Breast and Ovarian Cancer: from bench to clinic and back

Edna M. Mora, MD, FACS, MS
Professor
Department of Surgery, School of Medicine, Medical Sciences Campus, UPR
University of Puerto Rico Comprehensive Cancer Center

CENTRO COMPRENSIVO DE CÁNCER
universidad de puerto rico

Disclosures

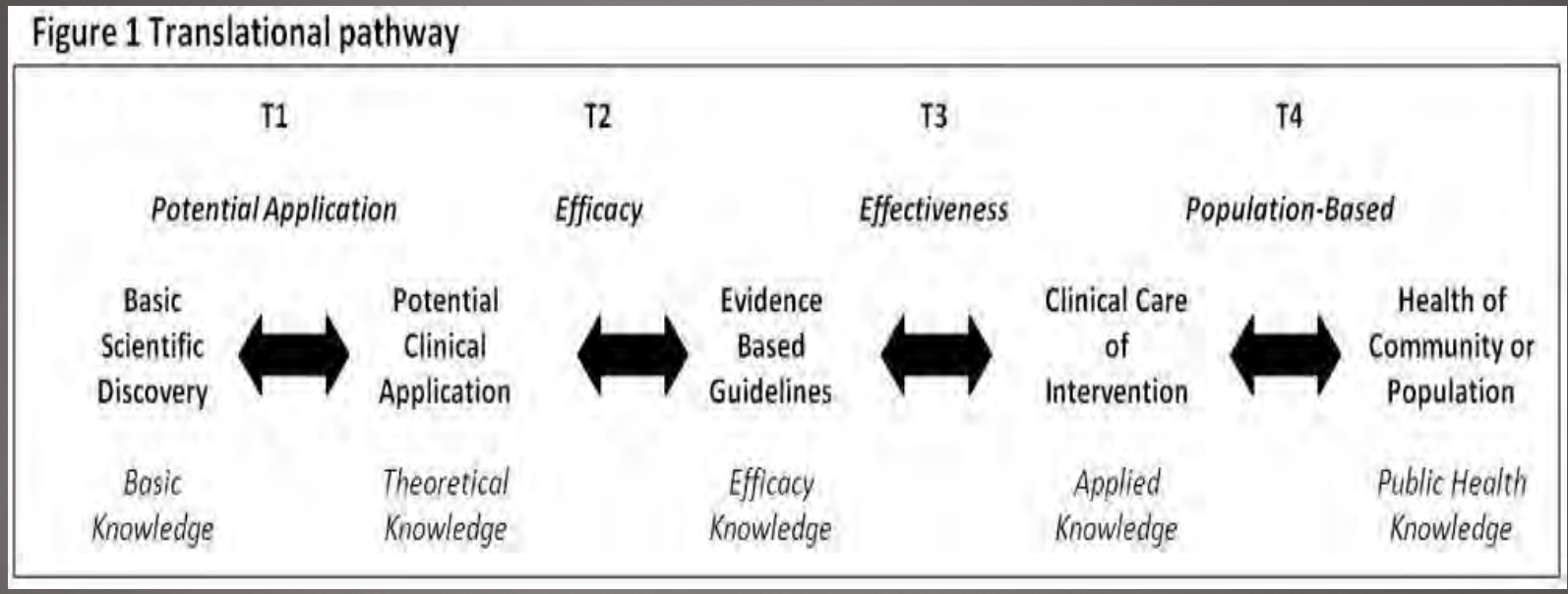
I, or my immediate family member including spouse/partner, have at present and/or have had within the last 12 months, or anticipate NO financial interest/arrangement or affiliation with one or more organizations that could perceived as a real or apparent conflict of interest in context to the design, implementation, presentation, evaluation etc. of this presentation.

Presentation

- Translational research definitions
- Developing concepts: circulating tumor cells
- Developing concepts: cancer stem cells
- Target therapy definition
- Developing concepts: breast endocrine therapy
- Developing concepts: breast cancer Her-2 inhibition
- Treatment of ovarian cancer ascites
- Translational research at the UPRCCC

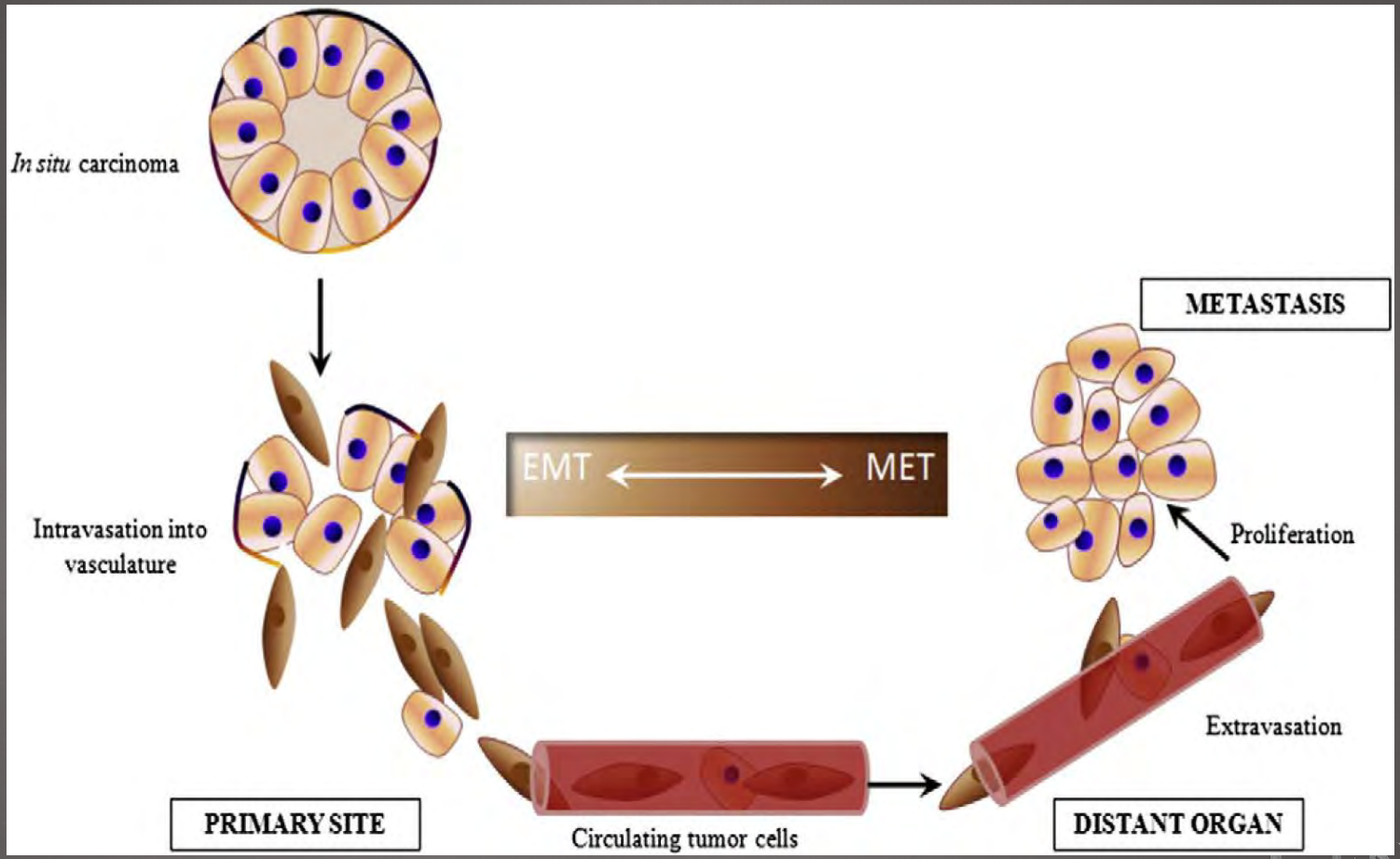
CENTRO COMPRENSIVO DE CÁNCER
universidad de puerto rico

Translational Research



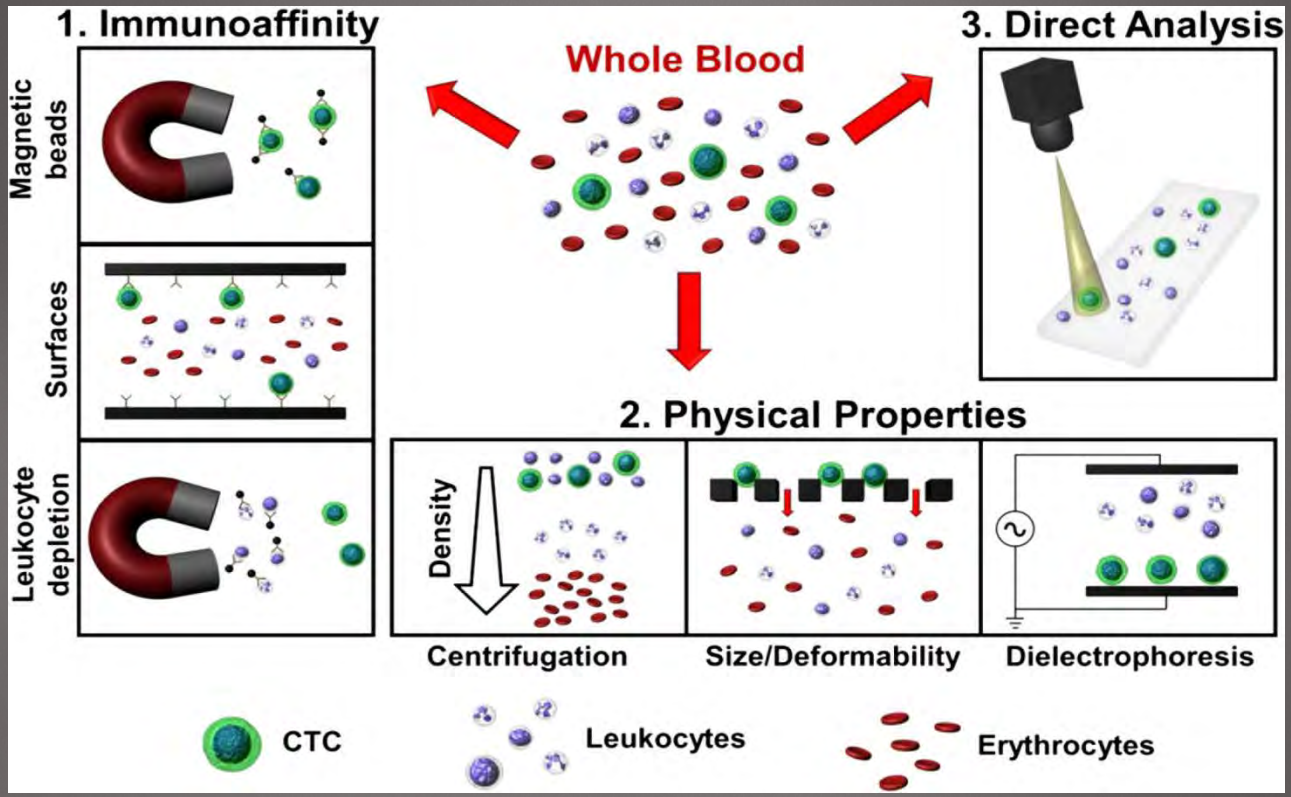
CENTRO COMPRENSIVO DE CÁNCER
universidad de puerto rico

Developing concepts: circulating tumor cells (CTCs)



