Obesity, Stem Cells and Cancer

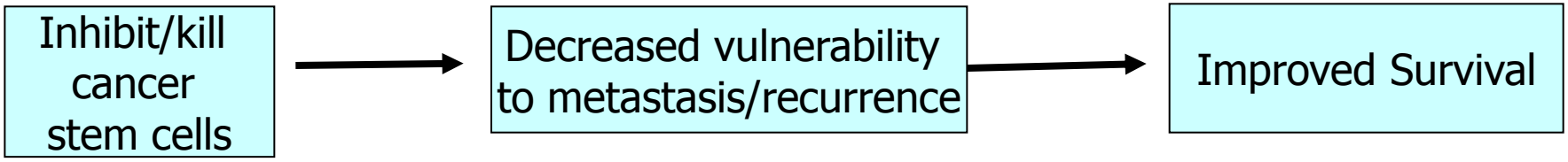
Madhuri Kakarala MD, PhD
Division of Hematology/Oncology
University of Michigan

Outline

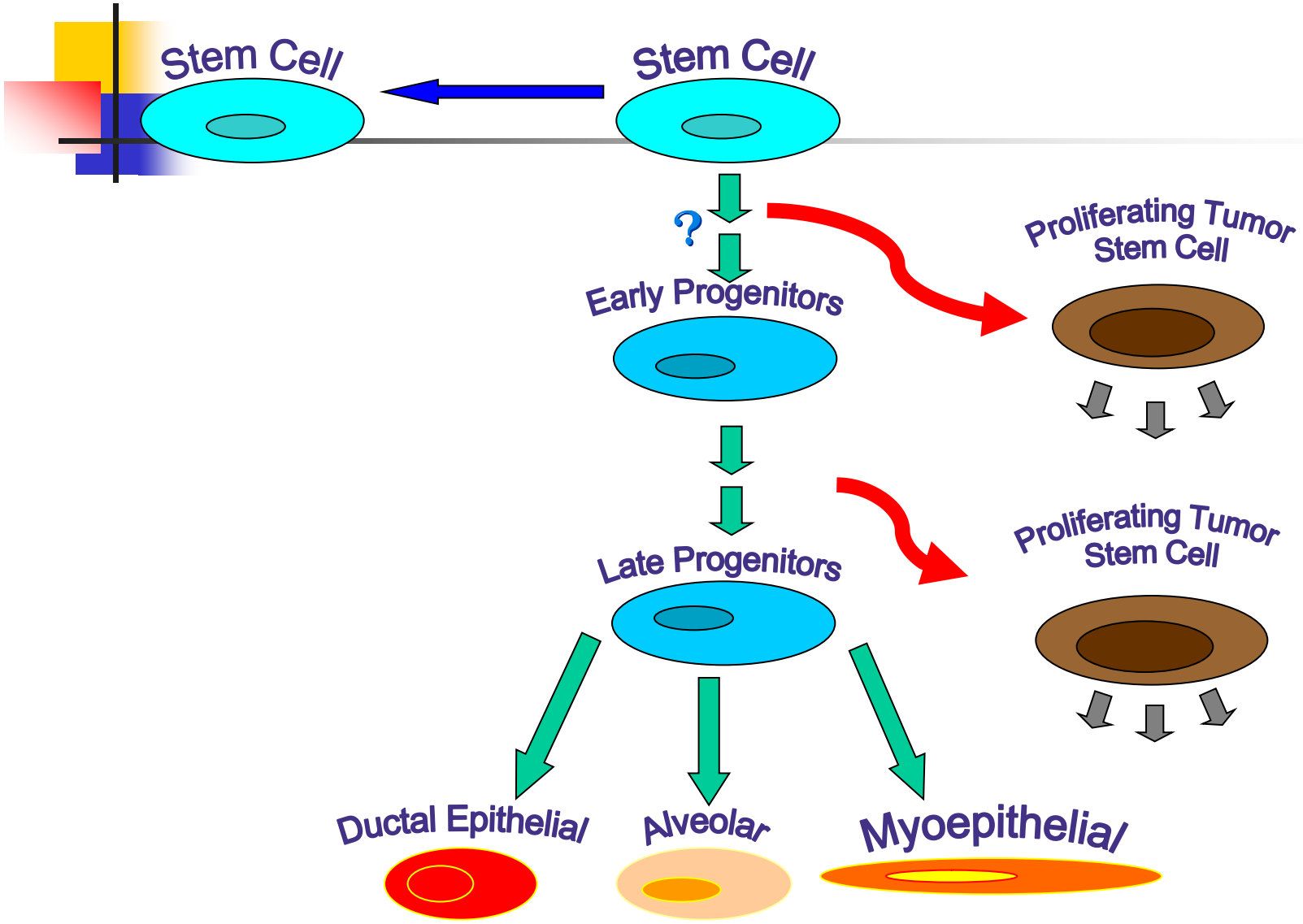
- Discuss cancer stem cell model of carcinogenesis, metastasis, recurrence
- Models for study of stem cell biology; limitations/strengths/needs
- Screening system for potential interventions: dietary components eg. curcumin/piperine or drugs eg. Metformin/IL6 receptor Ab/Akt inhibitors
- Complexities of human clinical trials assessing stem cell endpoints

