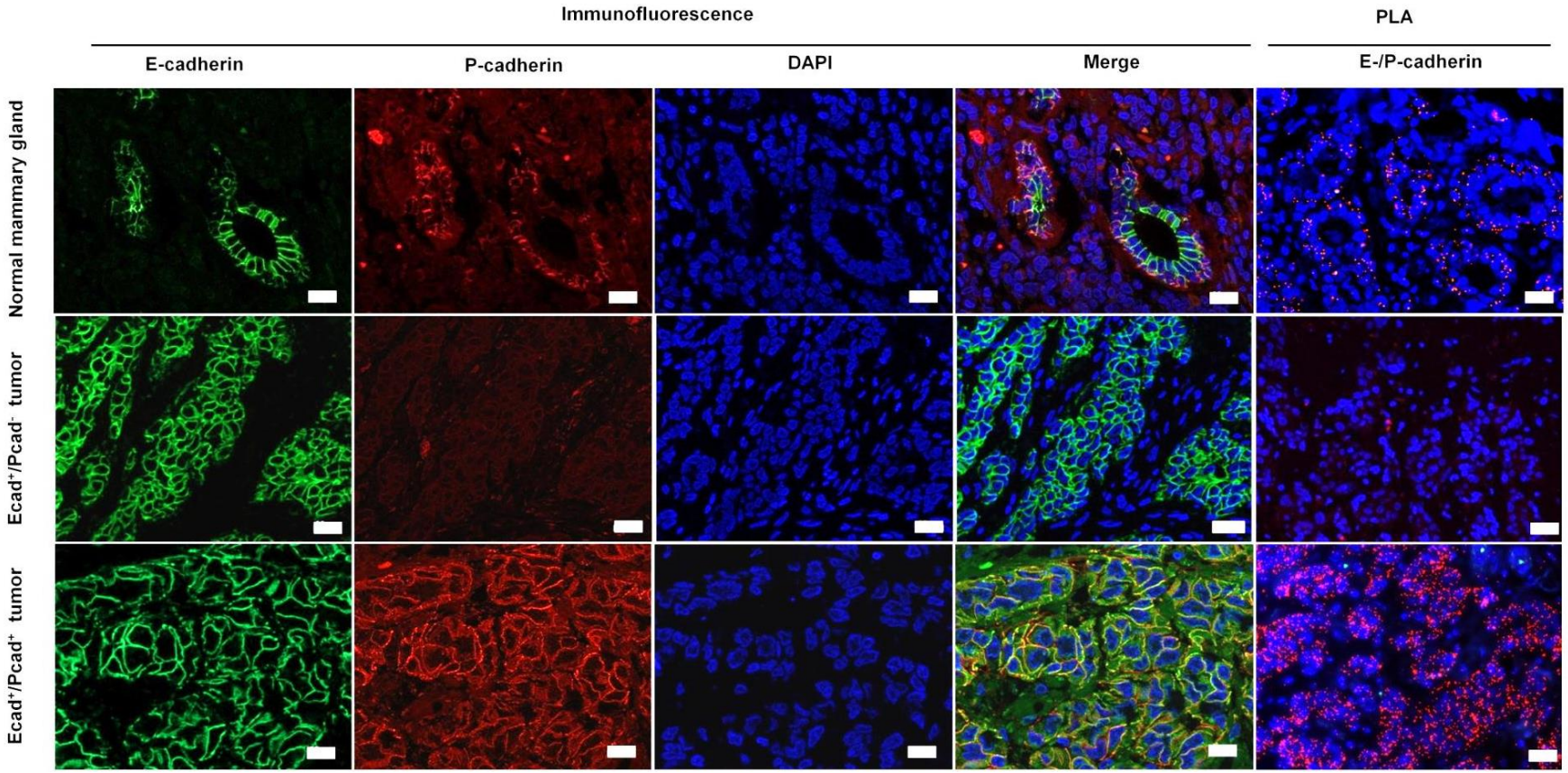






Ribeiro AS et al. Oncogene 29:392-402, 2010

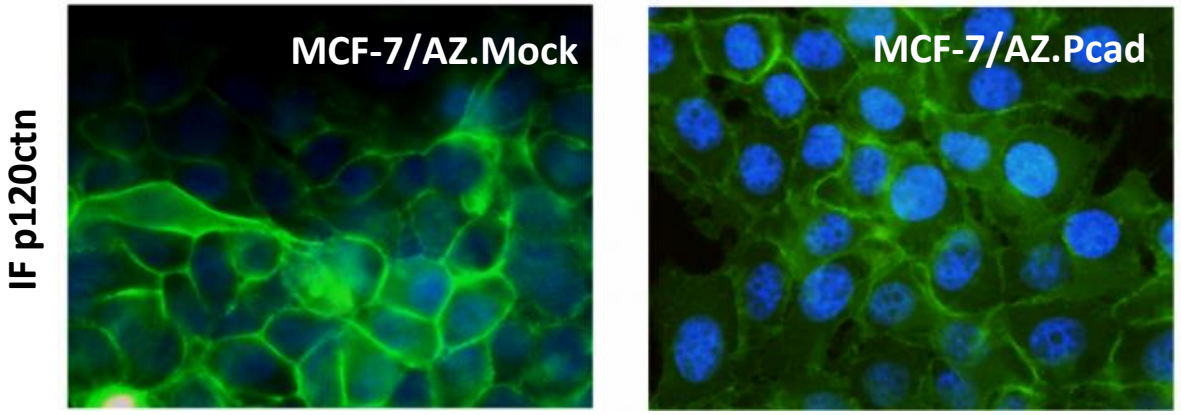
E AND P-CADHERIN INTERACTIONS IN BREAST CANCER

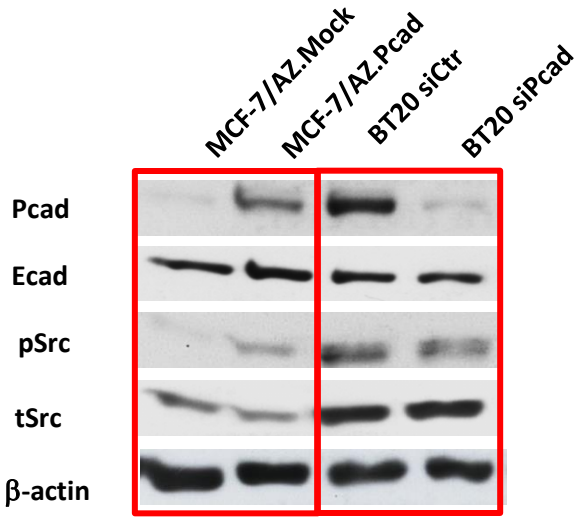


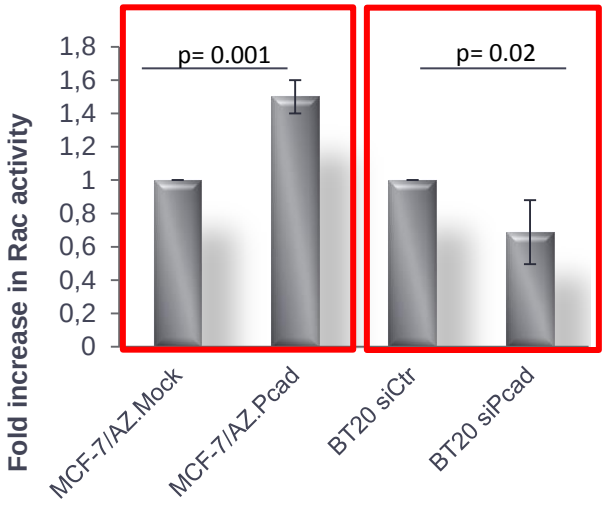
E- and P-cadherin proteins are in close proximity in co-expressing tumors

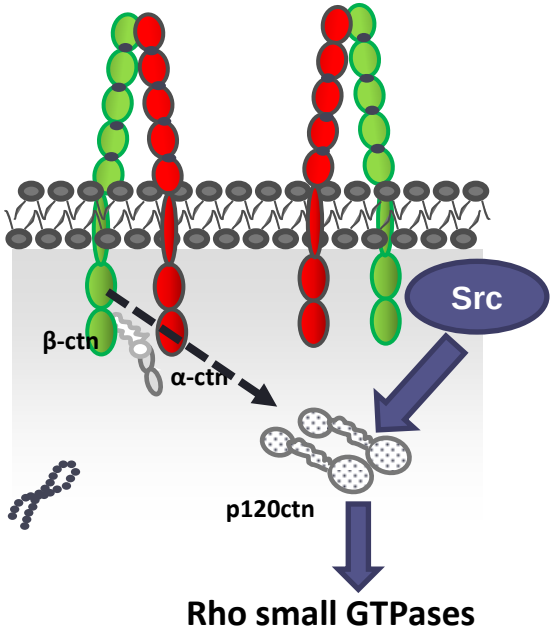
Ribeiro AS et al. J Pathol 2013

P-Cadherin expression delocalize p120ctn to the cytoplasm and activate signalling pathways





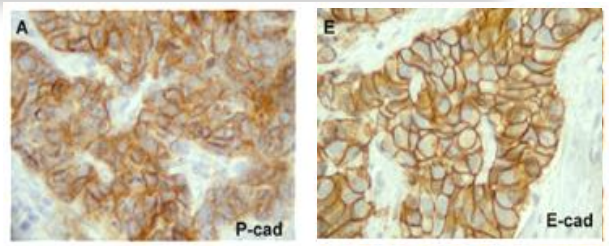


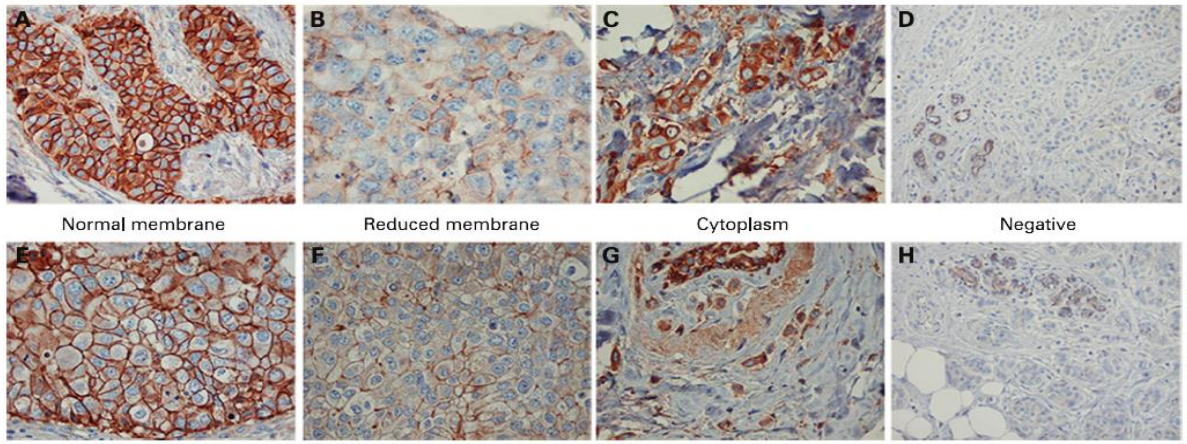


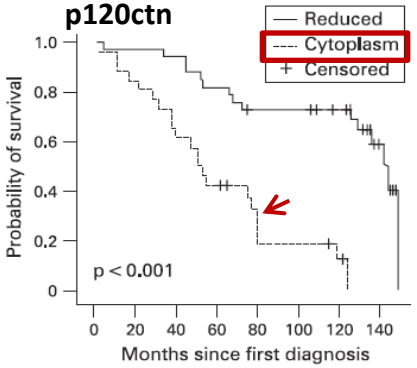
P-cad overexpressing cells show increased delocalization of p120ctn to cytoplasm, activation of Src Kinase and Rac.