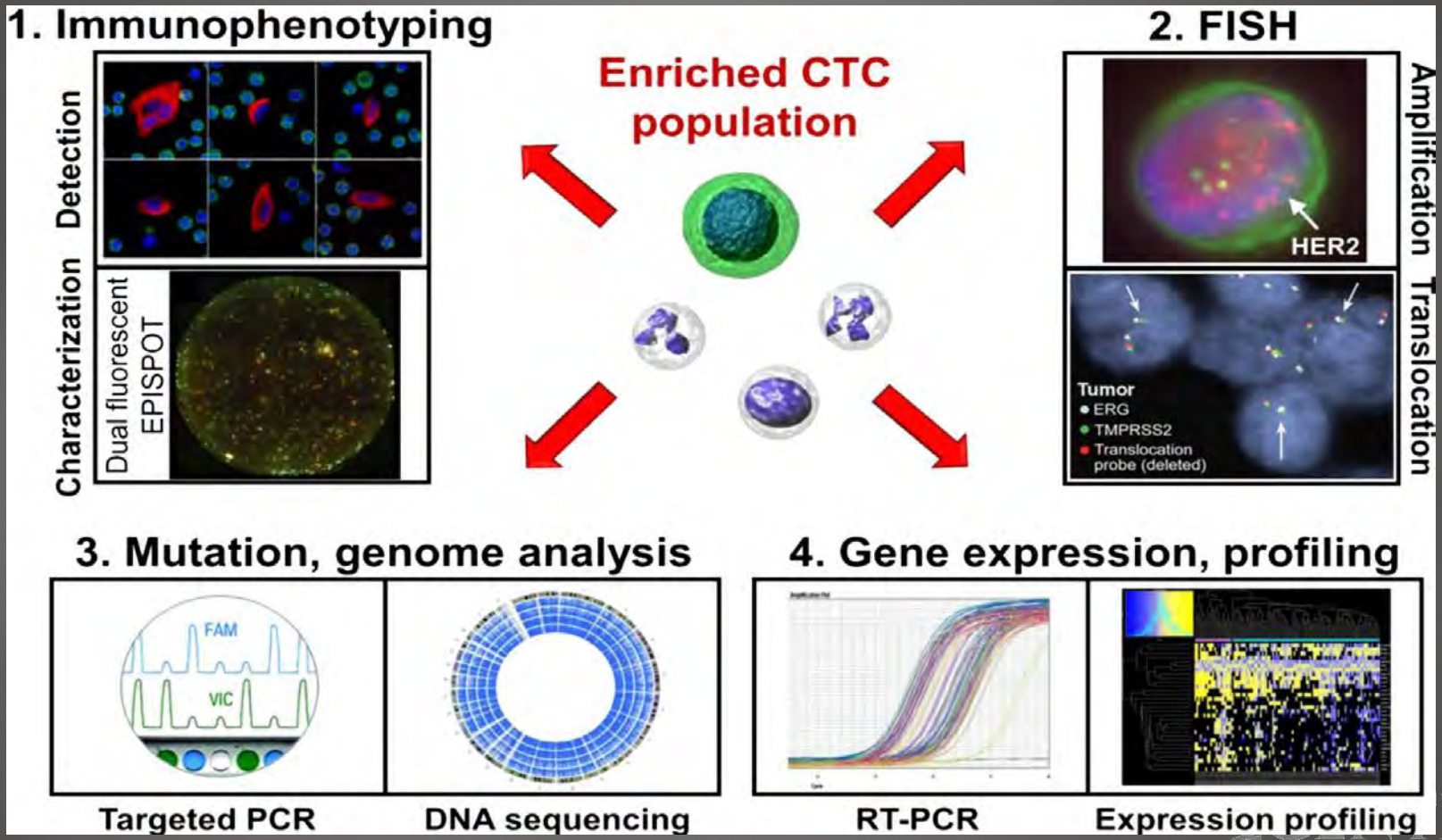
Friedlander, TW et al. 2014 142: 271-280.

Circulating tumor cells: isolation



Harouaka R, et al. 2014 Pharmacology and Therapeutics 141: 209-221.

Circulating tumor cells: analysis



Harouaka R, et al. 2014 Pharmacology and Therapeutics 141: 209-221.

Circulating tumor cells: applications

- CTC enumeration as a prognostic biomarker for overall survival
- CTC enumeration as an indicator of response
- Exploratory studies on predictive biomarkers with CTCs
- Plasma DNA as an alternative technology

Harouaka R, et al. 2014 Pharmacology and Therapeutics 141: 209-221.

Alternative Technology: Circulating tumor DNA

Table 1
Detection of cf-DNA and its alterations in patients with solid tumors.

Cf-DNA alterations	Molecular alterations				
	Breast	Lung	Colorectal	Prostate	Ovary
Mutation	TP53 (28–31,37) PIK3CA (32–34,37)	RAS (63–67) EGFR (72–77)	RAS, TP53, APC (10,84,90,92–94)	–	TP53 (127)
DNA integrity	Serum DNA integrity (40,41)	–	Serum DNA integrity (100)	Serum DNA integrity (102,115)	Serum DNA integrity (129)
Microsatellite alterations	LOH and MSI (9,11,42,43)	LOH and MSI (8, 78)	–	LOH and MSI (110,112)	LOH (128)
Methylation	RASSF1A, APC, DAPK, ESR1, BRCA1, MGMT, GSTP1, Stratifin, MDR1, HSD17B4, HIC1, NEUROD1 (48–53)	P16 (65, 79) 14-3-3sigma (80)	SEPT9, ALX4, HLTF, HPP1 (84, 95–99)	GSTP1, RASSF1A, RARB2, AR (111–114)	RASSF1A, PGR PROX, BRCA1, APC, DAPK, CDKN2A, HMLH1 (124, 126)

LOH, loss of heterozygosity; MSI, microsatellite instability.

Esposito A, et al. 2014 Cancer Treatment Rev 40: 648-655.

Alternative Technology: Circulating tumor DNA

Table 2

Ongoing clinical trials that study cf-DNA in solid tumors with therapeutic intervention.

Clinical trial	Status	Therapeutic intervention	Setting
NCT00899548*	Recruiting	Predict response after systemic therapy	MBC
NCT01198743*	Recruiting	Validate prognostic value of cf-DNA	Stage II–III CRC
NCT00977457*	Recruiting	Predict recurrence	Prostate cancer undergoing surgery
NCT01617915*	Recruiting	Correlate cf-DNA with response to neoadjuvant CT	BC candidate to neoadjuvant CT
NCT01776684*	Recruiting	Evaluation of EGFR TKI resistance mechanism	NSCLC
NCT01836640*	Not yet recruiting	Evaluate cf-DNA as a surrogate for tumor biopsy to identify tumor genetic alterations	MBC

CT, chemotherapy; CRC, colorectal cancers; cf-DNA, circulating cell-free DNA; MBC, metastatic breast cancer; NSCLC, non small cell lung cancer; BC, breast cancer; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

* http://clinicaltrials.gov/

Esposito A, et al. 2014 Cancer Treatment Rev 40: 648-655.

CENTRO COMPRENSIVO DE CÁNCER
universidad de puerto rico

Developing concepts: cancer stem cells (CSC)

- Cancer stem cells= tumor-infiltrating cells=cancer metastasis-initiating cells
- Characteristics:
  - Self renewal
  - Differentiation potential
  - Resistance to chemotherapy
  - Resistance to radiation therapy
- Common seed for therapy-resistant recurrence and metastasis

Badve S, et al. 2012 Lancet Oncology e43-e48.

Cancer Stem Cells

- 40% of breast cancer patients relapse.
- ***60-70% of these recurrences are distant metastases.***
- Reasons- therapeutic deficiencies (under treatment, local tumor missed at surgery, micrometastases)

  - breast cancer stem cells

Badve S, et al. 2012 Lancet Oncology e43-e48.

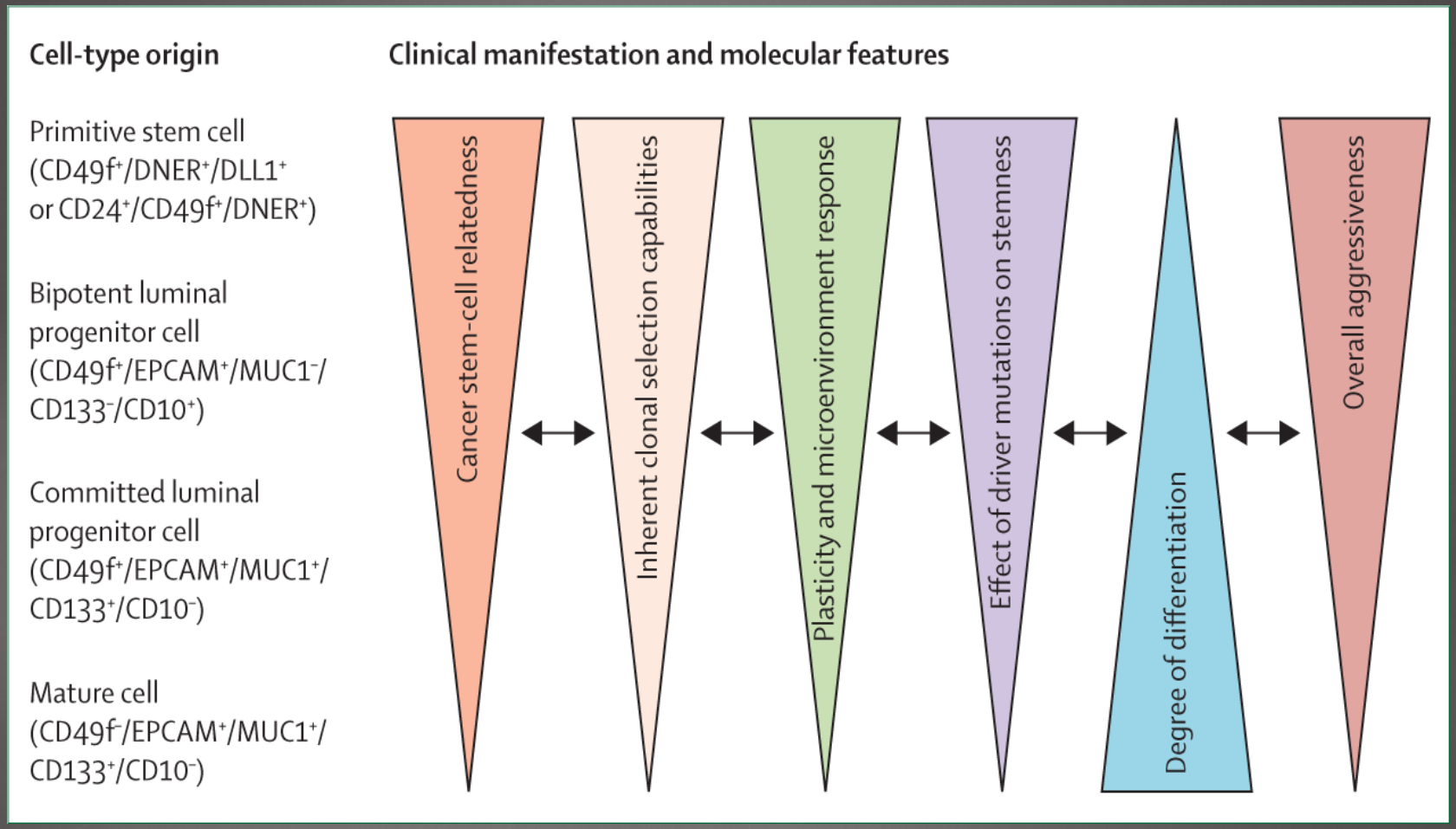
CENTRO COMPRENSIVO DE CÁNCER
universidad de puerto rico

Cancer Stem Cells

- Adult stem cells- undifferentiated cell, found among differentiated cells in a tissue or organ that can renew itself and can differentiate to yield some or all of the major specialized cell types of the tissue or organ.
- Subpopulation of cancer cells similar to adult stem cells.
- Mammary cancer stem cells- CD44, CD24, ALDH1
- Contribute to heterogeneicity and EMT.
- Dormant (G0)- low proliferation
- Exclude intracellular toxins (chemotherapy)