Epithelial and mesenchymal stem cells in carcinogenesis, metastasis and recurrence

- Cancers Originate From Tissue Stem Or Progenitor Cells
- Cancers Are "Driven" By Epithelial Cells With Stem Cell Properties supported by mesenchymal stem cells in the niche
- Stem cell properties: self renewal, differentiation, epithelial to mesenchymal transition and mesenchymal to epithelial transition
- Stem Cell Hypothesis:

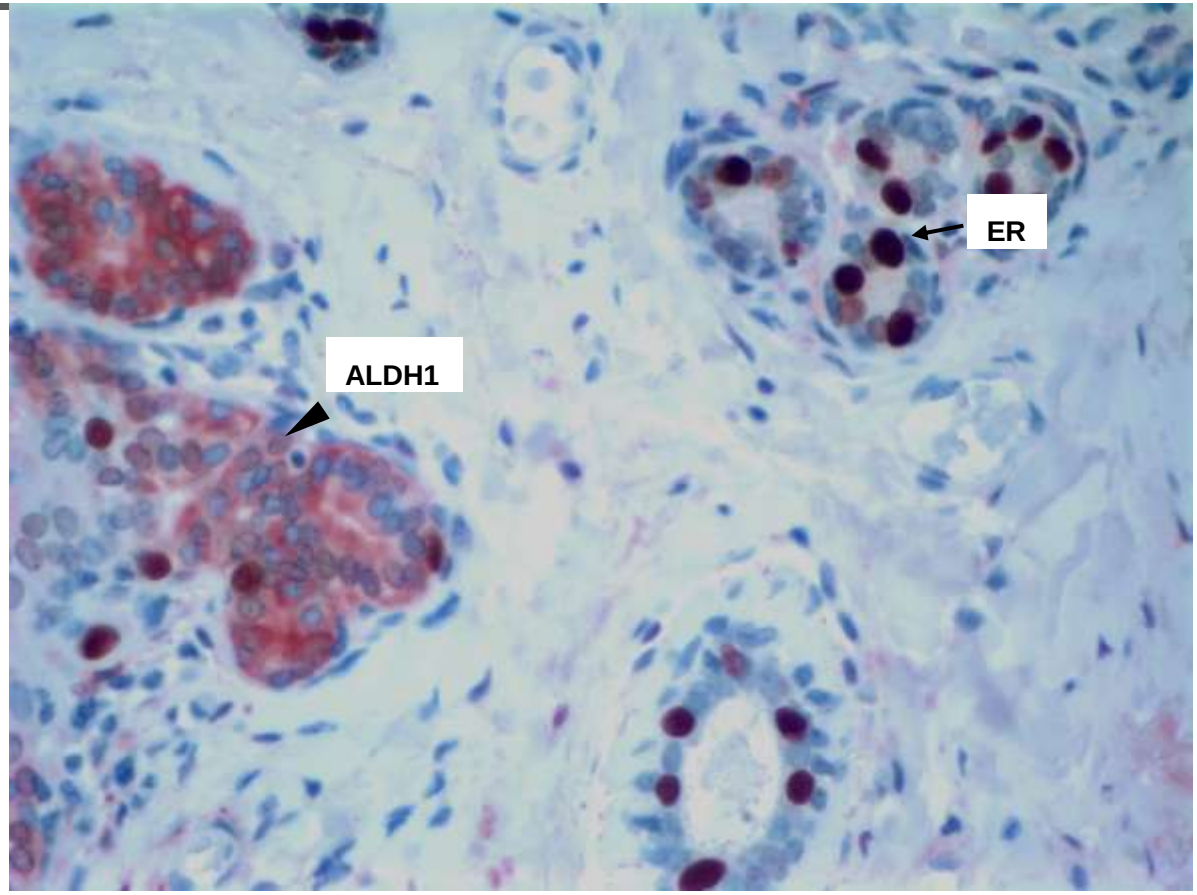


Development of the Mammary Gland and Mammary Tumors



Dontu, 2004

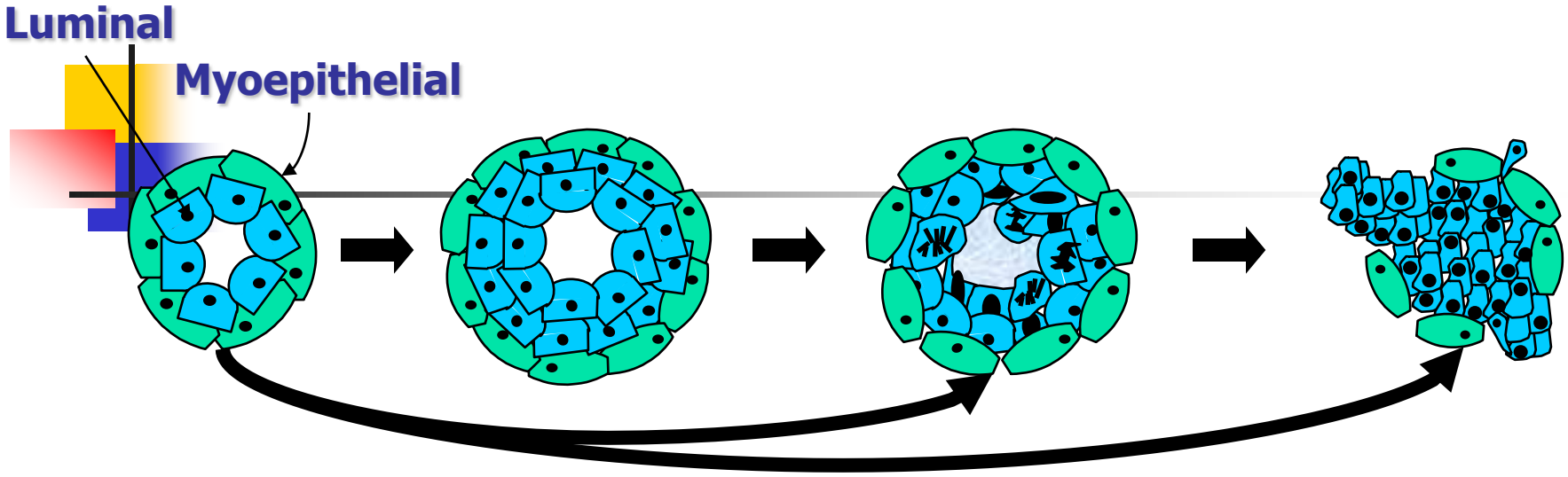
Example of dysregulated clonal expansion of stem cells



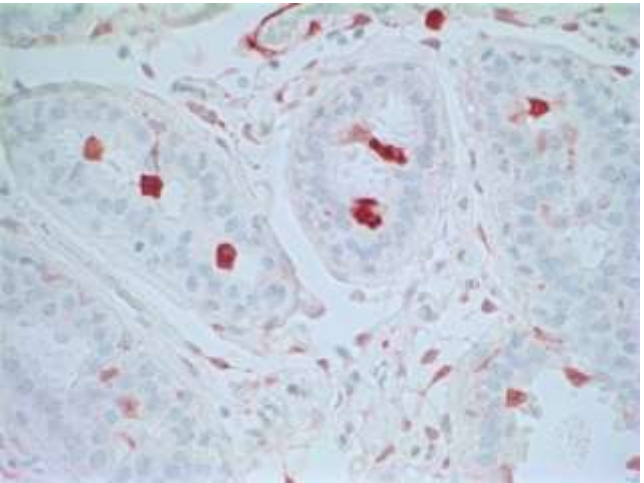
Red: ALDH1; Brown: ER
ALDH1 in breast epithelium from BRCA1-carriers