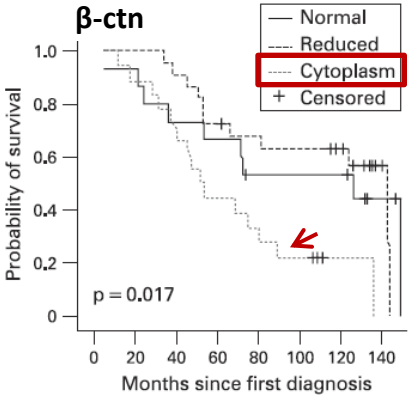
Cadherin/catenin complex in tissue samples

149 invasive breast carcinomas









P+/E+ **P-/E+**

		P-/E-cadherin expression			
		+/+	−/−	+/−	−/+
p120ctn	n = 90	16	28	17	29
	Normal	1 (6.3%)	2 (7.1%)	0 (0%)	6 (20.7%)
	Reduced	5 (31.2%)	12 (42.9%)	6 (35.3%)	19 (65.5%)
	Cytoplasm	10 (62.5%)	14 (50%)	9 (52.9%)	4 (13.8%)
	Negative	0 (0%)	0 (0%)	2 (11.8%)	0 (0%)
	p value	0.002			

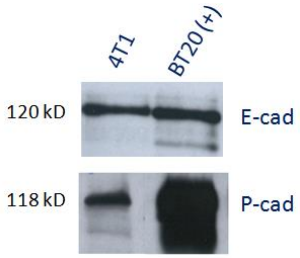
P+/E+ **P-/E+**

		P-/E-cadherin expression			
		+/+	−/−	+/−	−/+
βctn	n = 93	16	29	19	29
	Normal	6 (37.4%)	4 (13.8%)	1 (5.3%)	15 (51.7%)
	Reduced	5 (31.3%)	14 (48.3%)	7 (36.8%)	10 (34.5%)
	Cytoplasm	5 (31.3%)	7 (24.1%)	9 (47.4%)	4 (13.8%)
	Negative	0 (0.0%)	4 (13.8%)	2 (10.5%)	0 (0%)
	p Value	0.004			

E- and P-cadherin co-expressing tumors show increased catenins cytoplasmic localization

Paredes J et al. J Clin Pathol, 2008

P-cadherin and metastasis
4T1 metastatic breast cancer model

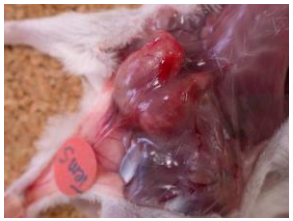


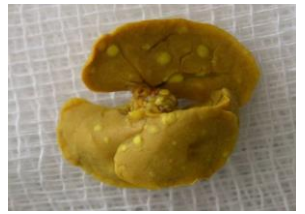
Day 0

Orthotopic injection of 4T1 cells (100 000) in the mammary fat pad.

Balb/c mice

Day 21

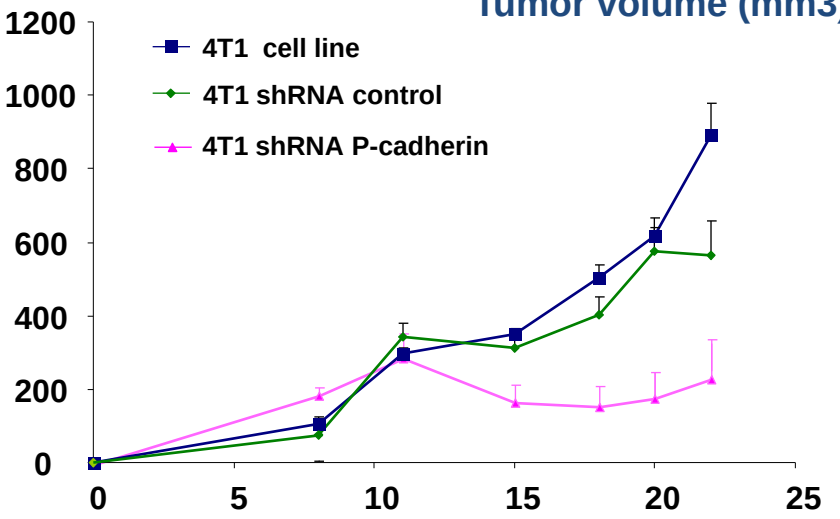




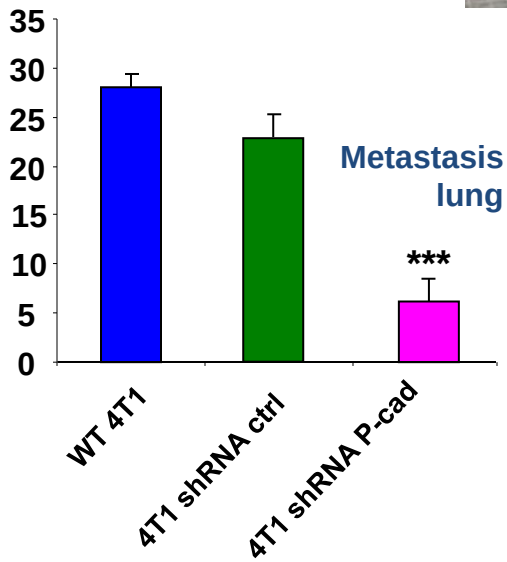
3 groups injected with:
- 4T1 cell line
- 4T1 shRNA control
- 4T1 shRNA P-cadherin

D8 D11 D15 D18 D20 D22

Tumor volume (mm3)



Metastasis number at the lung surface



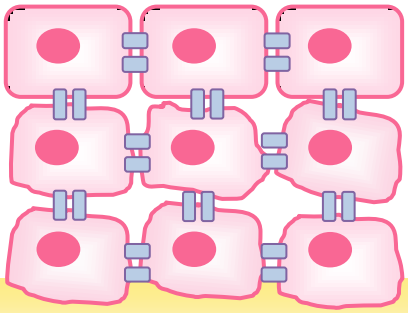
In collaboration with Françoise Bono, Sanofi Aventis Rechérche & Devolepment, Toulouse, France

Financial support: SAR&D

Schematic representation of the different types of breast cancer in what concerns cadherin expression

E-cadherin expressing cells

(E^+/P^-)

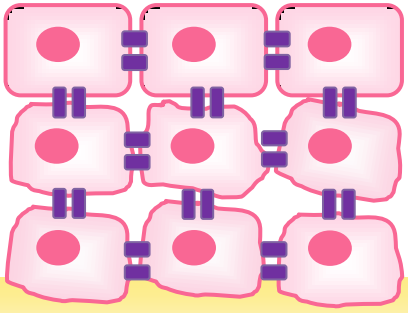


Tumors:
Good prognostic tumors

Cells with:
Intercellular adhesions
Low ability to migrate
Low ability to invade
Sensitive to apoptosis
Low tumorigenic potential

P-cadherin expressing cells

(E^-/P^+)

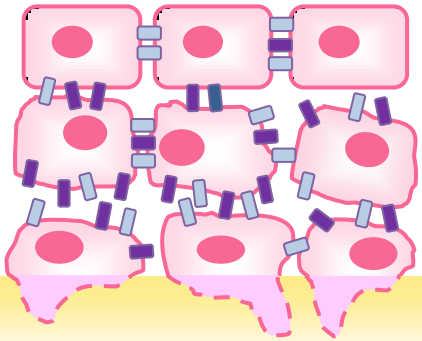


Tumors:
Under represented group

Cells with:
Intercellular adhesions
High ability to migrate
Low ability to invade
Resistant to apoptosis
Moderate/Low tumorigenic potential

E/P-cadherin co-expressing cells

(E^+/P^+)

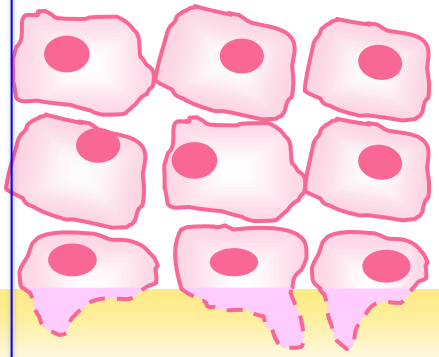


Tumors:
Poor prognostic tumors

Cells with:
Intercellular adhesions
High ability to migrate
High ability to invade
Resistant to apoptosis
High tumorigenic potencial

E/P-cadherin negative cells

(E^-/P^-)

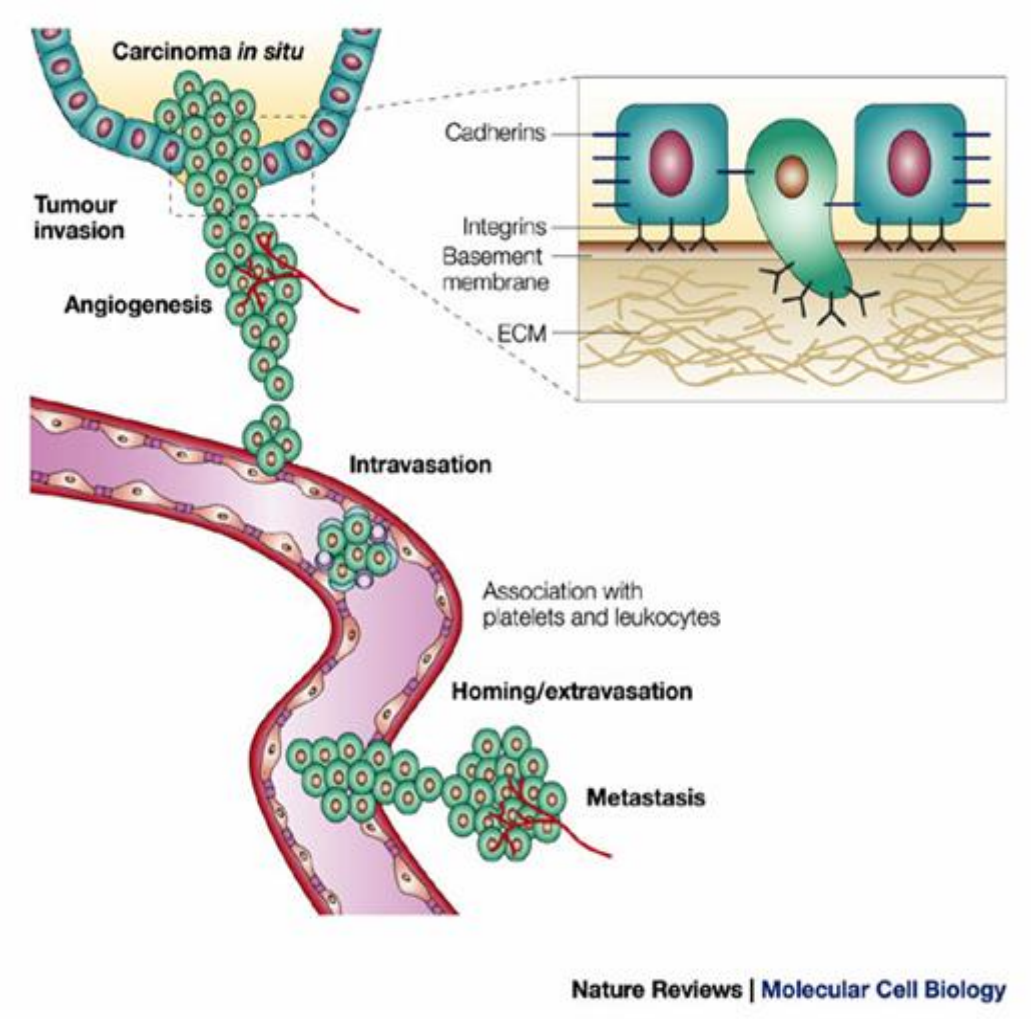


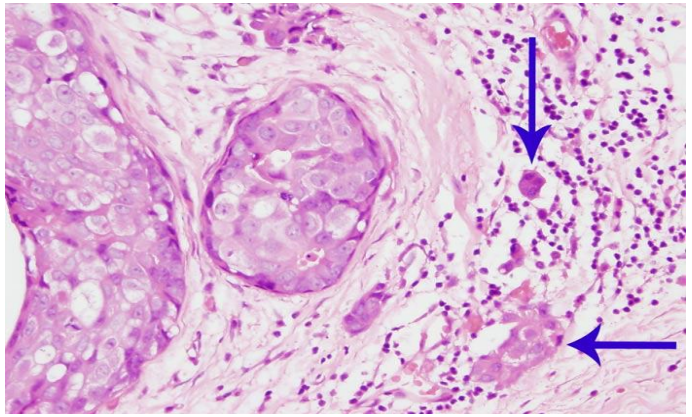
Tumors:
Poor prognostic tumors

Cells with:
Without intercellular adhesions
Low ability to migrate
High ability to invade
Resistant to apoptosis
High tumorigenic potencial