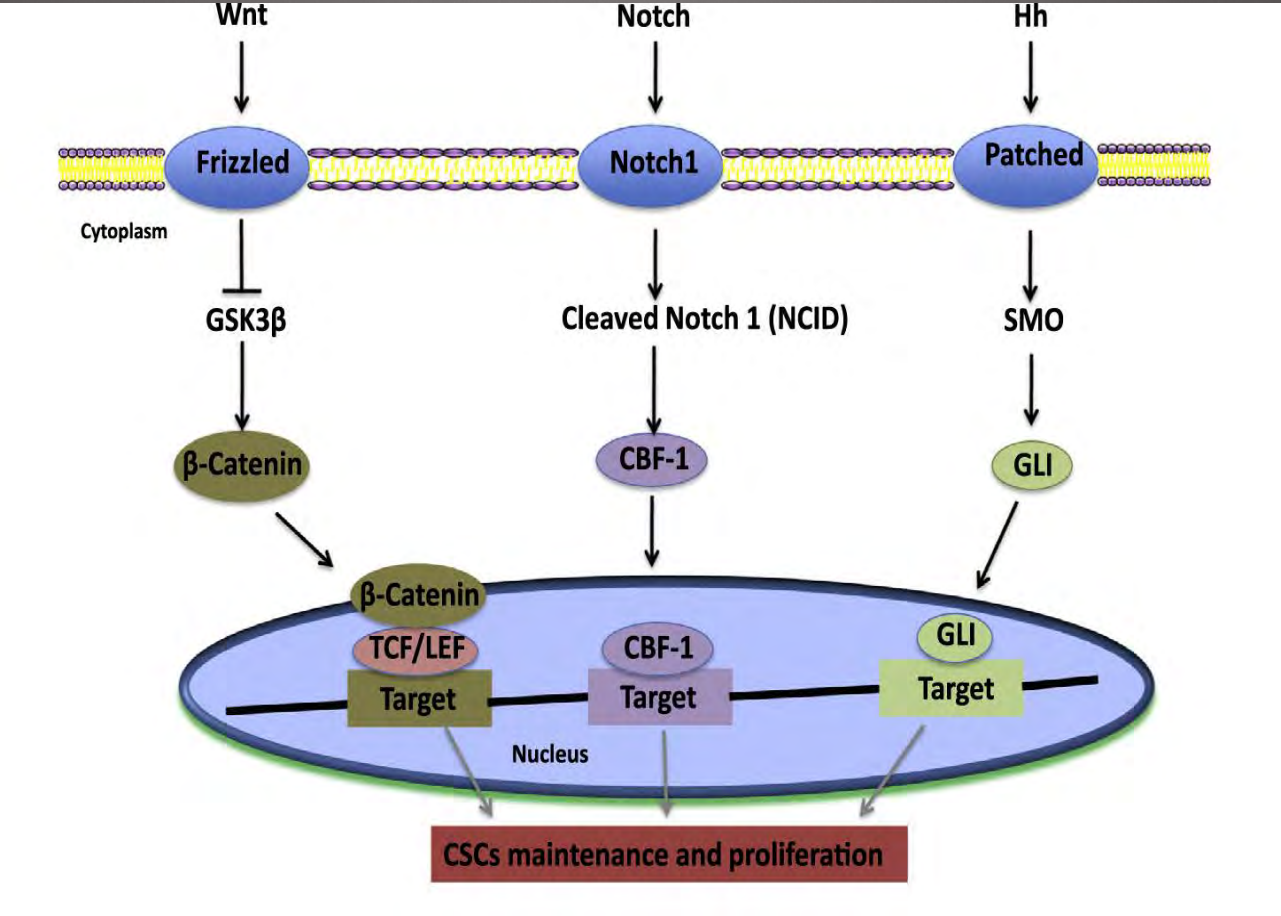
Badve S, et al. 2012 Lancet Oncology e43-e48.

Breast Cancer Stem Cells



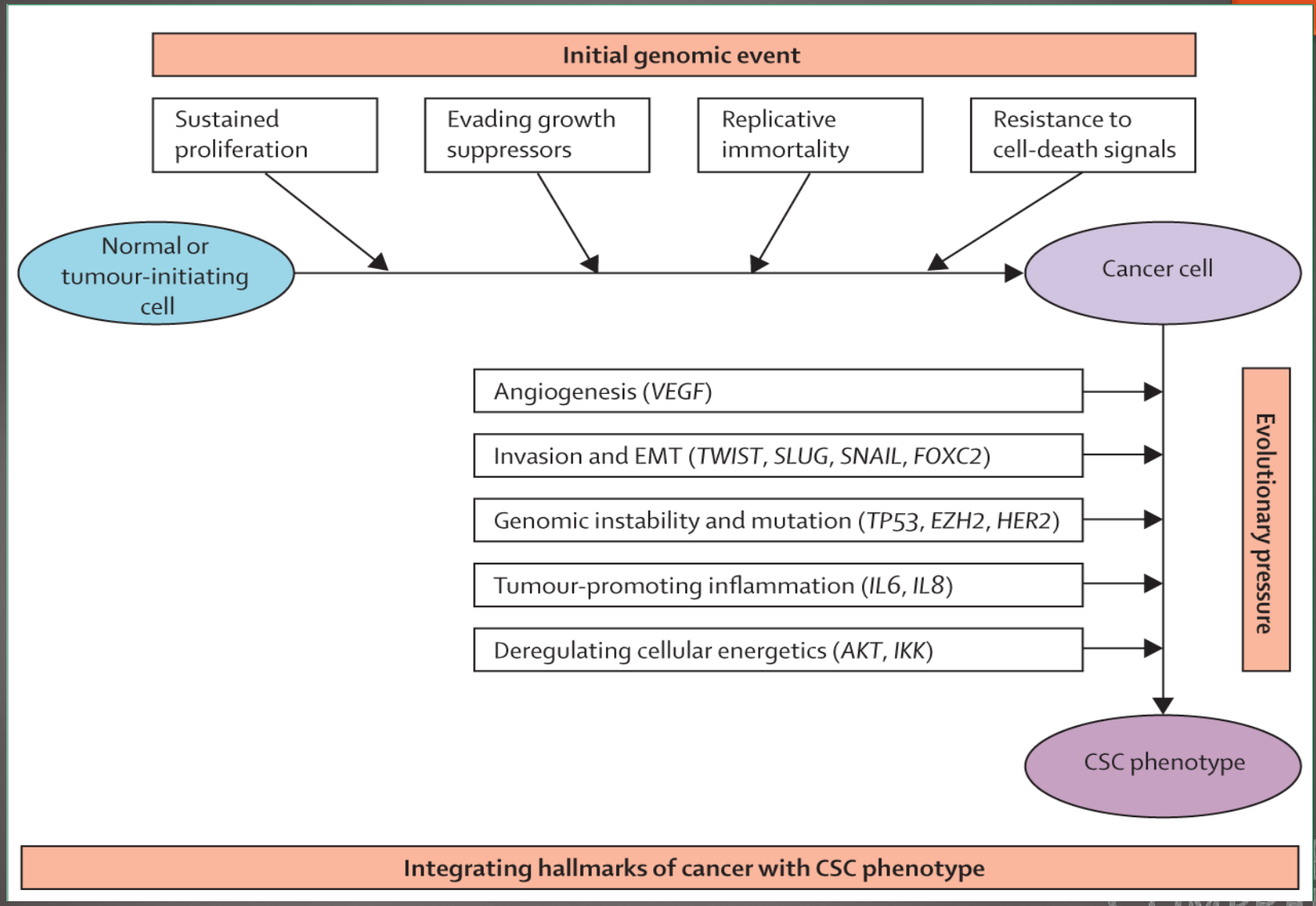
Badve S, et al. 2012 Lancet Oncology e43-e48.

Breast Cancer Stem Cells: self-renewal pathways



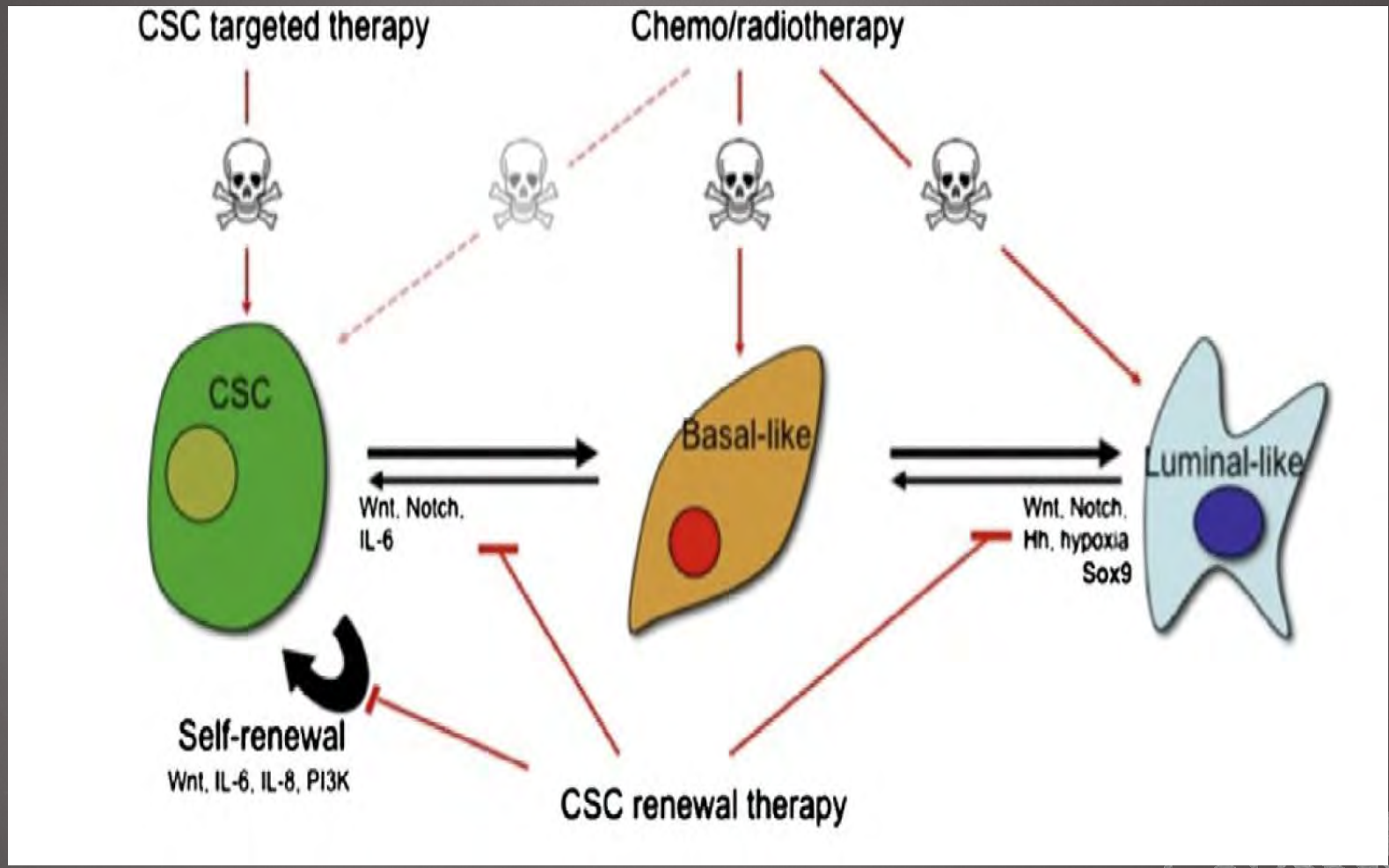
Geng S-Q, et al. 2014 Cancer letters April 17.