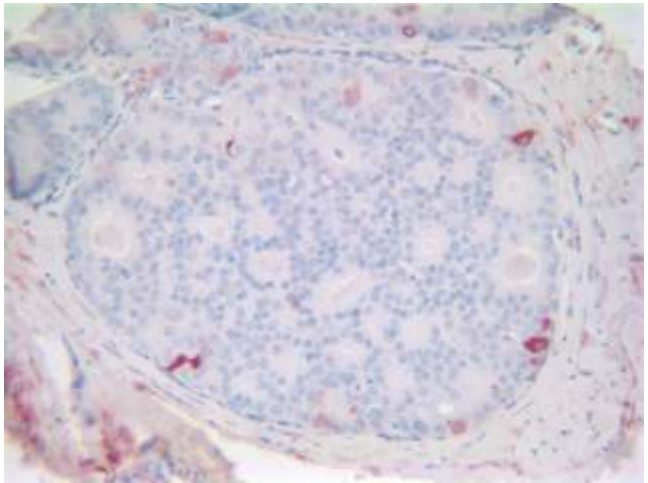
Ginestier, Wicha 2008

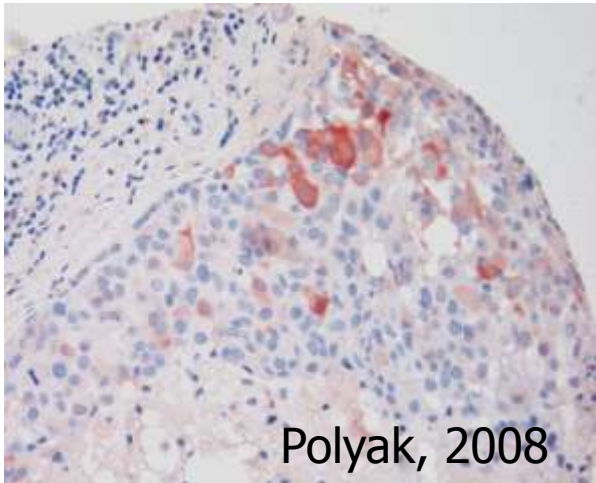
Breast Cancer Development



Normal duct Hyperplasia In situ carcinoma Invasive carcinoma





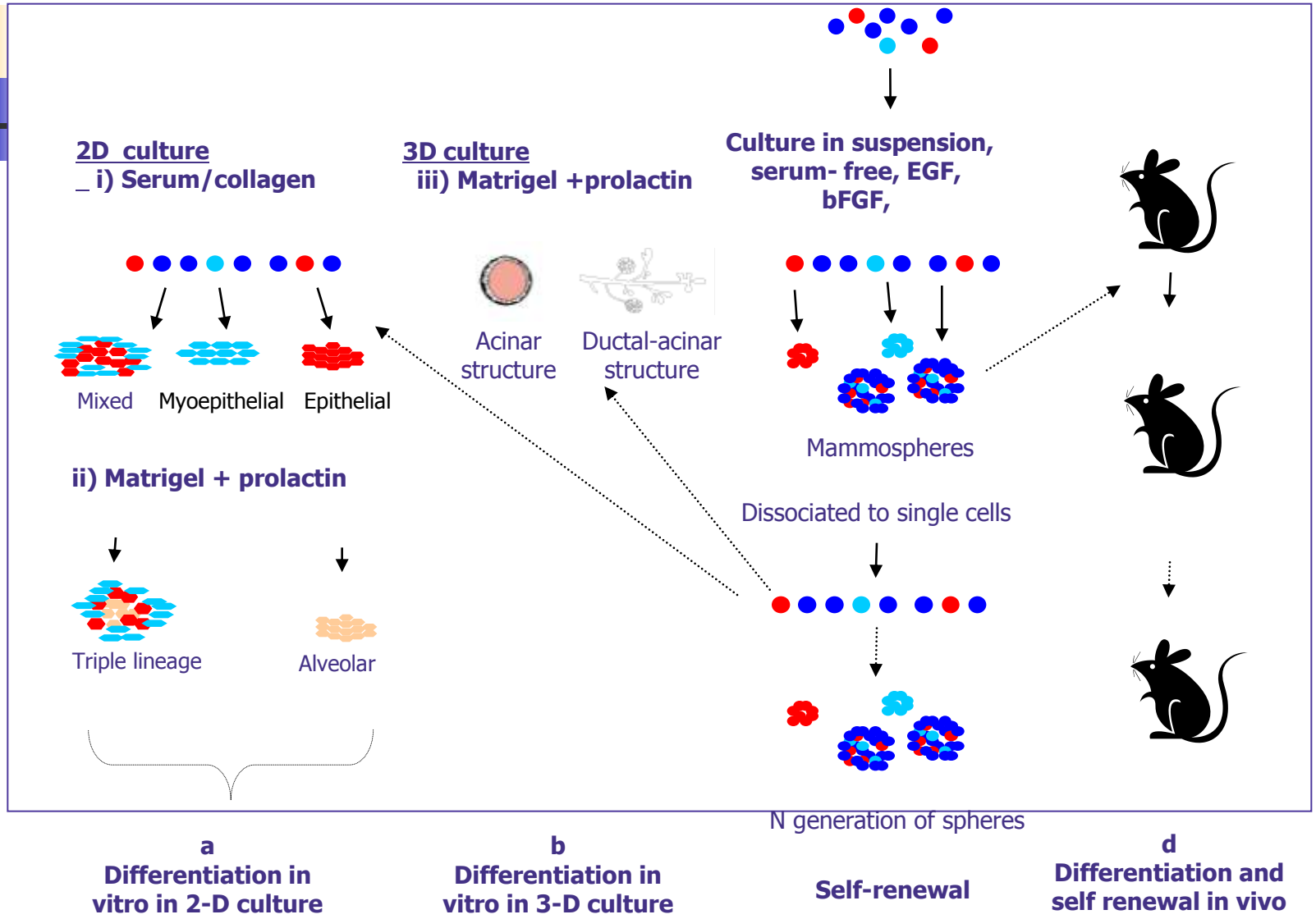


"Cancer Stem Cell" Markers

Tumor Type	CD44	CD24	CD133	ALDH	ESA	B1	Beta-6