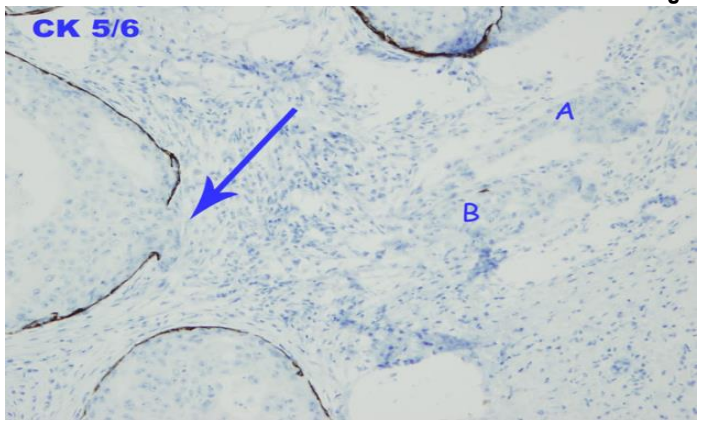
Ribeiro AS et al. J Pathol 2013

INVASION and MIGRATION

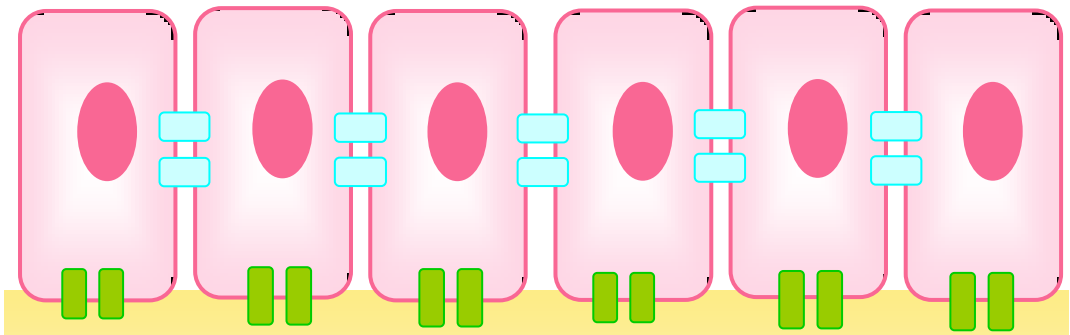




CK 5/6 Immunostainng



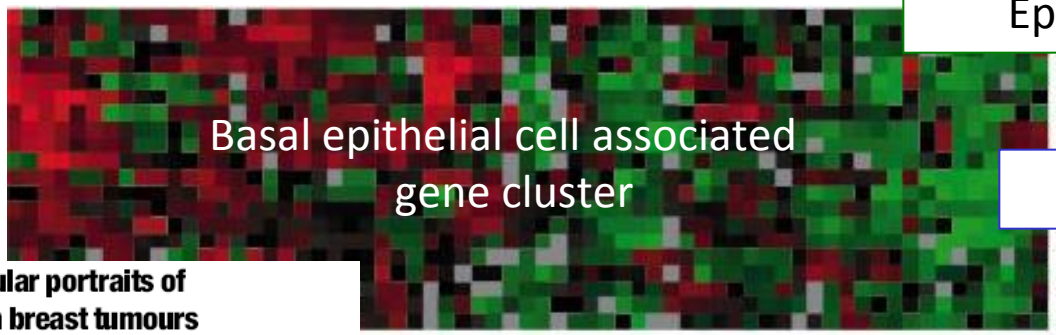
Adherens Junctions



Focal Adhesions

Integrins (cten)

Epidermal growth factor receptor

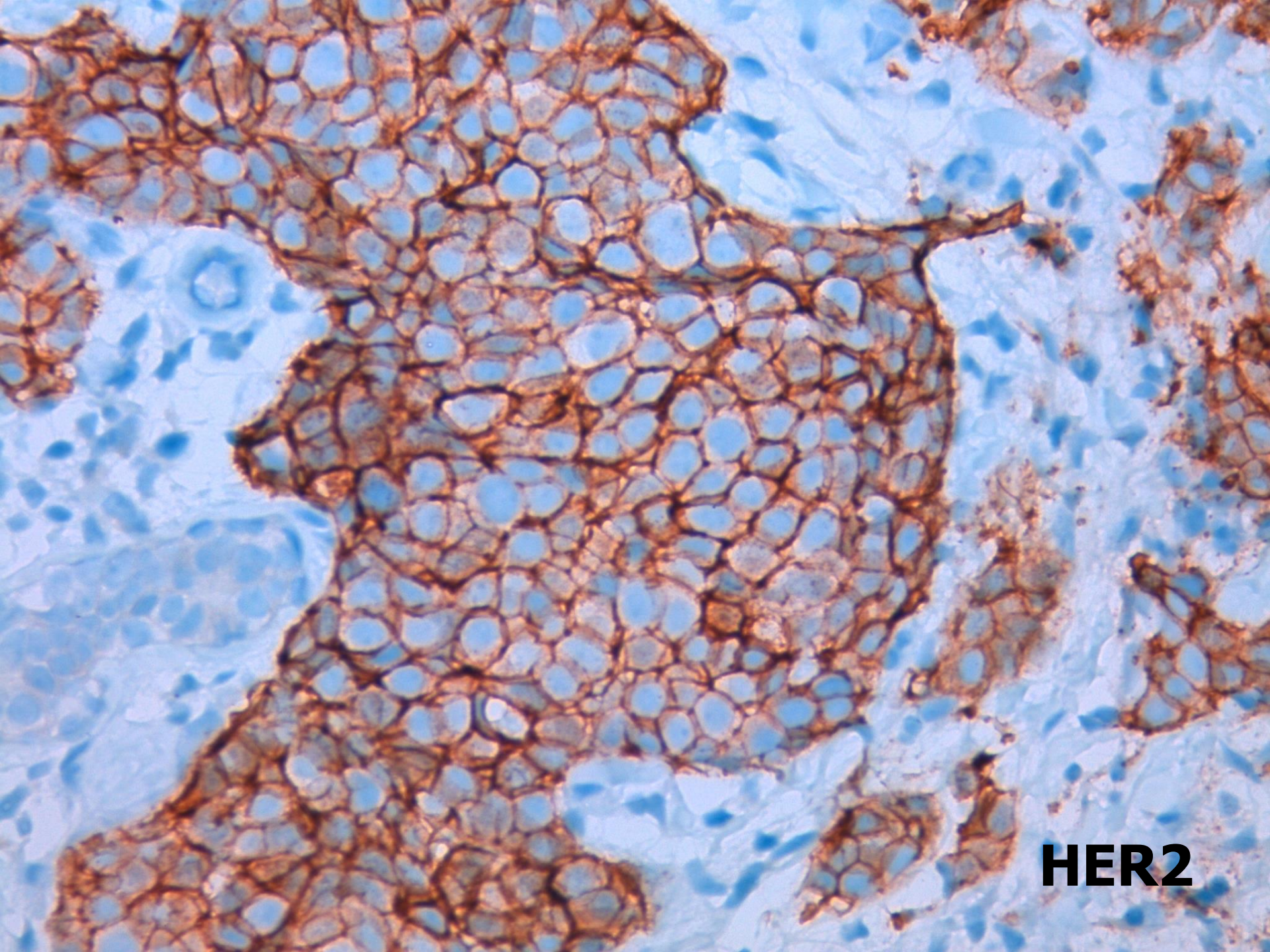


P-cadherin

HUMAN DNA-BINDING PROTEIN ABP/ZF MRNA, COMPLETE CDS
ANTILEUKOPROTEINASE
FATTY ACID BINDING PROTEIN 7, BRAIN
CHITINASE 3-LIKE 2
TRANSMEMBRANE 4 SUPERFAMILY MEMBER 1
SRY SEX-DETERMINING REGION Y-BOX 9 CAMPOMELIC DYSPLASIA
KERATIN 13
KERATIN 13
2255917
INTEGRIN, BETA 4
TROPONIN I, SKELETAL, FAST

Molecular portraits of human breast tumours

Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning**, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein*


HER2

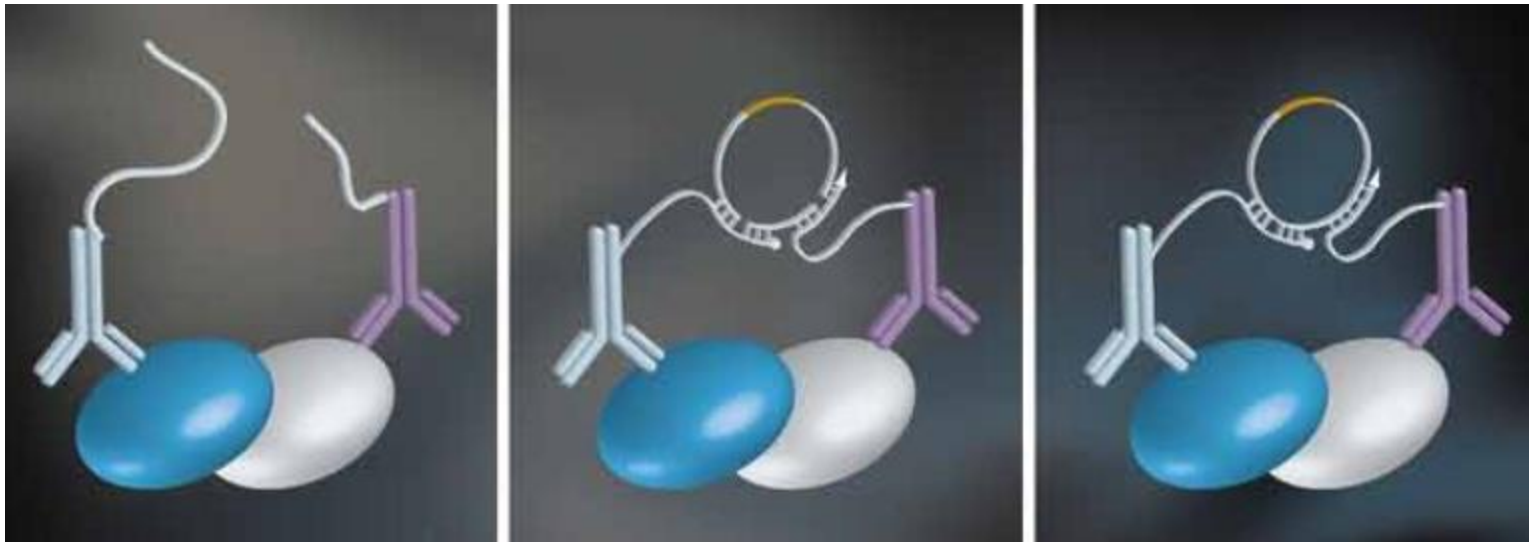
EXPERT REVIEWS

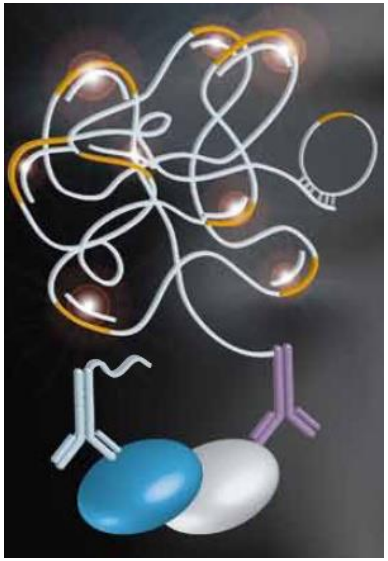
Proximity ligation assays: a recent addition to the proteomics toolbox