Breast Cancer Stem Cells



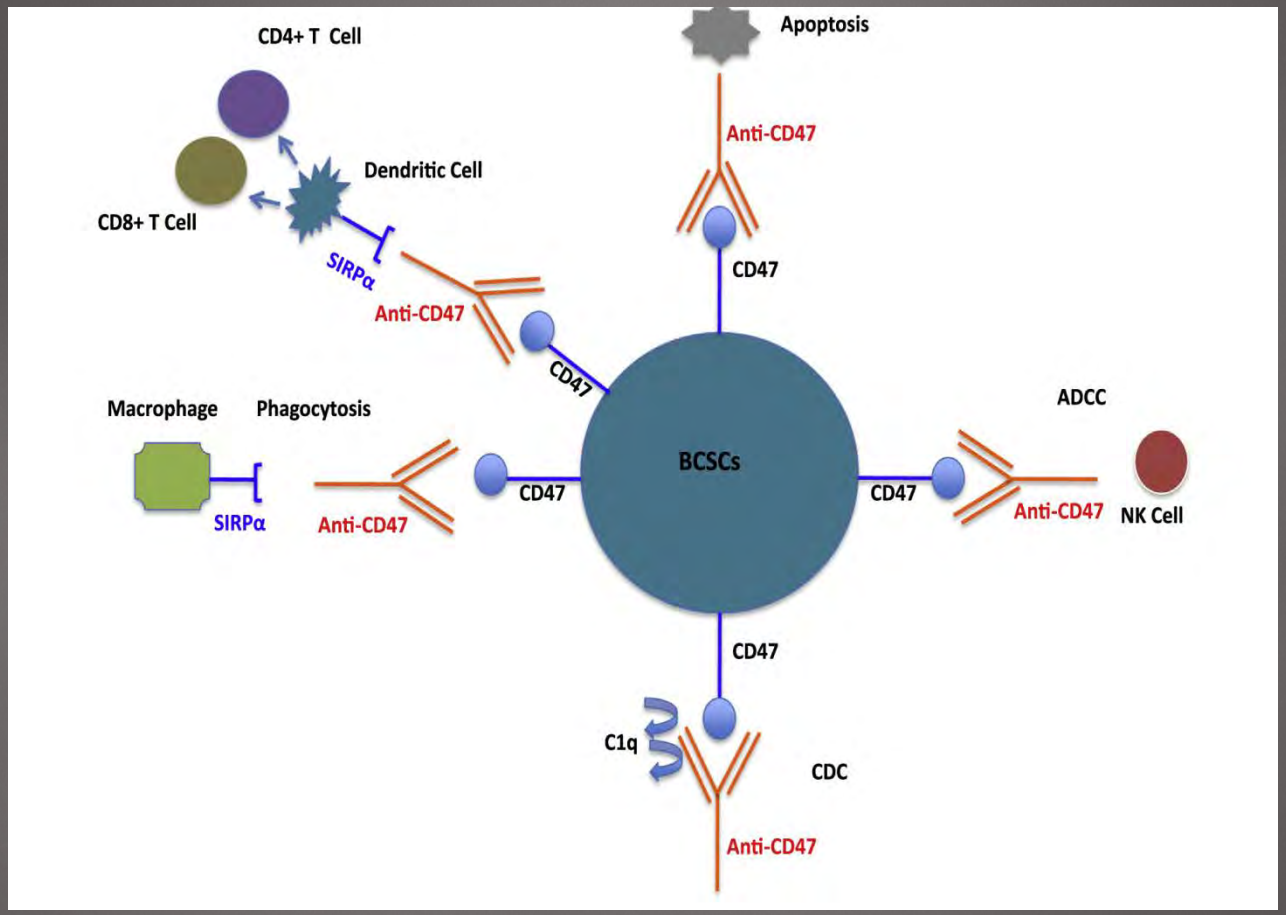
Badve S, et al. 2012 Lancet Oncology e43-e48.

Breast Cancer Stem Cells



Smalley M, eta l. 2012 Cancer Letters http://dx.doi.org/10.1016/j.canlet.2012.04.023

Breast Cancer Stem Cells: targeting CD47



Geng S-Q, et al. 2014 Cancer letters April 17.

Cancer Stem Cells

Important Questions

- **Do cancer start in normal mammary stem cells or some malignant cells acquire a CSC phenotype?**
- **Are the CSC different for different types of breast cancer? (plasticity vs. dynamic changes)**
- **Are CSC different in metastatic sites?**
- **Do limitations in detection reflect a flaw in the concept?**
- **Should we change Phase II and Phase III goals to assess CSC therapy?**

CENTRO COMPRENSIVO DE CÁNCER
universidad de puerto rico

Developing Concepts: Target Therapy

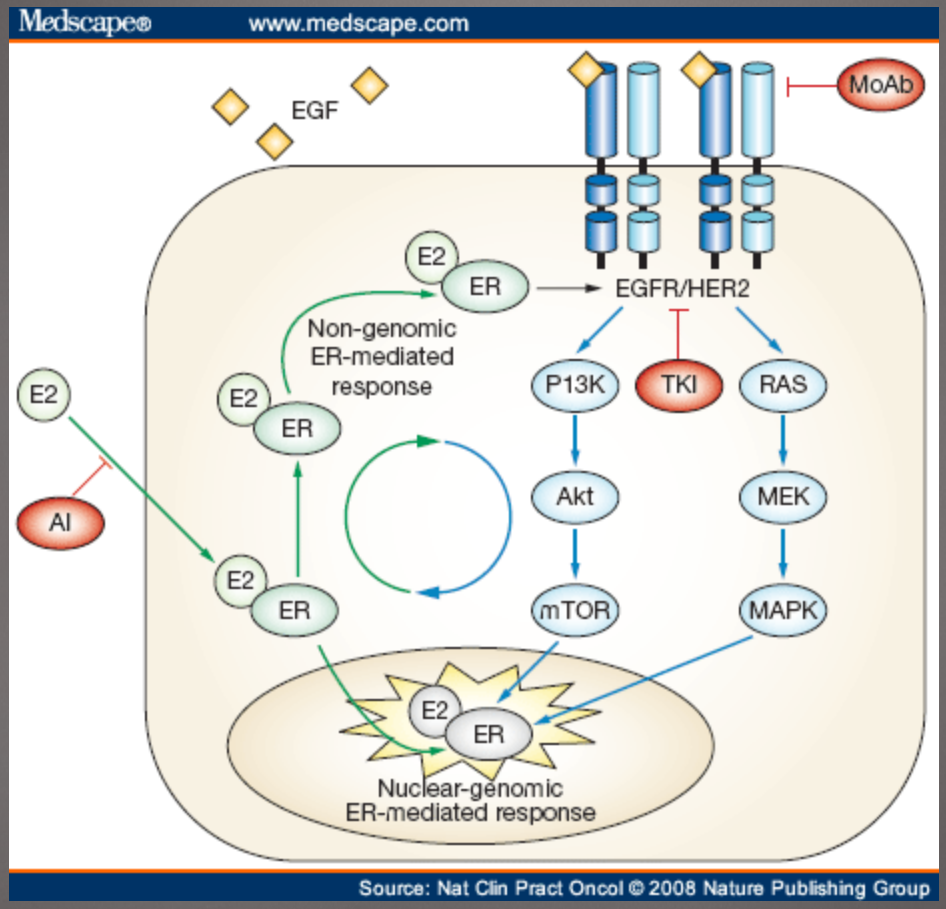
- A type of treatment that uses drugs or other substances to identify and attack specific types of **cancer** cells with less harm to normal cells.
- Targeted **therapy** or molecularly targeted **therapy** is a type of medication that blocks the growth of **cancer** cells by interfering with specific targeted molecules needed

Target Therapy

Table 10-14 Selected FDA-Approved Targeted Therapies

Generic Name	Trade Name	Company	Target	FDA Approval Date	Initial Indication
Trastuzumab	Herceptin	Genentech	HER2	9/1998	Breast cancer
Imatinib	Gleevec	Novartis	c-kit, bcr-abl, PDGFR	5/2001, 12/2002	CML, GIST
Cetuximab	Erbitux	ImClone Systems	EGFR	2/2004	Colorectal cancer
Bevacizumab	Avastin	Genentech	VEGF	2/2004	Colorectal cancer, lung cancer
Erlotinib	Tarceva	Genentech, OSI Pharmaceuticals	EGFR	11/2004	Non-small cell lung cancer
Sorafenib	Nexavar	Bayer	Raf, PDGF, VEGFR, c-kit	12/2005	RCC
Sunitinib	Sutent	Pfizer	VEGFR PDGFR c-kit, Fit-3, RET	1/2006	GIST, RCC
Dasatinib	Sprycel	Bristol-Myers Squibb	bcr-abl, src family, c-kit, EPHA2, PDGFR-β	6/2006	CML
Lapatinib	Tykerb	GlaxoSmithKline	EGFR and HER2	3/2007	Breast cancer
Temsirolimus	Torisel	Wyeth	mTOR	5/2007	RCC

Developing concepts: breast endocrine therapy



Breast cancer endocrine therapy resistance

- 66% of breast cancers express hormone receptors
- 50% of breast cancers express hormone receptors and Her-2.
- Expression of Her-2 confers hormonal resistance to treatment.
- Tumors that initially express HR eventually do not respond to therapy

Patani N. et al 2014 Mol Cell Endocrinology 382: 683-694.

Breast cancer endocrine therapy: resistance mechanisms

- Down-regulation of ER expression
- ER mutations
- Altered expression of ER co-regulators
- Ligand-independent activation of ER and co-activators by growth factor receptor kinases

Patani N. et al 2014 Mol Cell Endocrinology 382: 683-694.