Breast	+	-	+/-	+		+	+
Colon	+		+	+	+		
Pancreas	+	+	+	+	+		
Prostate	+			+		+	
Brain			+				
Head/Neck	+			+		+	
Melanoma	+		+			+	

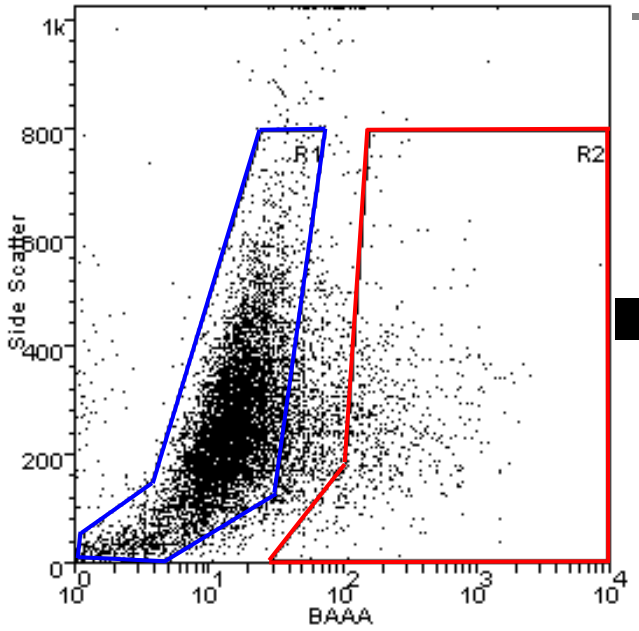
Wicha, 2009

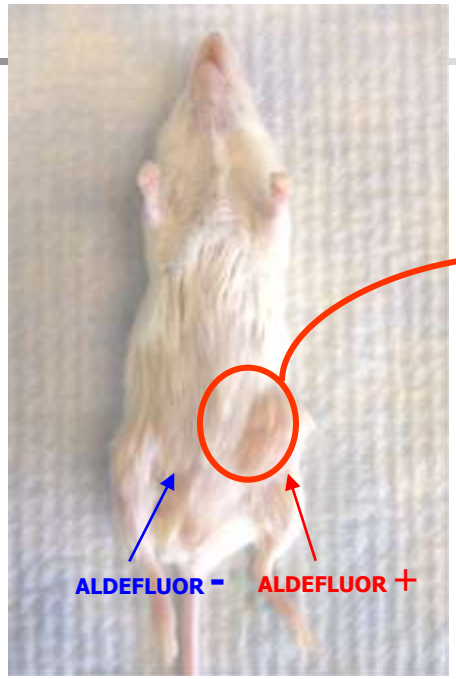
Mammosphere Assay and ALDH breast stem cell marker