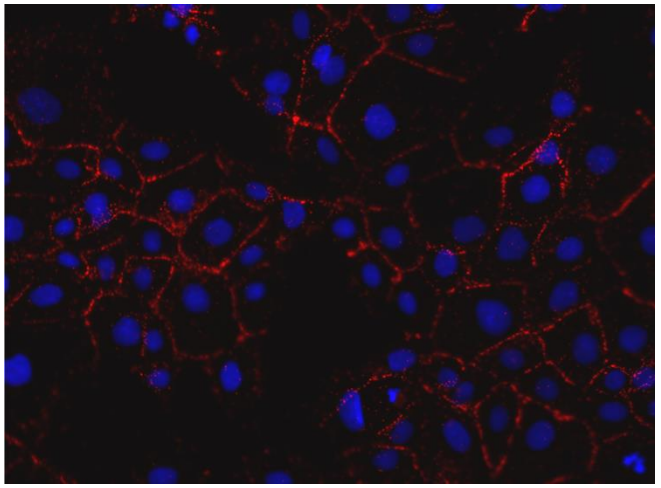
Expert Rev. Proteomics 7(3), 401–409 (2010)

Irene Weibrecht[1], Karl-Johan Leuchowius[1], Carl-Magnus Clausson[1], Tim Conze[1], Malin Jarvius[1], W Mathias Howell[1], Masood Kamali-Moghaddam[1] and Ola Söderberg[†1]

[1]*Department of Genetics and Pathology, Rudbeck laboratory, University of Uppsala, 751 85 Uppsala, Sweden*







VOLUME 26 · NUMBER 7 · MARCH 1 2008

JOURNAL OF CLINICAL ONCOLOGY

Phase II Study of Predictive Biomarker Profiles for Response Targeting Human Epidermal Growth Factor Receptor 2 (HER-2) in Advanced Inflammatory Breast Cancer With Lapatinib Monotherapy

Stephen Johnston, Maureen Trudeau, Bella Kaufman, Hanouda Boussen, Kimberley Blackwell, Patricia LoRusso, Donald P. Lombardi, Slim Ben Ahmed, Dennis L. Citrin, Michelle L. DeSilvio, Jennifer Harris, Ron E. Westlund, Vanessa Salazar, Tal Z. Zaks, and Neil L. Spector

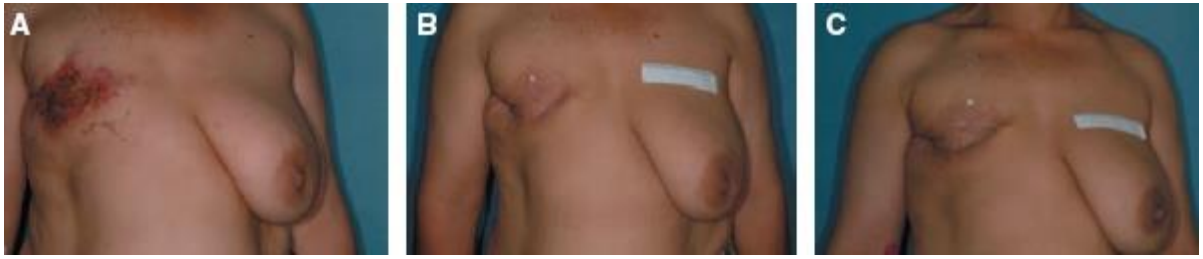


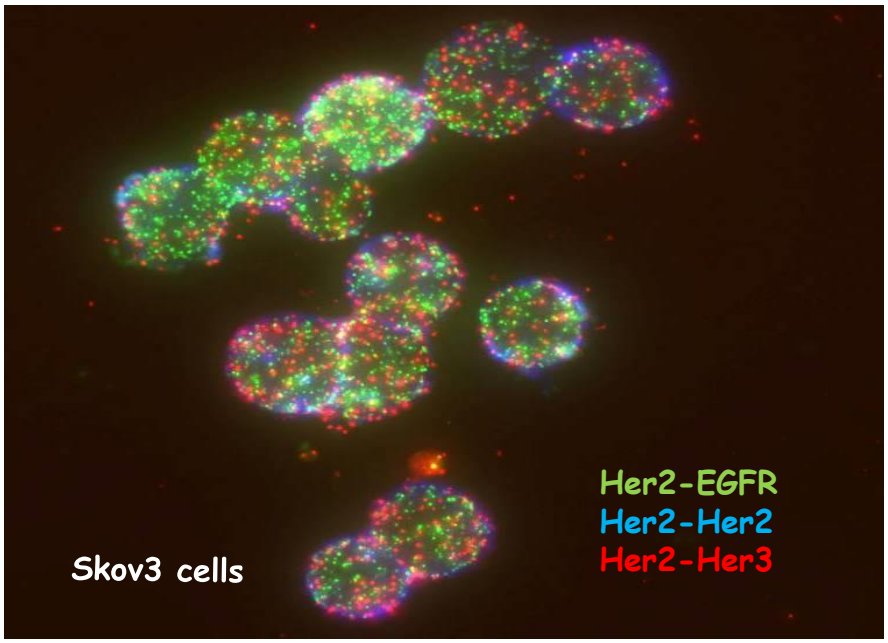
Table 4. Molecular Phenotype of Responding and Nonresponding Patients in Cohort A

Phenotype	Responders (n = 15)			Nonresponders (n = 15)		
	No. Affected	Total No.	%	No. Affected	Total No.	%
HER activation status						
pEGFR	5	11	45	9	14	64
pHER-2	11	12	92	13	14	93
pHER-3	10	12	83	5*	14	36
ErbB ligands						
Heregulin	12	12	100	15	15	100
TGF-α	12	12	100	14	14	100
IBC phenotype						
ER	4	12	33	3	14	21
PR	3	12	25	2	14	14
E-cadherin	12	12	100	15	15	100
IGF-1R	10	12	83	13	15	87
RhoC	9	9	100	15	15	100
Apoptosis and tumor suppressors						
PTEN deficient	8	12	67	8	14	57
p53	2	9	22	11†	15	73
Bcl2	5	10	50	5	15	33
β-catenin	12	12	100	14	15	93

Abbreviations: HER, human epidermal growth factor receptor; p-, phosphorylated; EGFR, epidermal growth factor receptor; TGF, transforming growth factor; IBC, inflammatory breast cancer; ER, estrogen receptor; PR, progesterone receptor; IGF, insulin-like growth factor; PTEN, phosphate and tensin homolog 10.