Breast cancer endocrine therapy

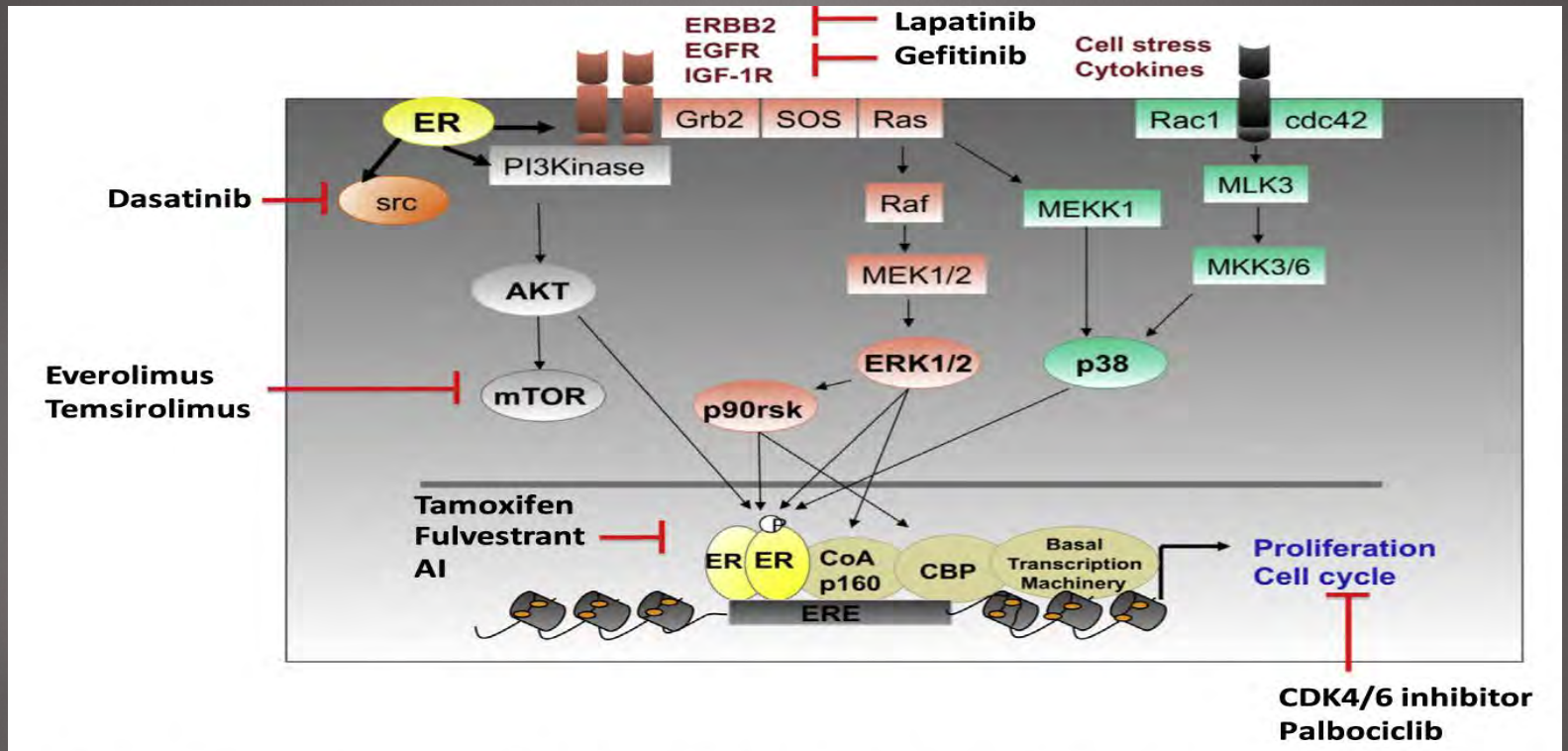


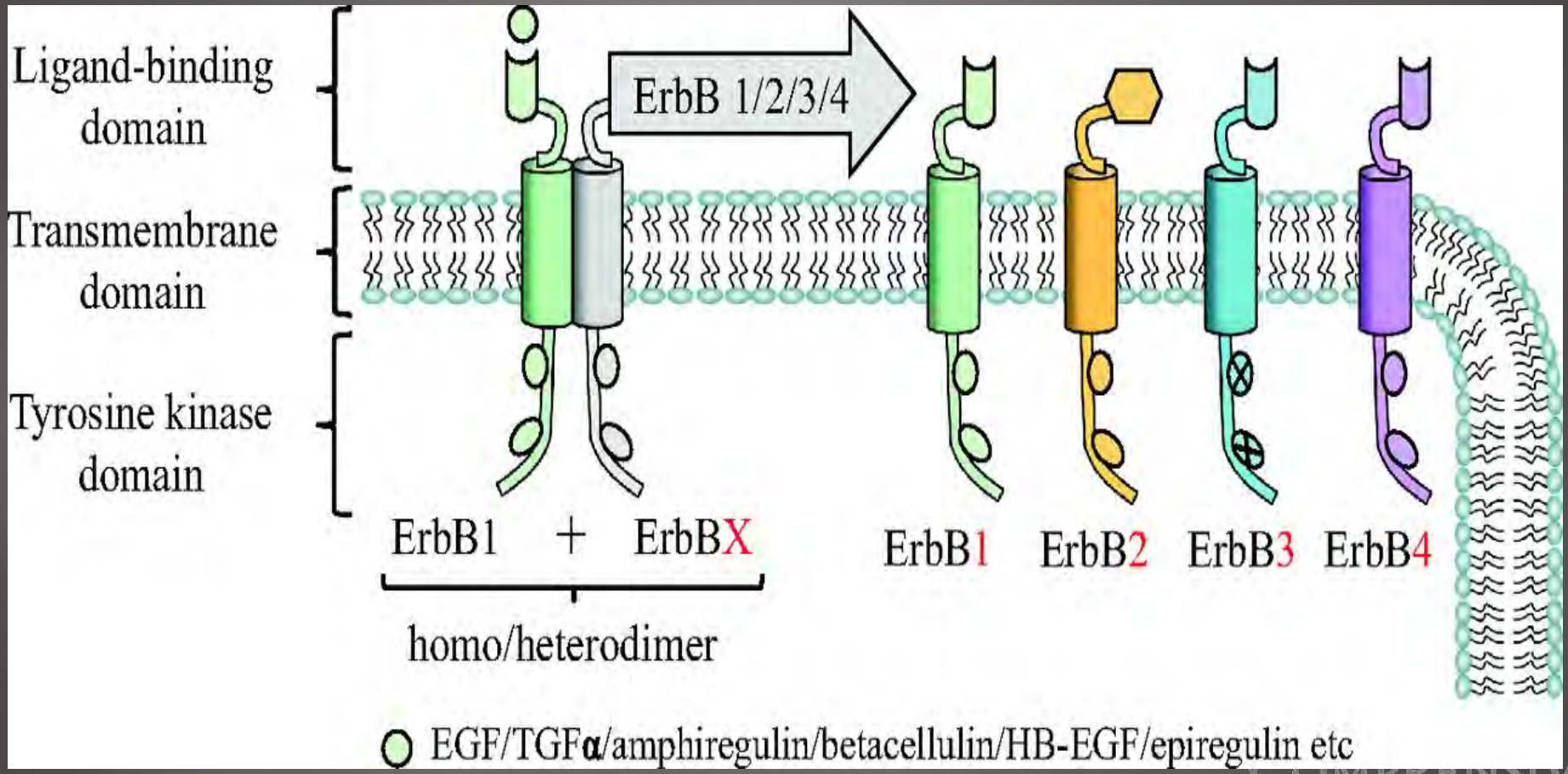
Fig. 2. Summary of targeted therapies and their sites of action in relation to endocrine treatment.

Patani N. et al 2014 Mol Cell Endocrinology 382: 683-694.

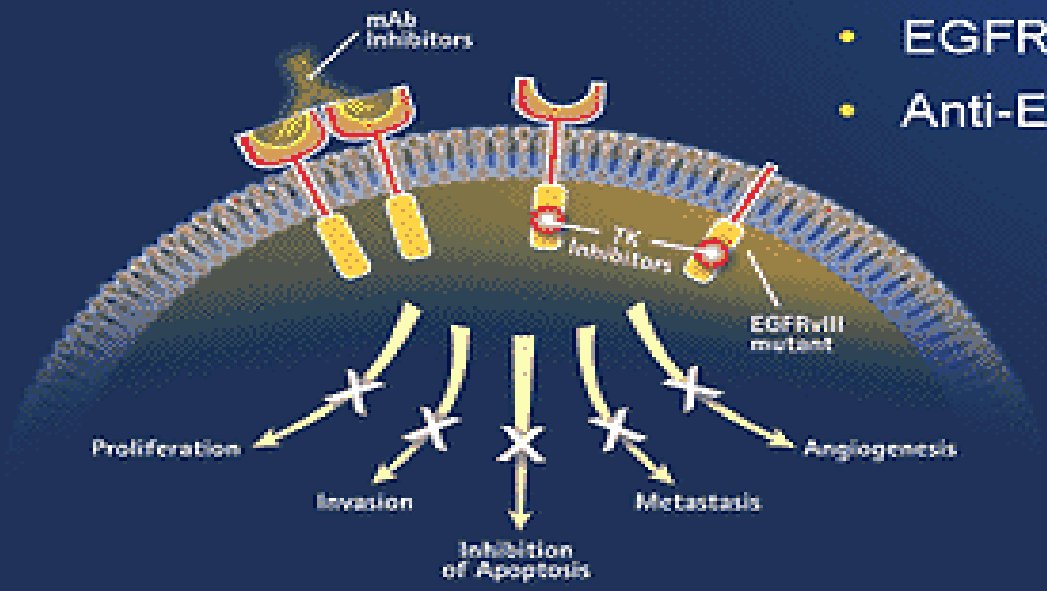
Therapeutic options for Her-2 positive breast cancer

- EGFR family-ErbB1 (HER-1), ErbB2 (Her-2/neu), ErbB3 (Her-3), ErbB4 (Her-4).
- Her-2 is amplified in 20-25% of breast cancer
- Her-2 is associated with adverse prognostic outcomes in early and advanced disease.
- Tratuzumab (Herceptin), Pertuzumab (Perjeta), Ado-trastuzumab emtansine (Kadcyla), Lapatinib (Tykerb).