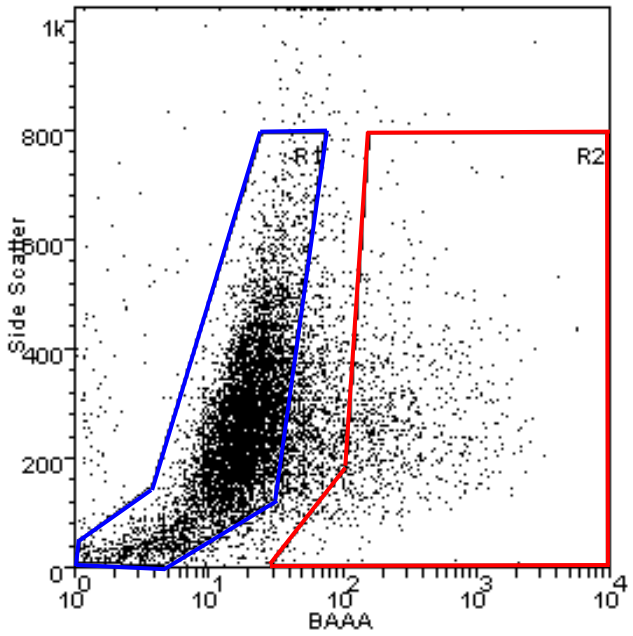


Dontu, Wicha 2003

ALDEFLUOR+ population and tumorigenicity



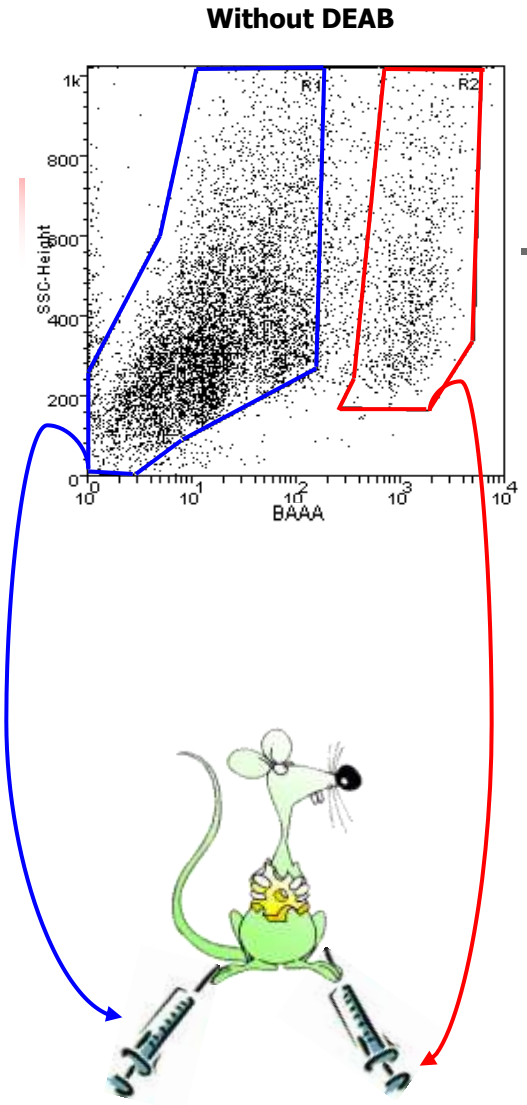


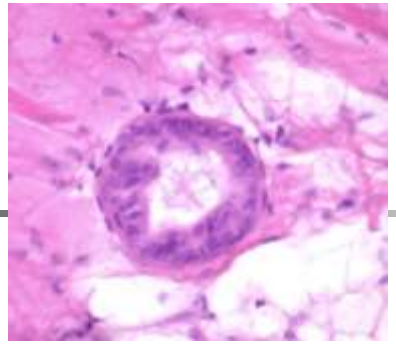


ALDEFLUOR+ population regenerates heterogeneity of the initial tumor