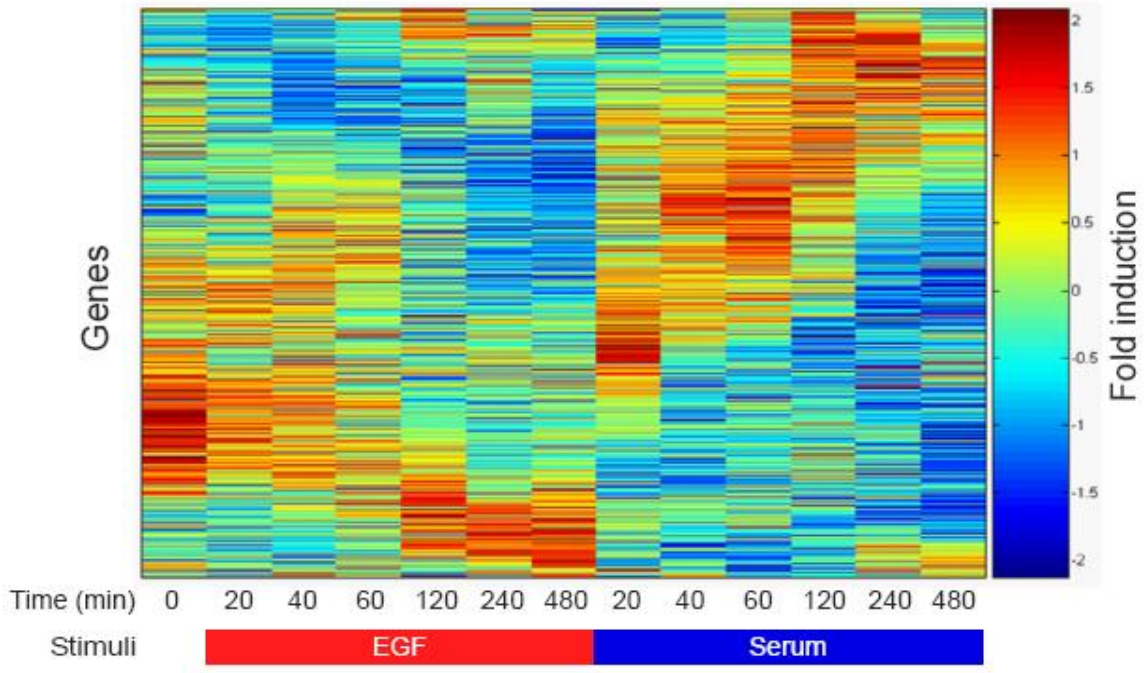
*$P = .021$

†$P = .033$



Courtesy from Ola Söderberg –Upsalla-Sweden

Identification of motility promoting genes driven by EGF Receptor Signaling



CTEN

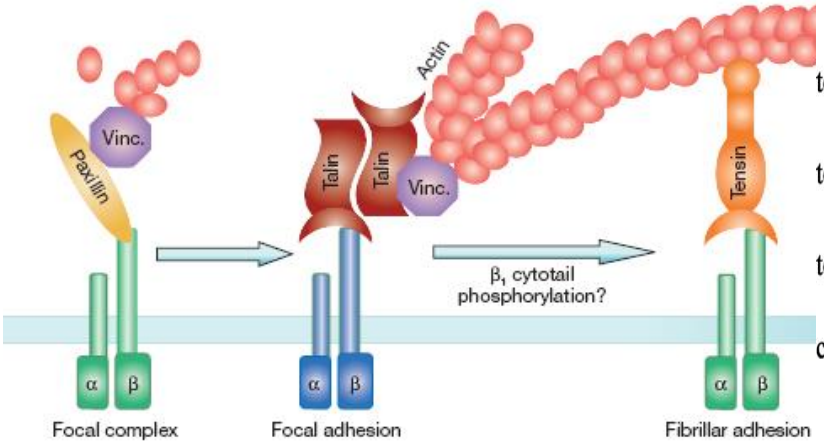
SYNJ 2

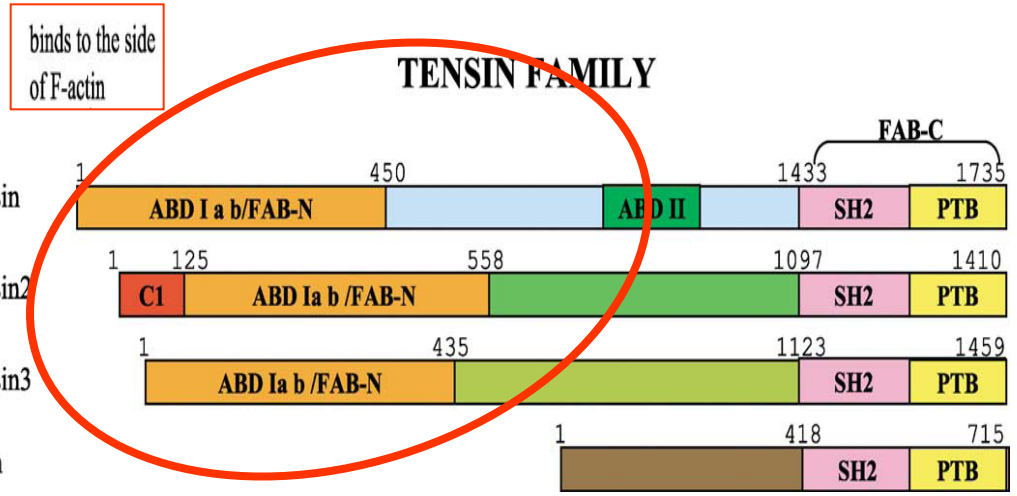
Amit et al., Nat Gen 2007

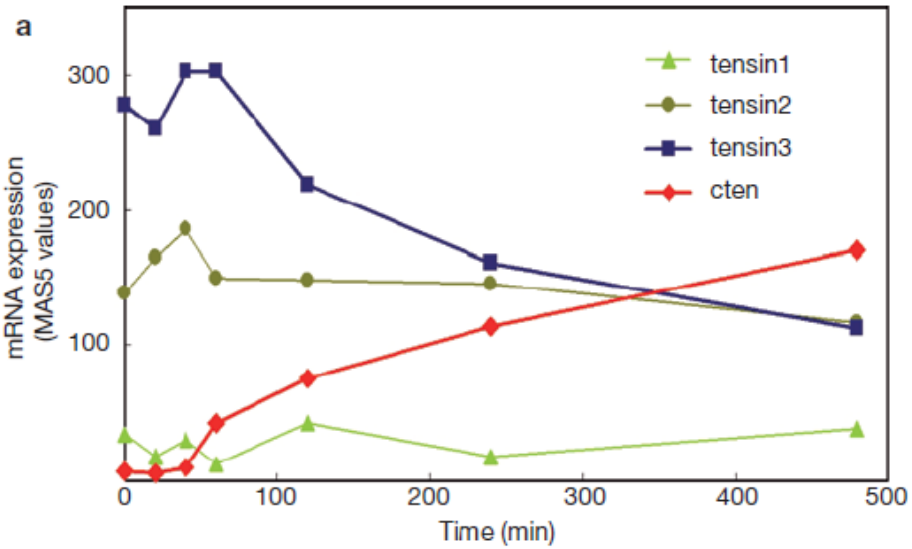
Tensin relief facilitates migration

Yuliya Pylayeva and Filippo G. Giancotti

NATURE CELL BIOLOGY VOLUME 9 | NUMBER 8 | AUGUST 2007





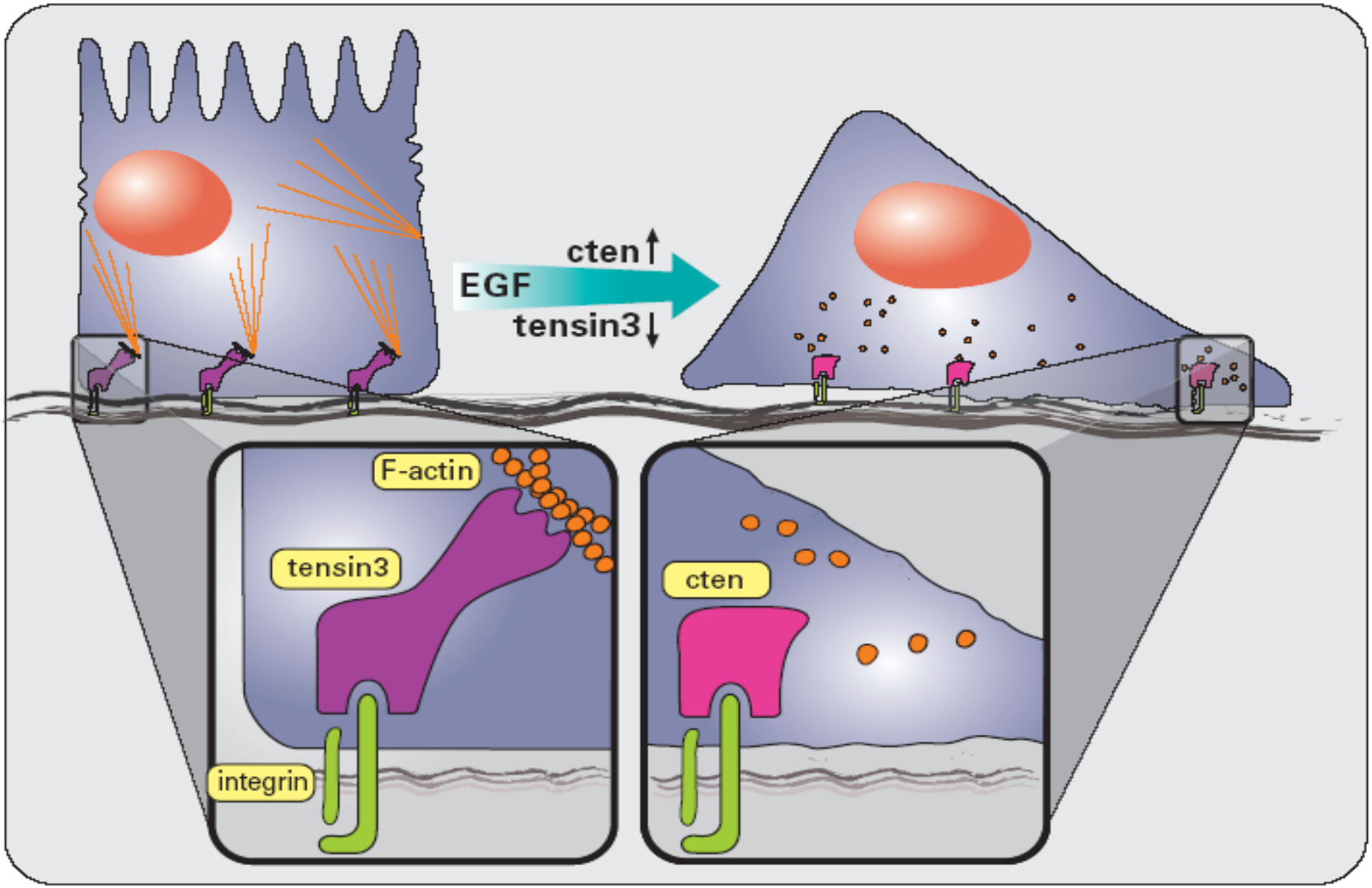


Nature Cell Biology (2007) 9: 961-969

nature cell biology

A reciprocal tensin-3–cten switch mediates EGF-driven mammary cell migration

Menachem Katz[1], Ido Amit[1], Ami Citri[1], Tal Shay[2], Silvia Carvalho[3], Sara Lavi[1], Fernanda Milanezi[3], Ljuba Lyass[4], Ninette Amariglio[5], Jasmine Jacob-Hirsch[5], Nir Ben-Chetrit[1], Gabi Tarcic[1], Moshit Lindzen[1], Roi Avraham[1], Yi-Chun Liao[6], Patricia Trusk[4], Asya Lyass[7], Gideon Rechavi[5], Neil L. Spector[8], Su Hao Lo[6], Fernando Schmitt[3,9], Sarah S. Bacus[4] and Yosef Yarden[1]

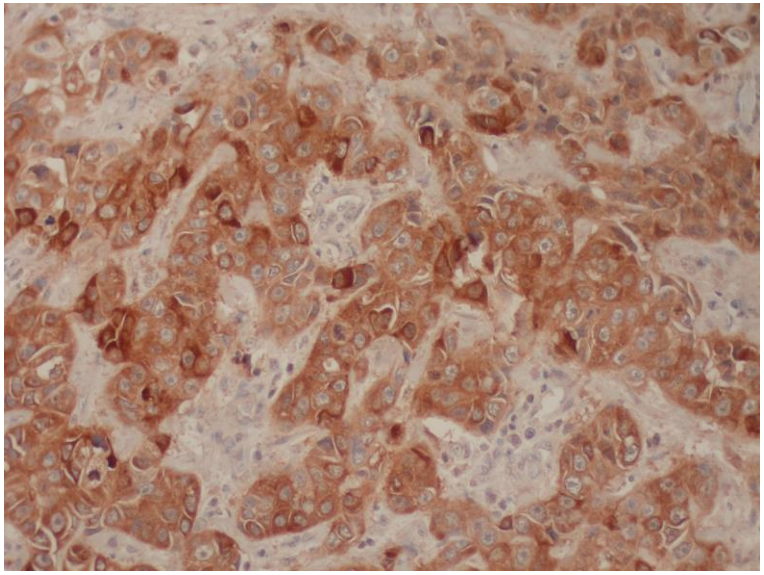


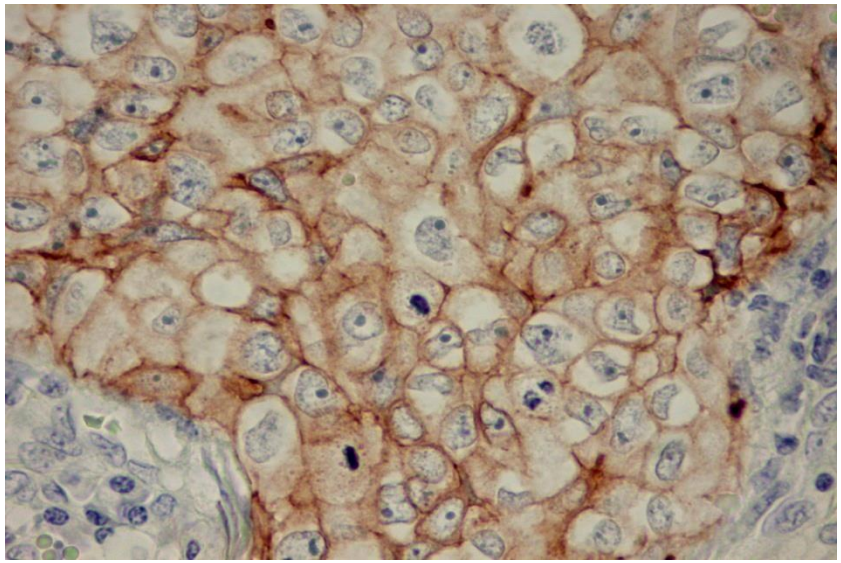
Nature Cell Biology (2007) 9: 961-969

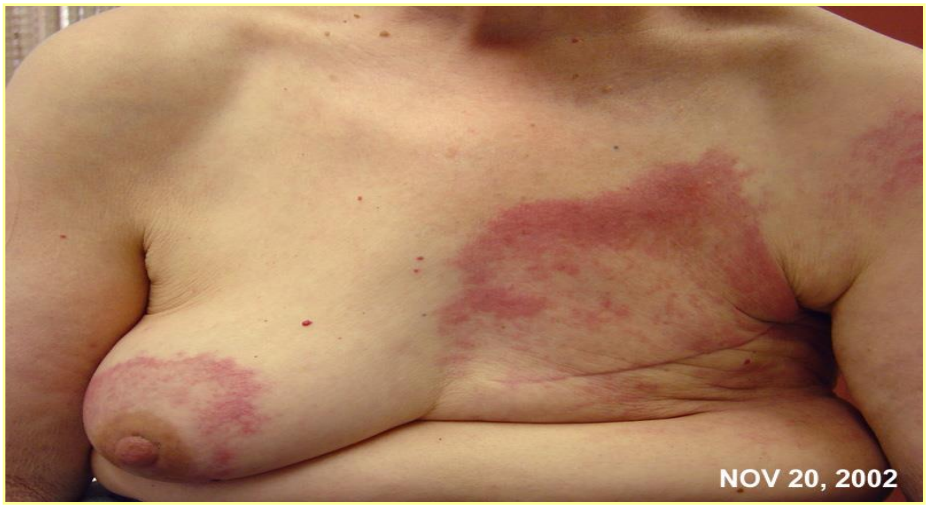
Table 1. Correlation in breast cancer patients between cten expression and disease parameters