The Epidermal Growth factor Receptors Family



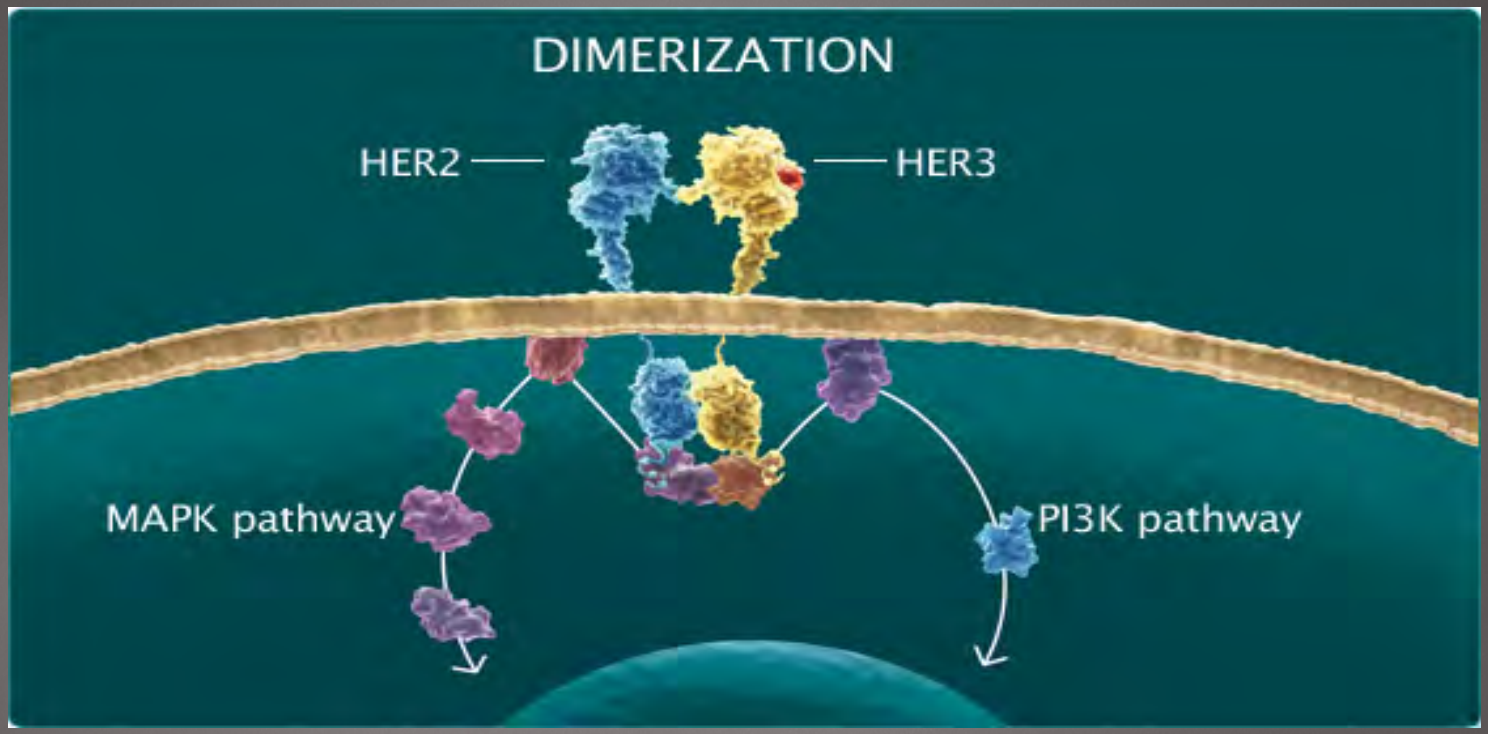
Two Mechanisms of EGFR Inhibition



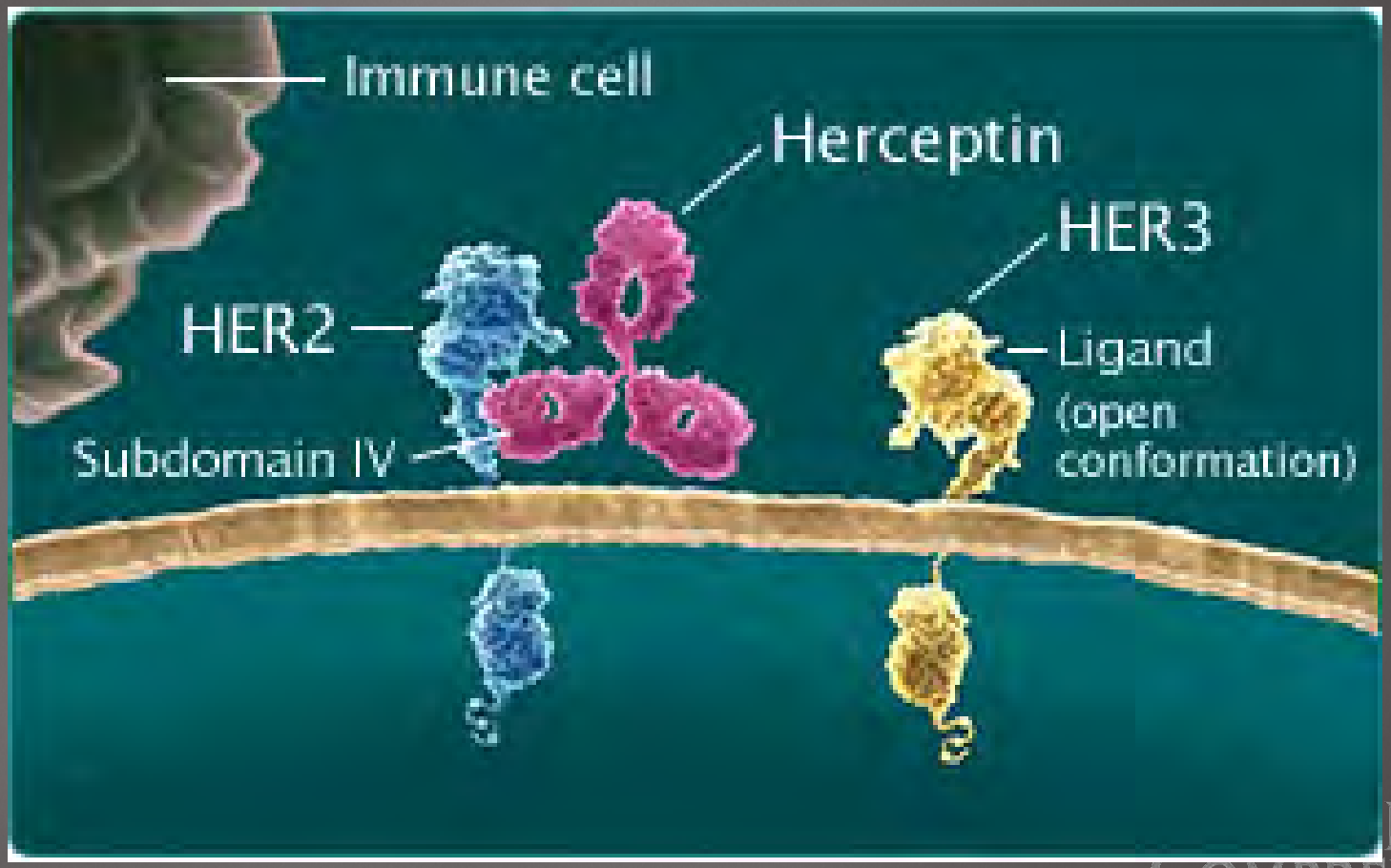
Inhibition Strategies:

- EGFR-TK inhibitors
- Anti-EGFR mAb inhibitors

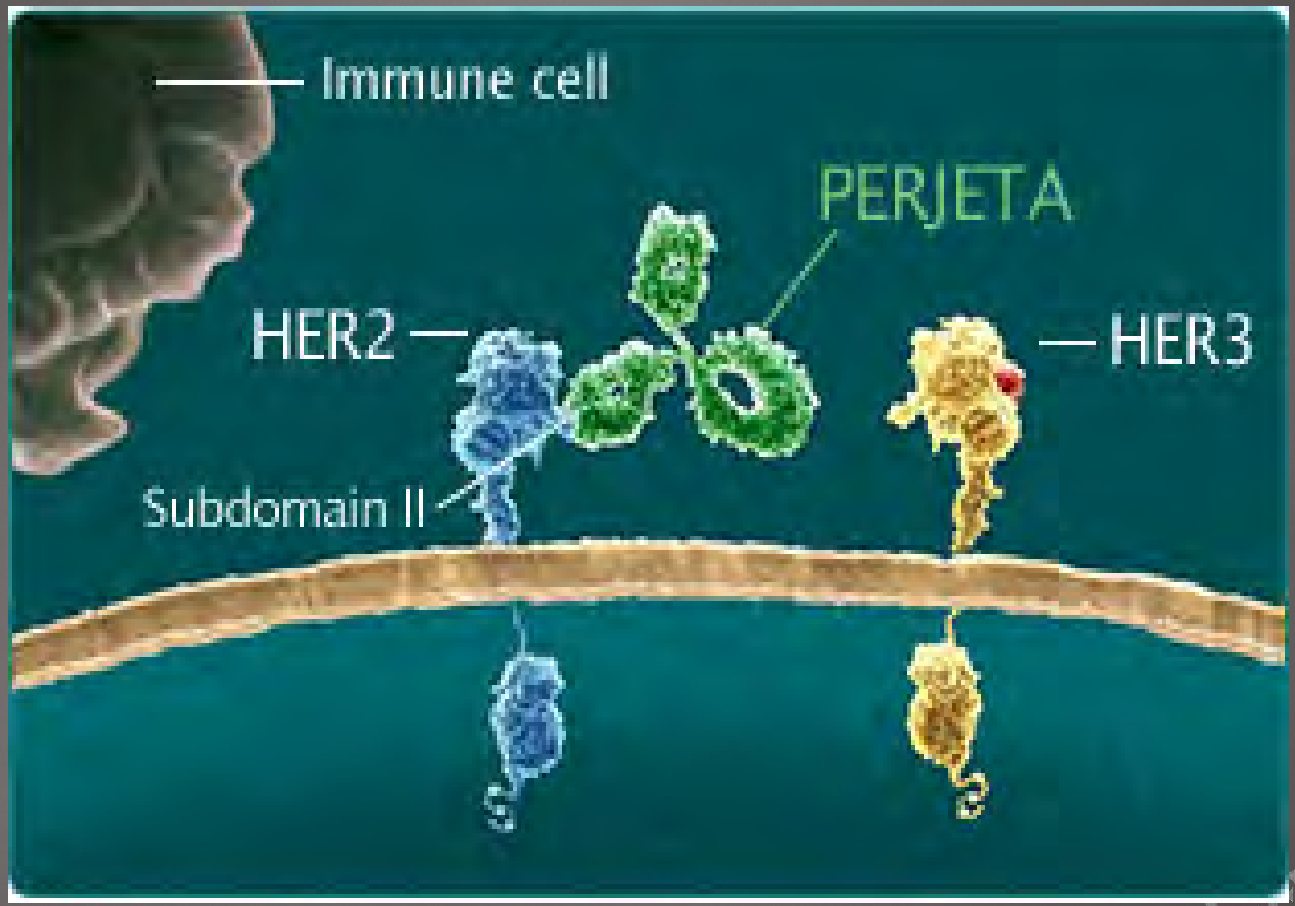
Mechanisms



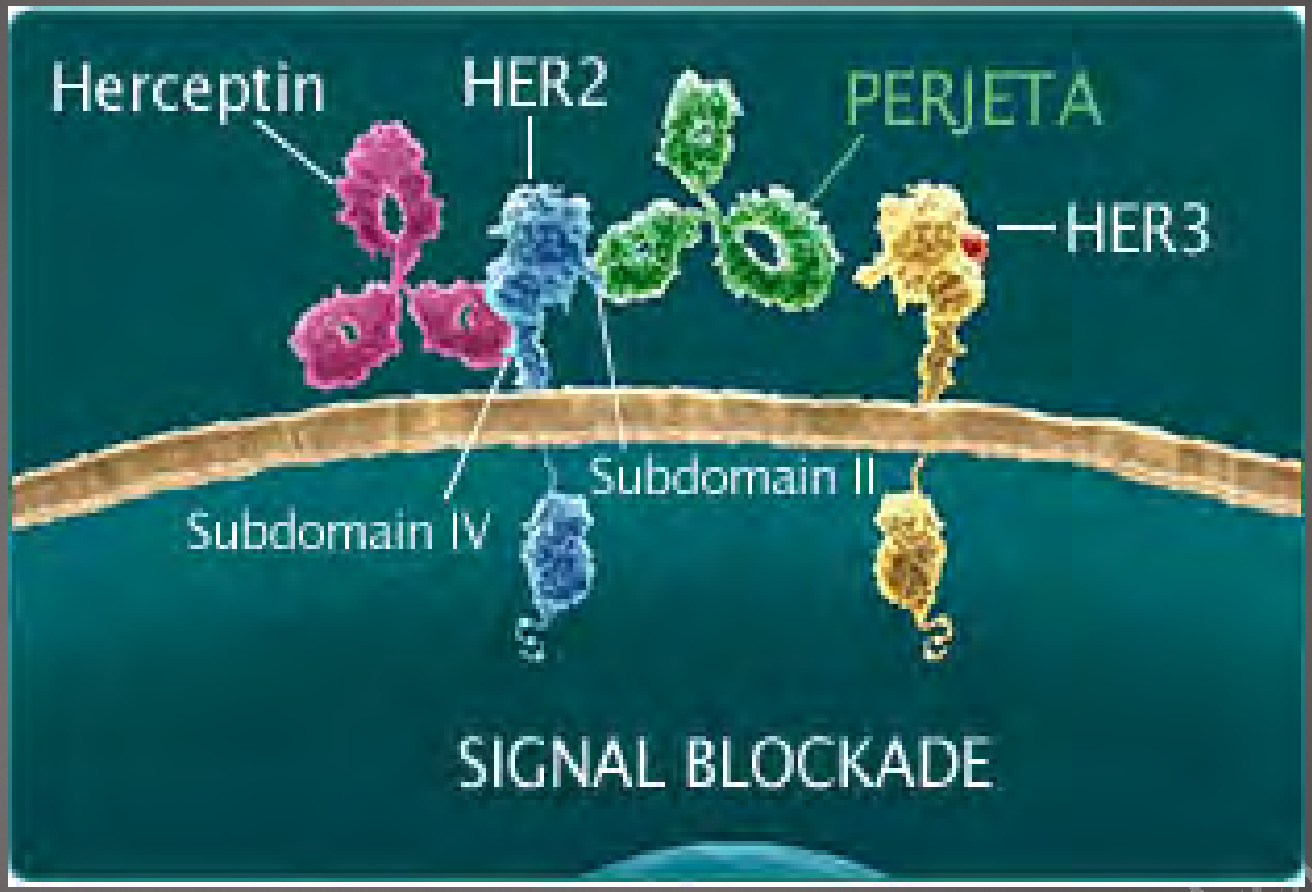
Mechanisms



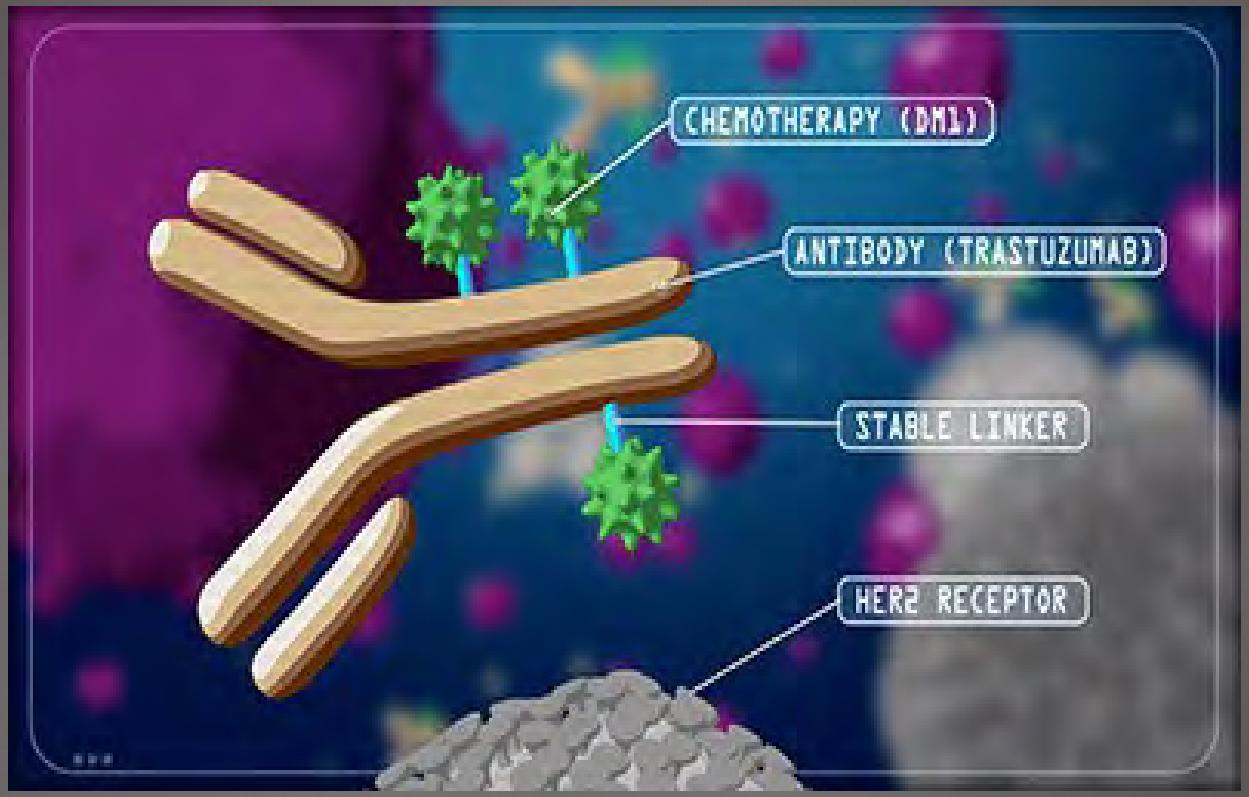
Mechanisms



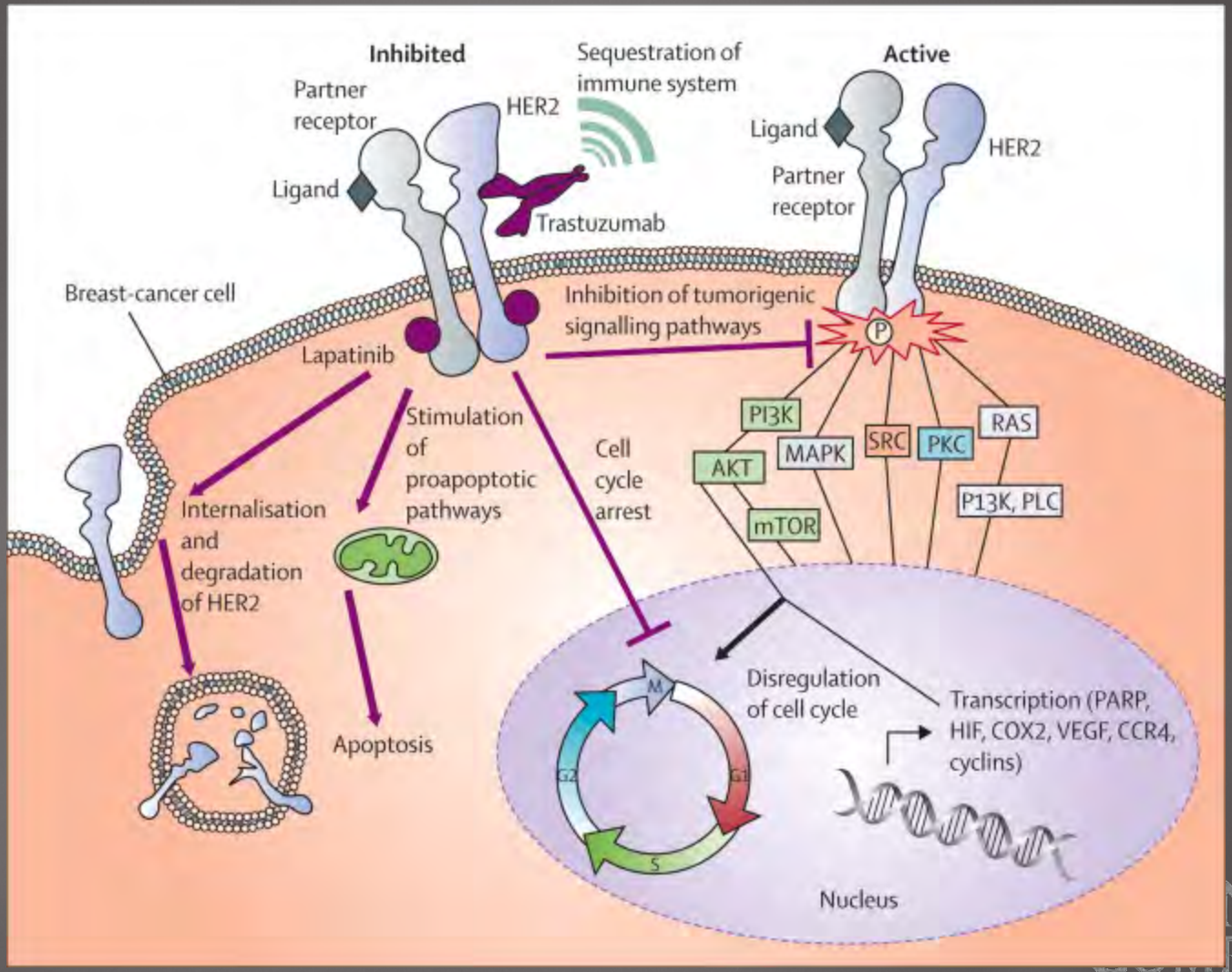
Mechanisms



Mechanism -Ado-trastuzumab emtansine (Kadcyla)



Summary of Mechanisms



Advances in Ovarian Cancer Ascites Treatment

- 66% of ovarian cancer patients develop malignant ascites.
- Malignant ascites definition- (NCI) accumulation of fluid containing cancer cells in the abdomen.
- Symptoms- abdominal pressure, distention, dyspnea, blotting, pelvic pain, bowel/bladder dysfunction.
- 40% of ovarian cancer patients with ascites live 5 years

  Thus, ascites is a chronic problem.
- Mechanisms:

  lymphatic obstruction

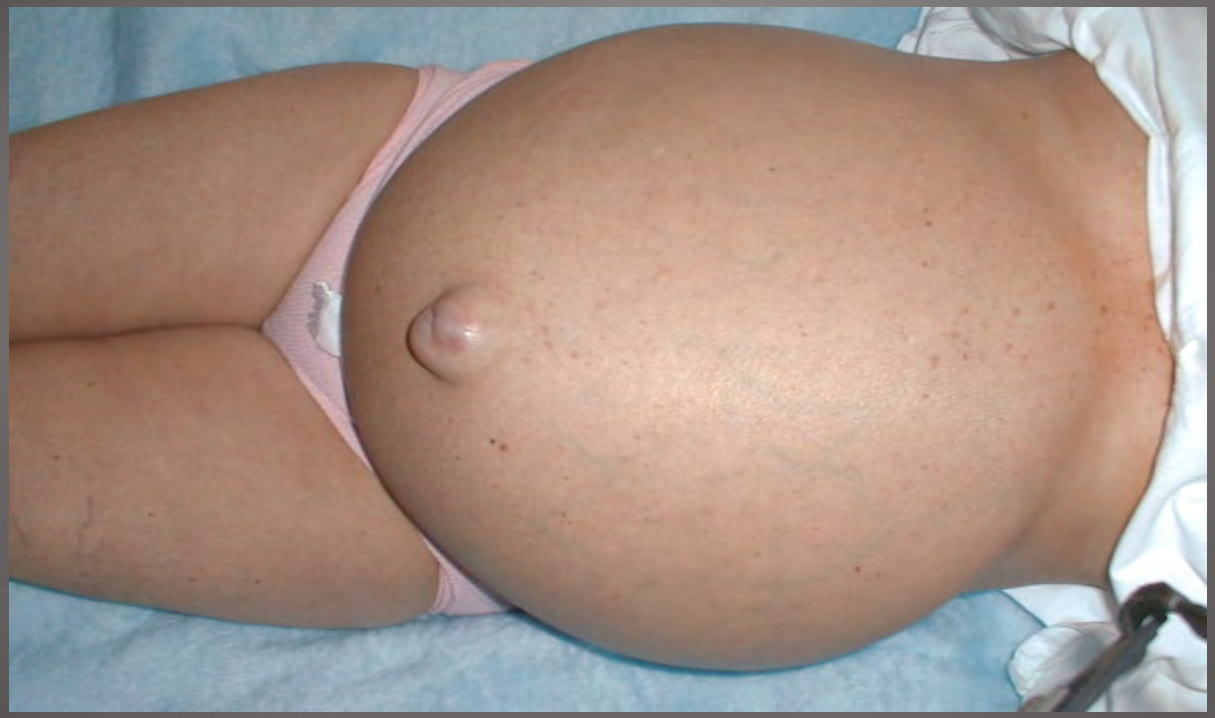
  increased vascular permeability

  release of inflammatory cytokines

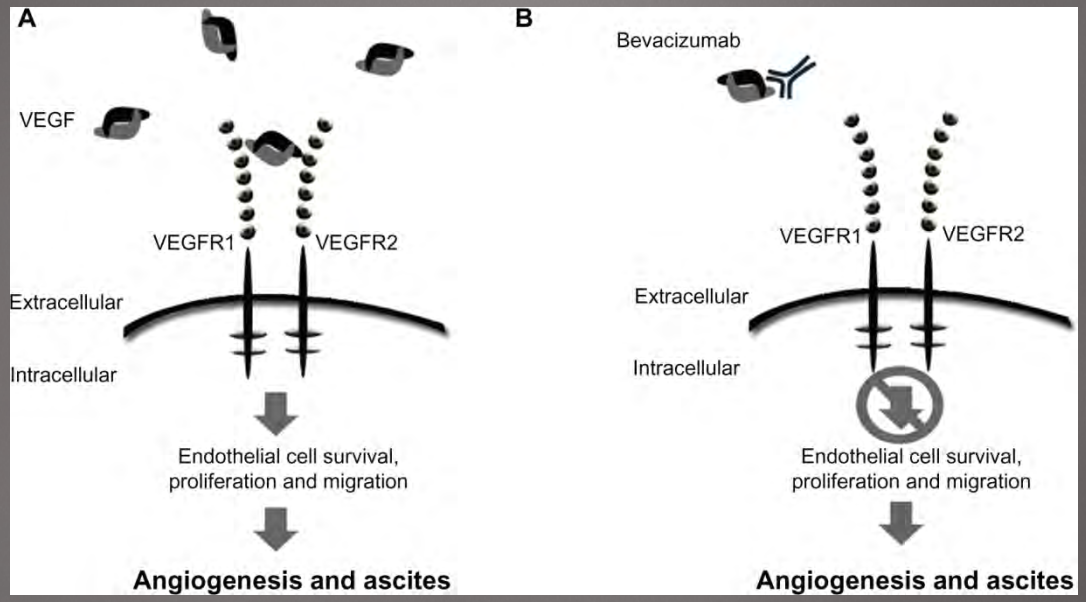
  direct increase of fluid production by the cancer cells lining the peritoneum.