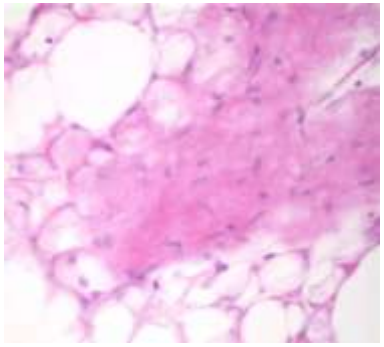
Ginestier, 2007

ALDEFLUOR+ cells have stem cell properties

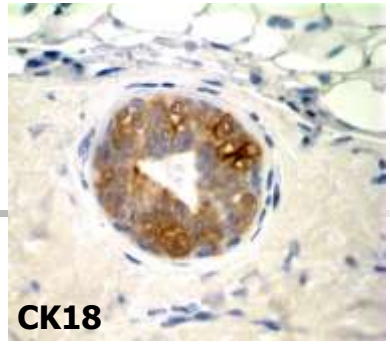


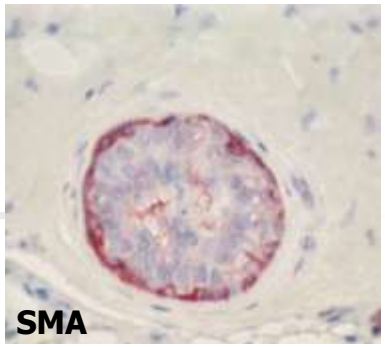


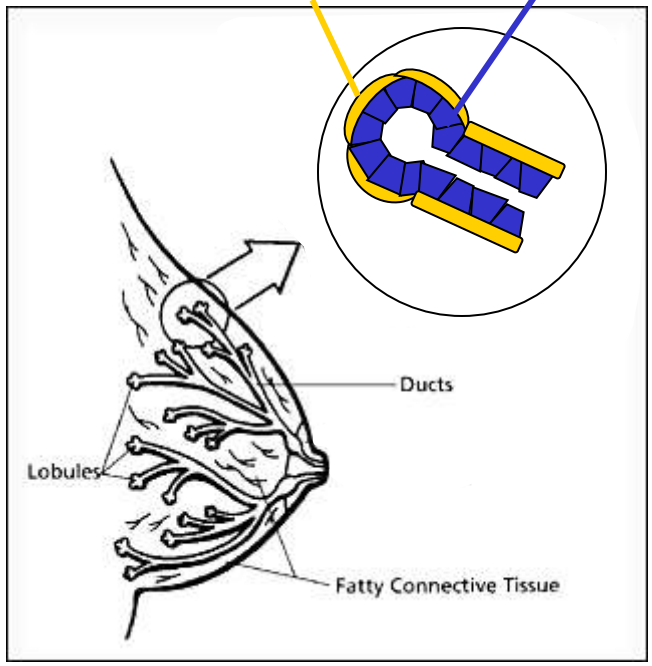
ALDEFLUOR+