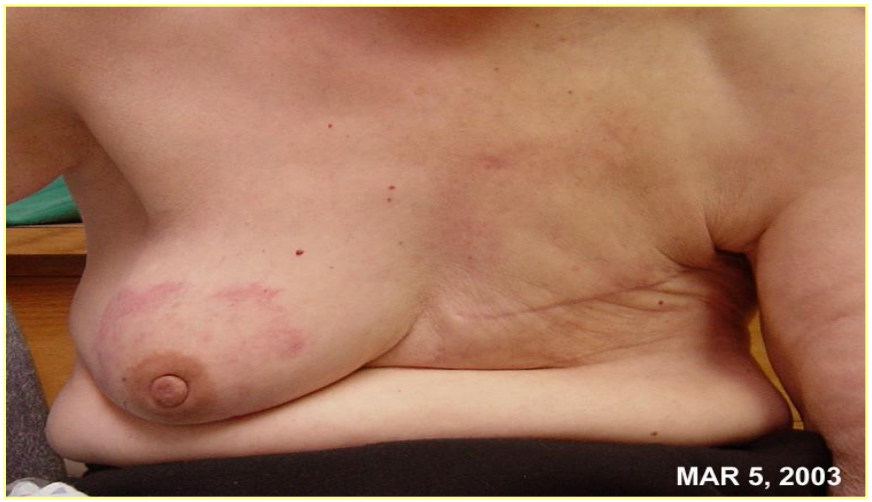
Cten correlation to:	Spearman rank correlation (Rho)	*P* value
EGFR	0.785	0.0006*
HER2/ErbB-2	0.67	0.004*
Oestrogen receptor	–0.48	0.004*
Lymph-node metastasis (number of lymph nodes: 0, 1–3, >3)	0.47	0.001*
Histological grade (I, II, III)	0.47	0.001*
Tumour size	0.01	0.84

The numbers were calculated on the basis of analyses performed using 272 samples derived from invasive breast tumours. Spearman's rank correlation test was used to determine the correlations. A False Discovery Rate test was used to correct the alpha value for multiple comparisons. Asterisks indicate statistically significant correlations. EGFR, epidermal growth factor receptor.





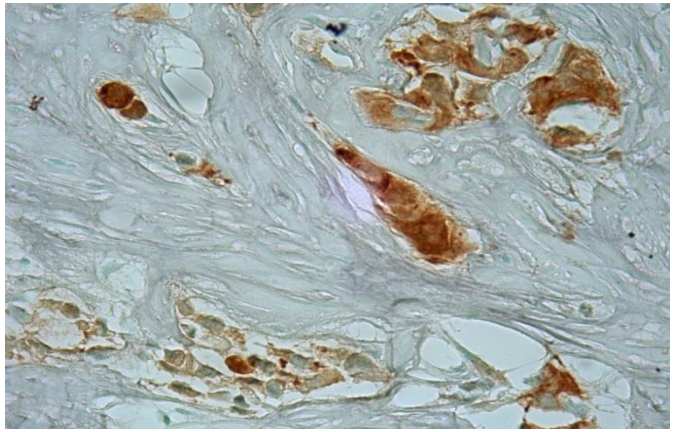


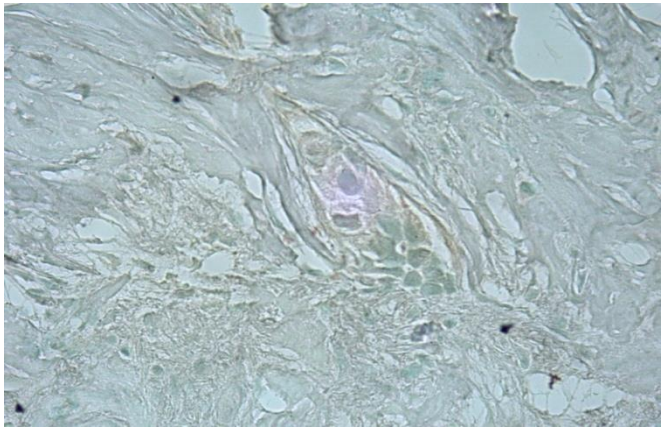


Before TKI treatment

After TKI treatment

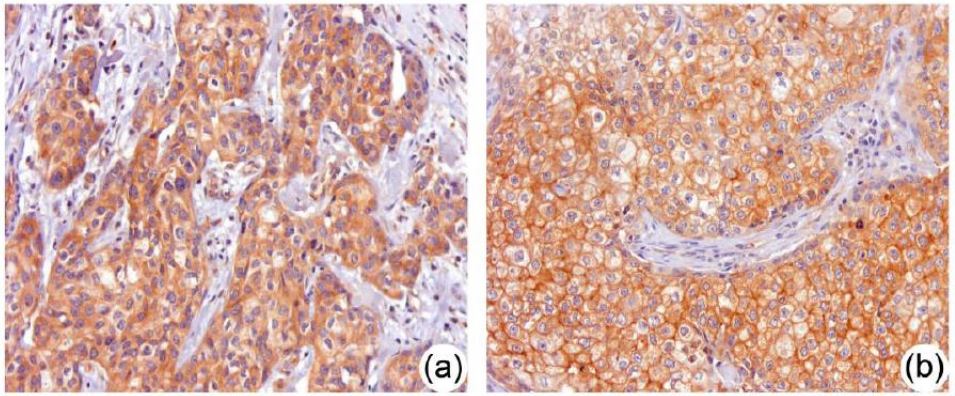
IHC Ab:
Cten





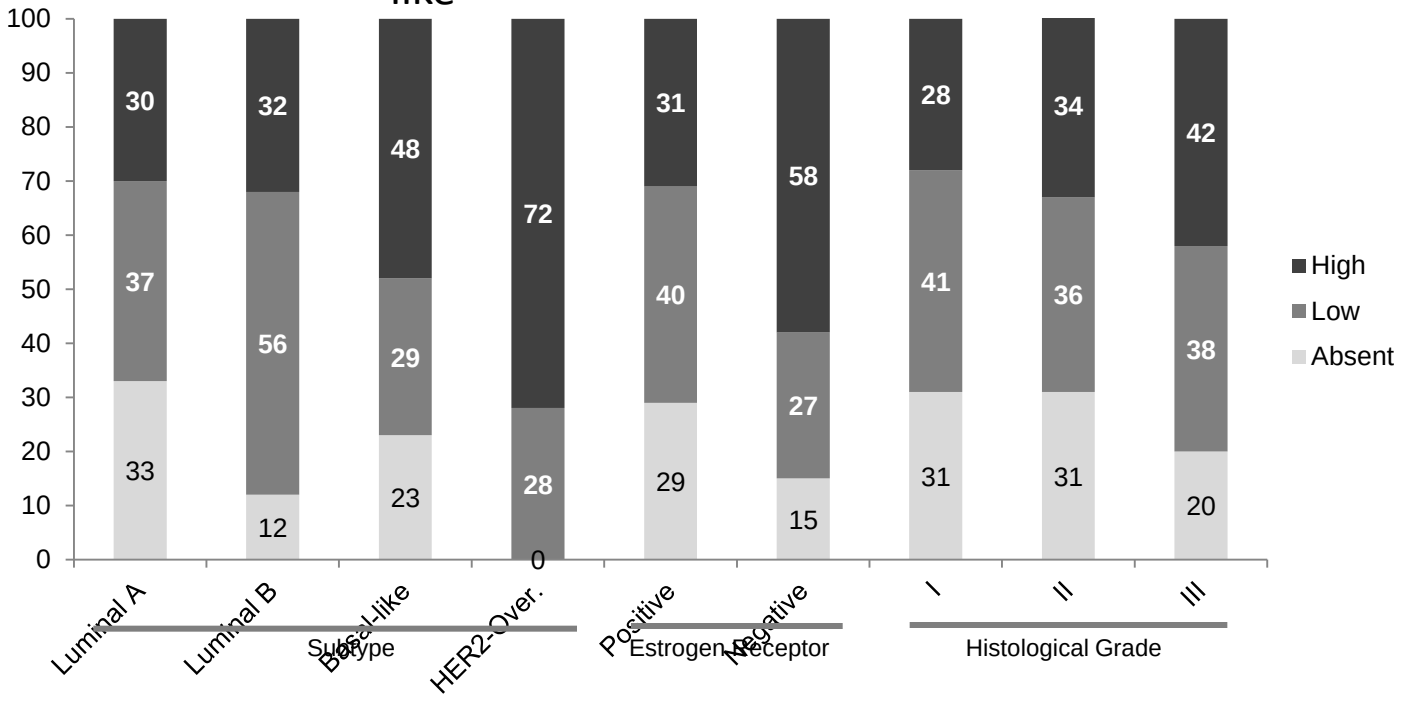
Breast Cancer Patients: cten undergoes down-regulation upon treatment with an EGFR Kinase Inhibitor

SYNJ2 Expression in Invasive Breast Carcinomas



Basal-like

HER2-overexpressing



Published online: February 12, 2015

Research Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

Navigator-3, a modulator of cell migration, may act as a suppressor of breast cancer progression

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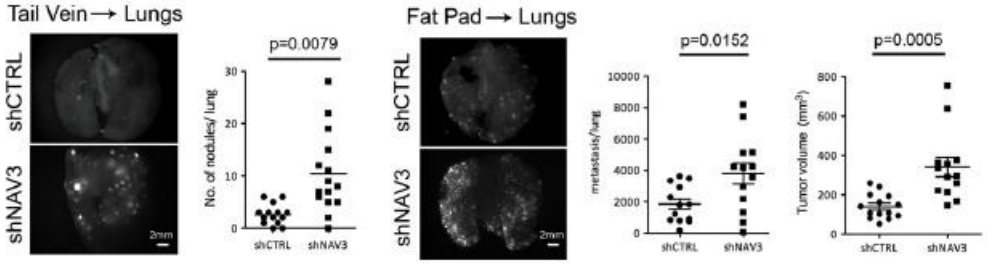

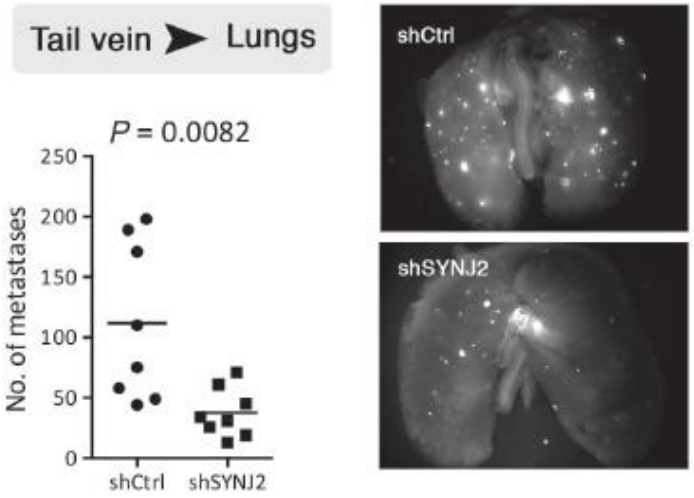

Synaptojanin 2 is a druggable mediator of metastasis and the gene is overexpressed and amplified in breast cancer