Advances in Ovarian Cancer Treatment

- Treatment is usually drainage as needed.

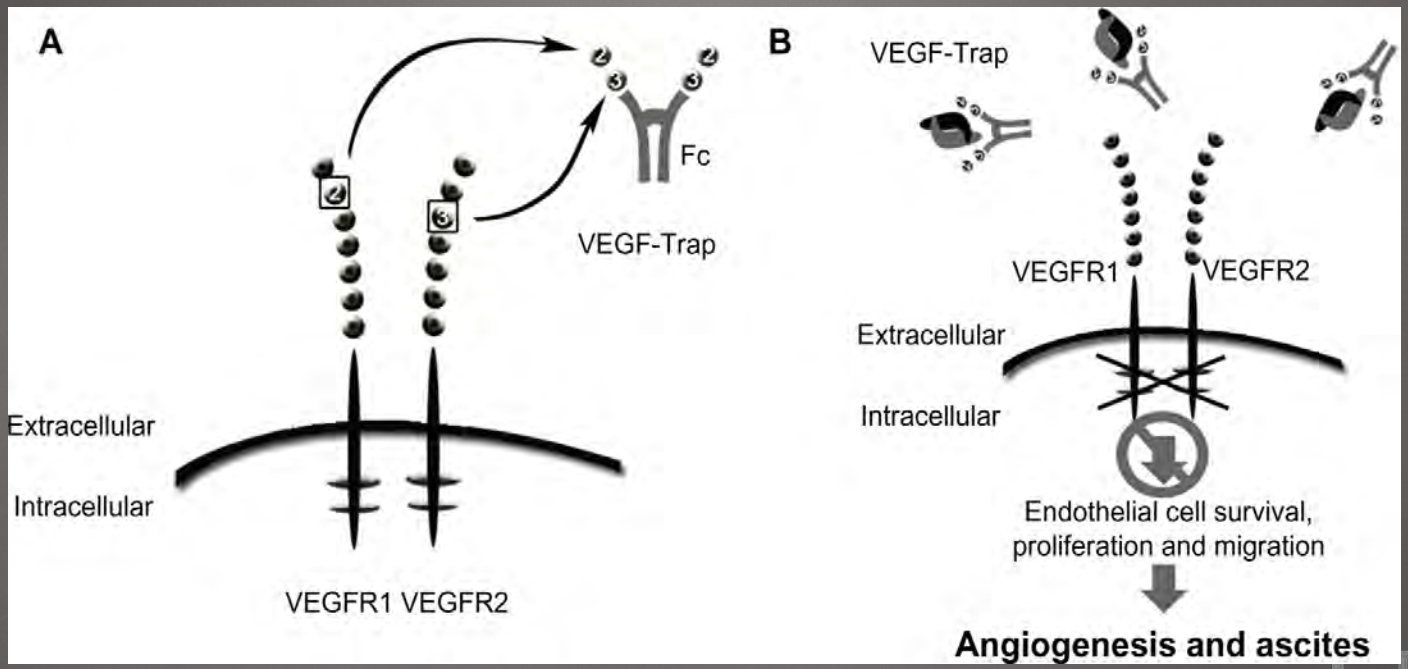


Advances in Ovarian Cancer Ascites Treatment: Antiangiogenics



Eskander RN, et al. Int J Women Health 2012 (4): 395-404.

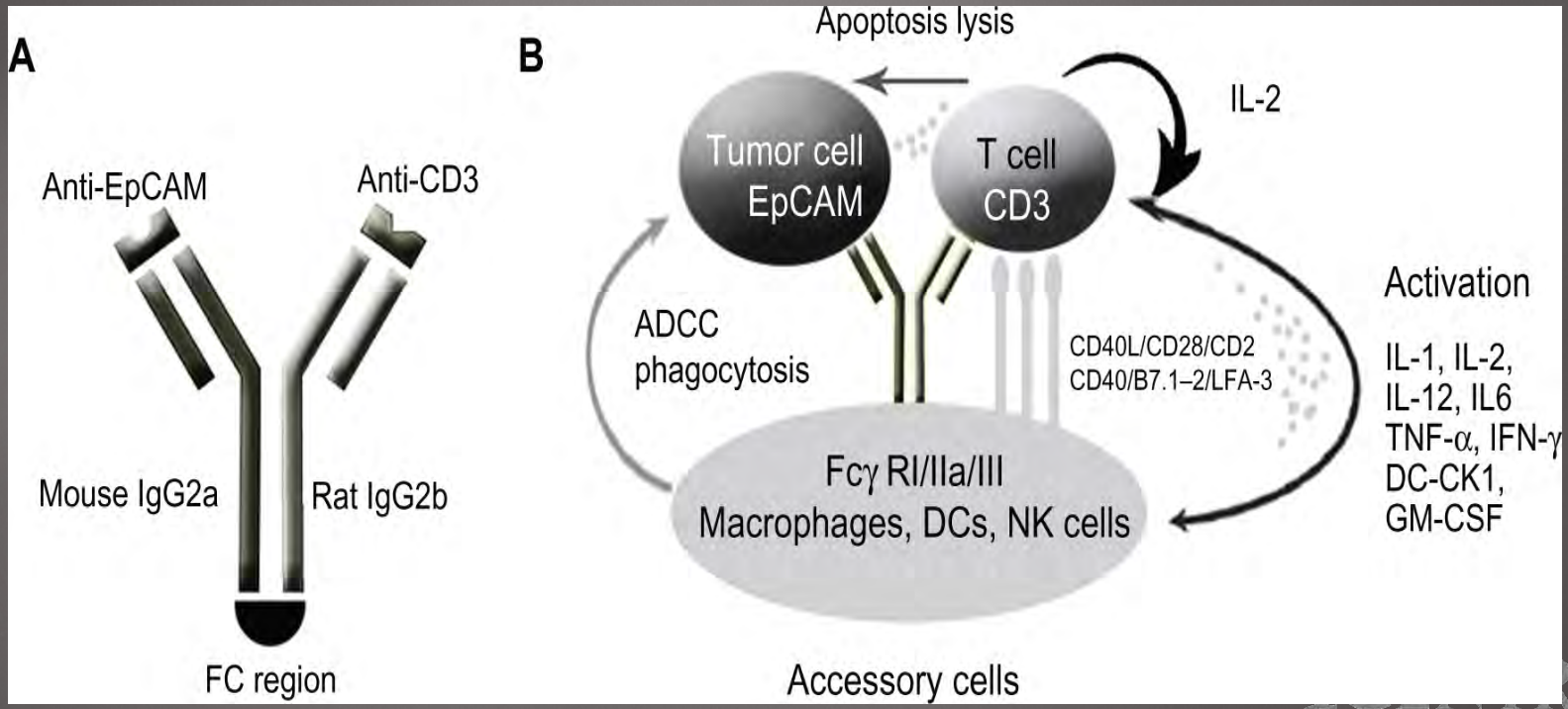
Advances in Ovarian Cancer Ascites Treatment: VEGF trap



Eskander RN, et al. Int J Women Health 2012 (4): 395-404

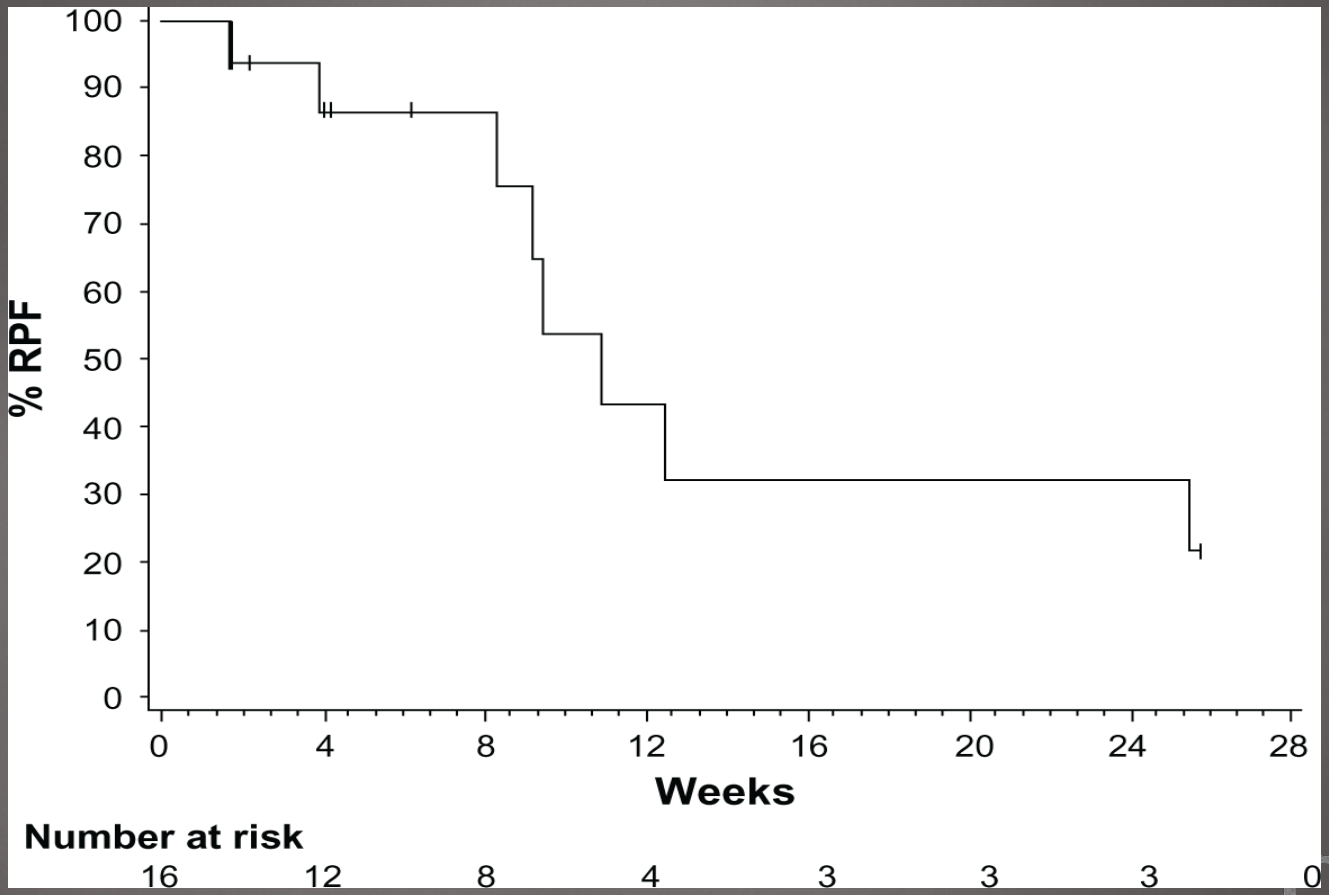
Advances in Ovarian Cancer Ascites Treatment:

Trifunctional antibody catumaxomab



Eskander RN, et al. Int J Women Health 2012 (4): 395-404

Advances in Ovarian Cancer Ascites Treatment:



Eskander RN, et al. Int J Women Health 2012 (4): 395-404

In summary……

- Translational Research Pathways
- Circulating Tumor cells
- Cancer Stem Cells
- Target therapy
- Endocrine Therapy
- Her-2 therapies
- Treatment of Ovarian Cancer Ascites

CENTRO COMPRENSIVO DE CÁNCER
universidad de puerto rico


Questions?