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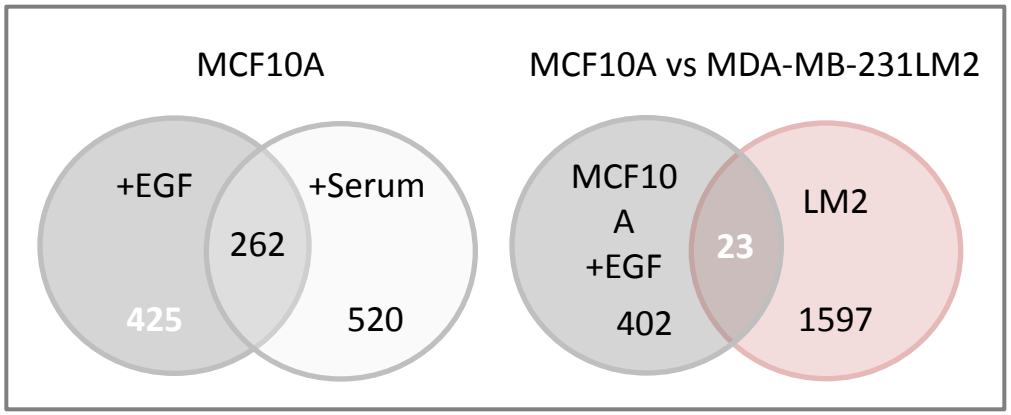
SYNJ2

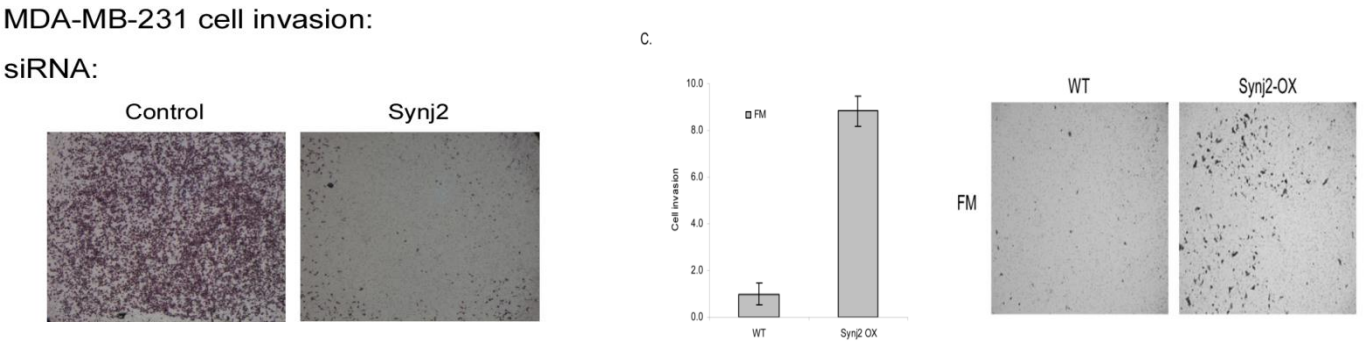
-Implicated in the regulation of cytoskeleton;

-Lamellipodia formation;

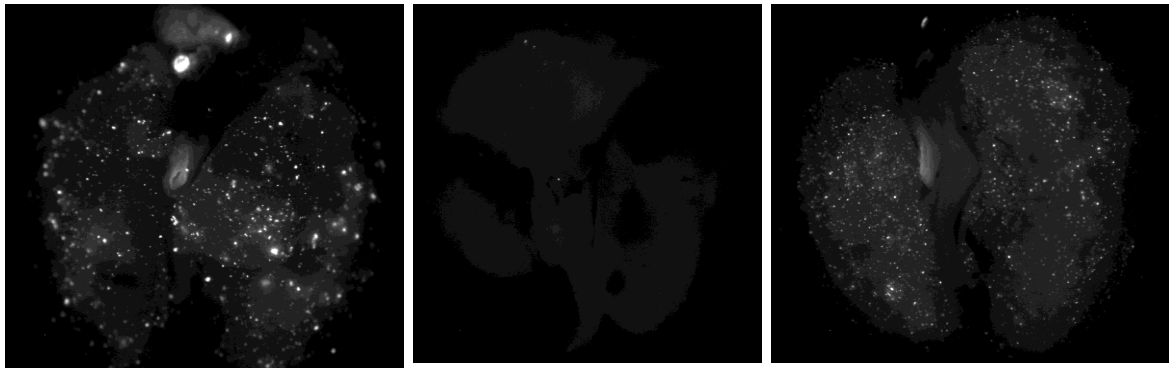
-Cell migration and invasion.



In vitro



In vivo



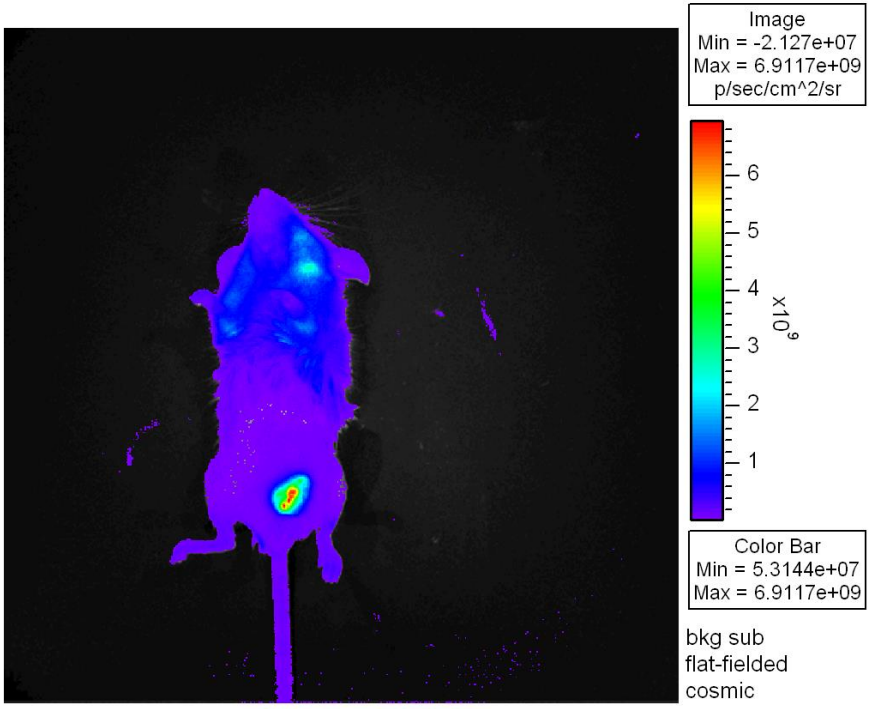
Control

shSYNJ2

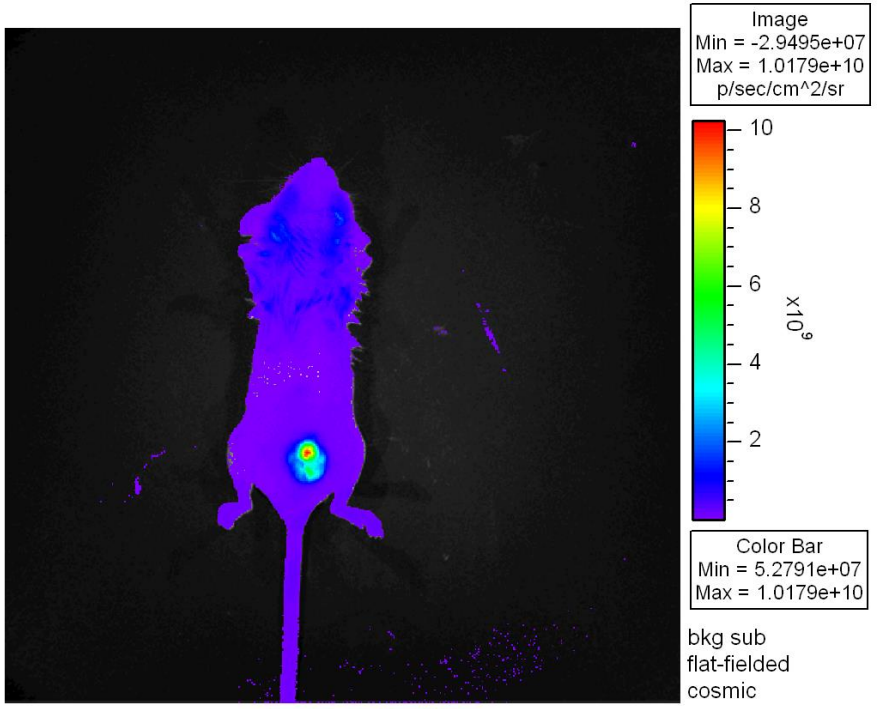
shSYNJ2 +
Wt rescue

Activity of SYNJ2 is necessary for distant metastasis of breast cancer

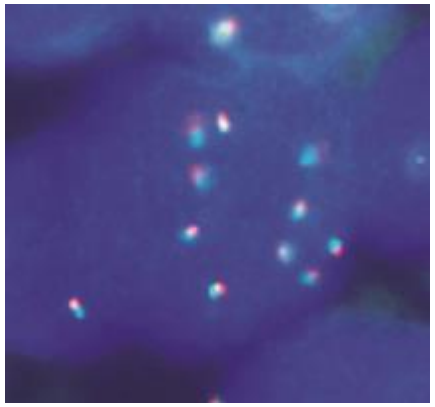
shControl

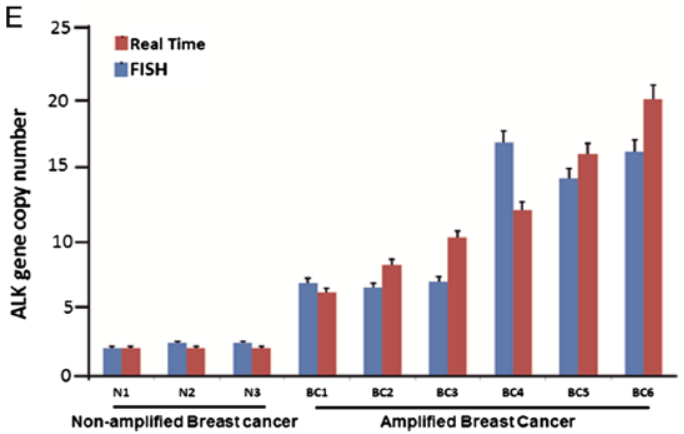


shSYNJ2

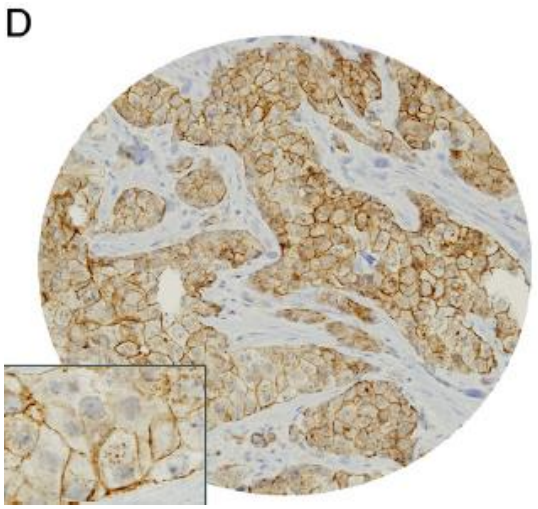


ALK alteration is a frequent event in aggressive breast cancers



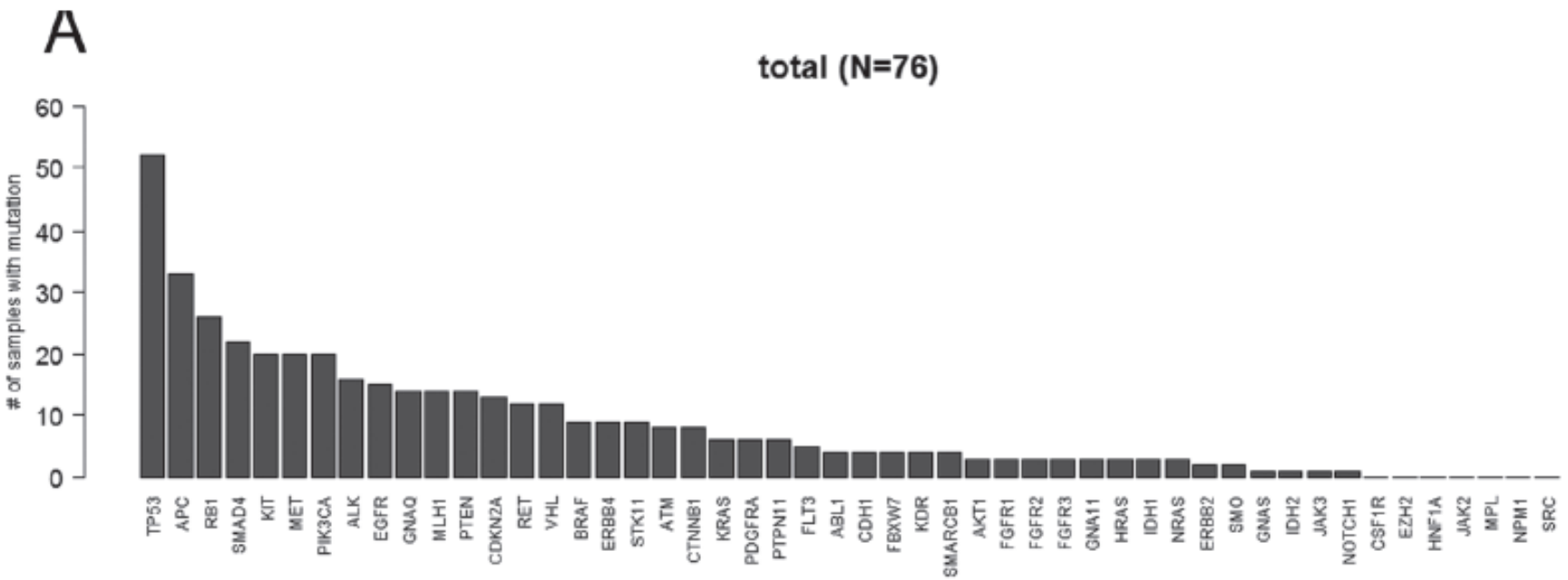


- ALK is amplified in 13.5% of breast carcinomas
- 75% of IBC have ALK amplification
- ALK amplification is related to worst prognosis and high proliferative index
- There is a good correlation between FIS, RT-PCR and IHQ



Siraj *et al. Breast Cancer Research* (2015) 17:127

INFLAMMATORY BREAST CARCINOMA (IBC) MOLECULAR STUDIES



- NGS results in 76 cases of LABC

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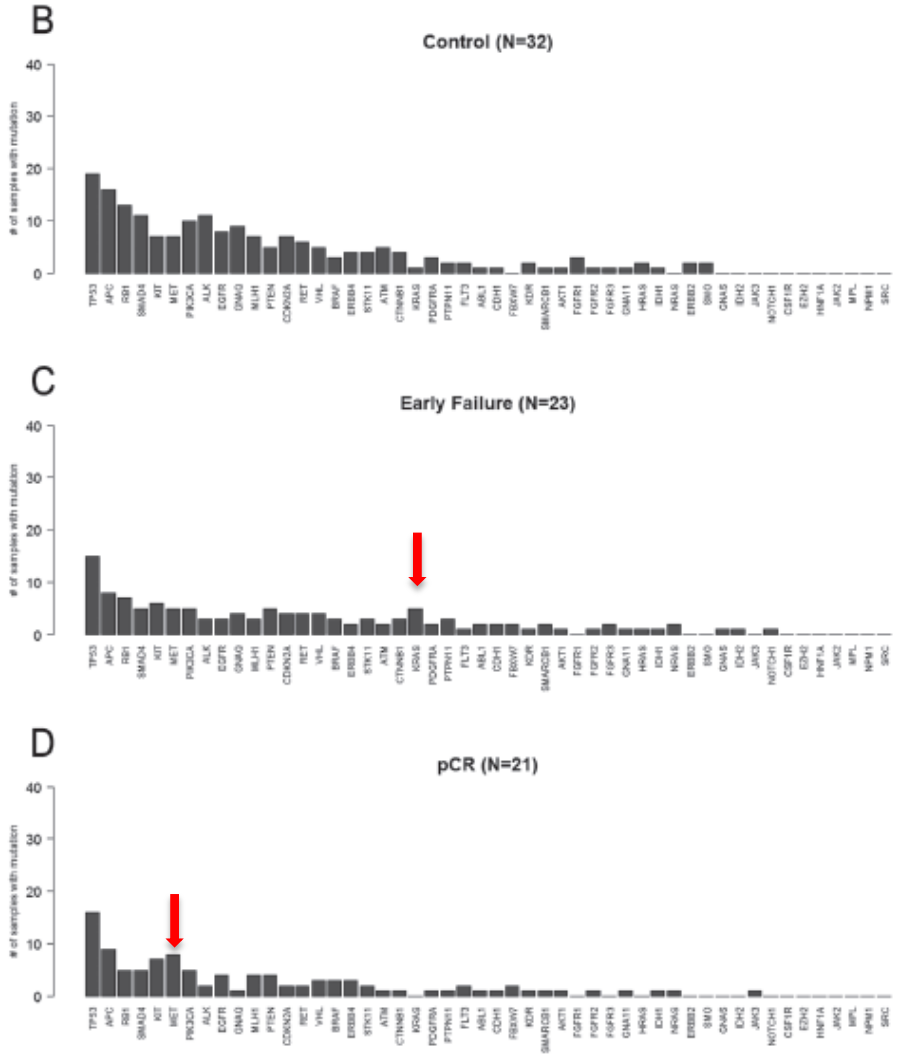
INFLAMMATORY BREAST CARCINOMA (IBC) MOLECULAR STUDIES and RESPONSE TO QT



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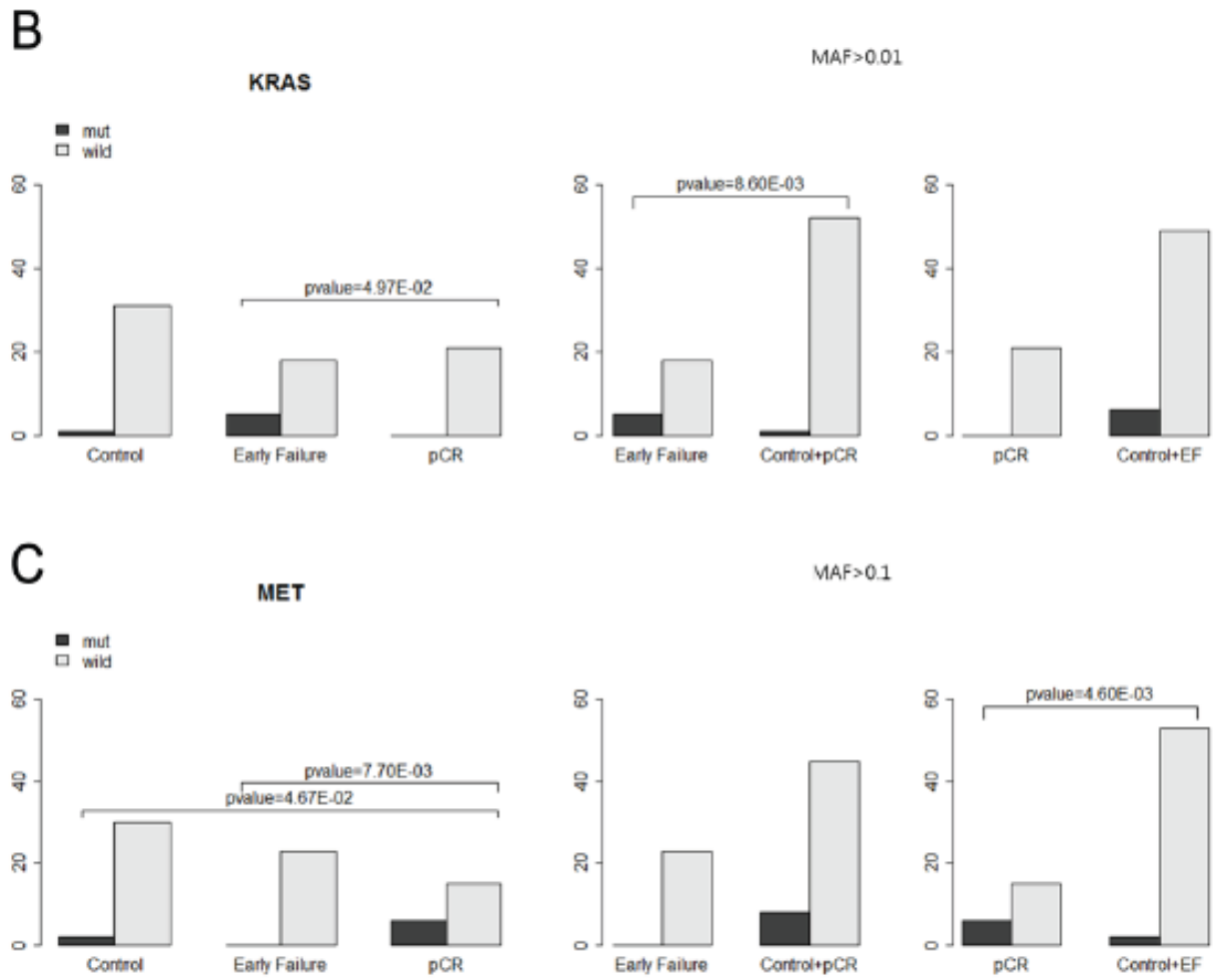

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LOCALIZED ADVANCED BREAST CANCER (LABC) CONCLUSIONS

- LABC is a heterogeneous disease that includes a wide range of clinical entities including IBC.

- The initial steps in the management of this disease is perform a biopsy to confirm the diagnosis and to study the biological characteristics of the tumour.

- These tumours are more frequently IDC, Grade III, ER-,PR-,HER2 positive and with high Ki67 index.

LOCALIZED ADVANCED BREAST CANCER (LABC) CONCLUSIONS

- Molecular profiling show that these tumours are more frequently HER2 overexpressing and triple negative.
- P53 mutation is the most common genetic alteration in the LABC.
- E and P-cadherin are co-expressed in IBC and this is related to the prognosis.

LOCALIZED ADVANCED BREAST CANCER (LABC) CONCLUSIONS

- ALK is expressed in 75% of cases of IBC and should be explored as therapeutic target.
- Preliminary NGS studies show that RAS and MET can predict response to chemotherapy.
- Despite the prognosis of LABC is still poor, improvement have been observed with use of multimodal therapy.
- LABC is a good model to follow *in vivo* evaluation of the efficacy of systemic therapy and creates opportunity to obtain specimens prior, during and after treatment.