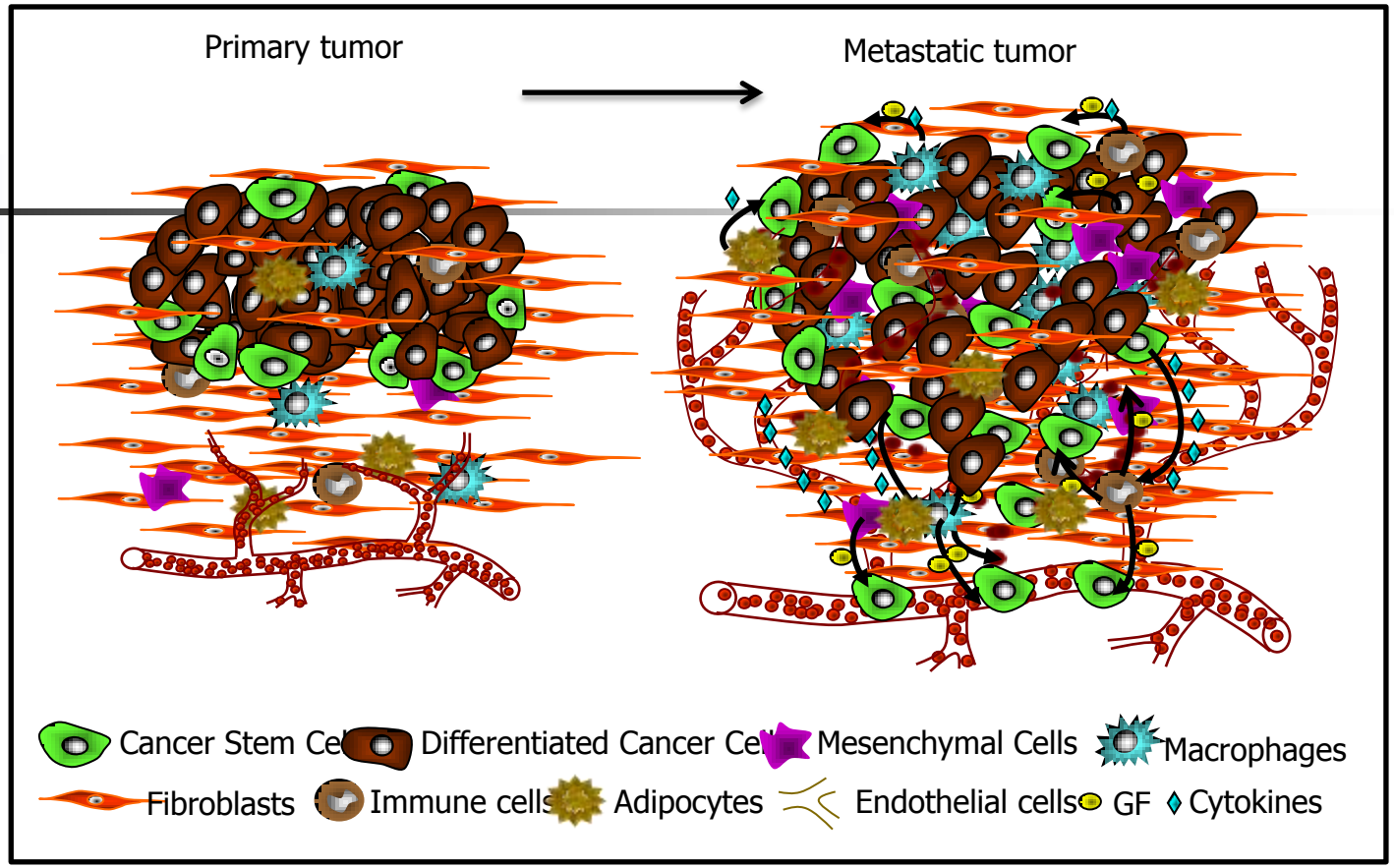
ALDEFLUOR-







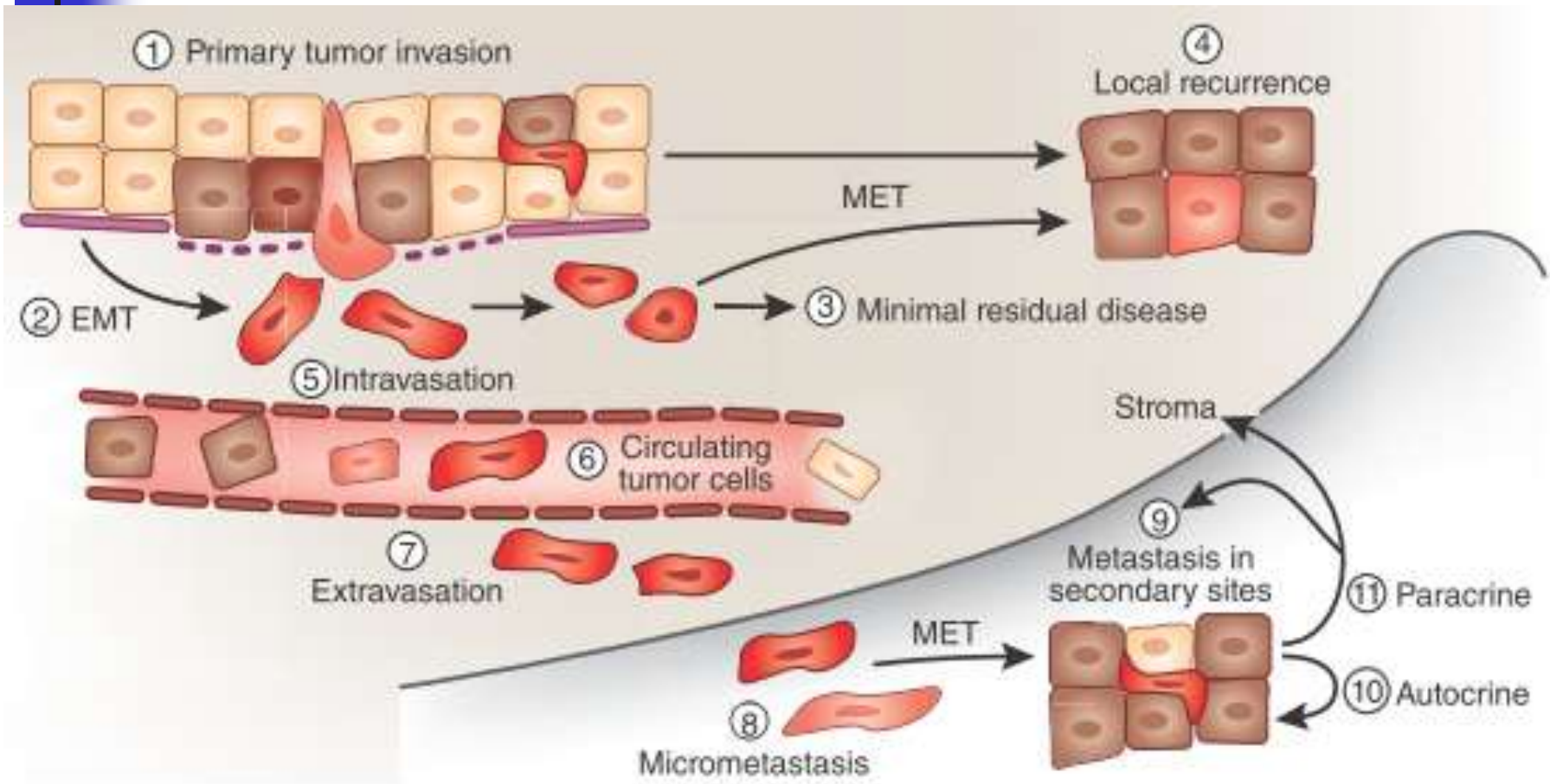
Ginestier, 2007



Supportive role of adipocytes and adipose derived mesenchymal cells in the niche in clonal expansion, proliferation, and dissemination of cancer stem cells

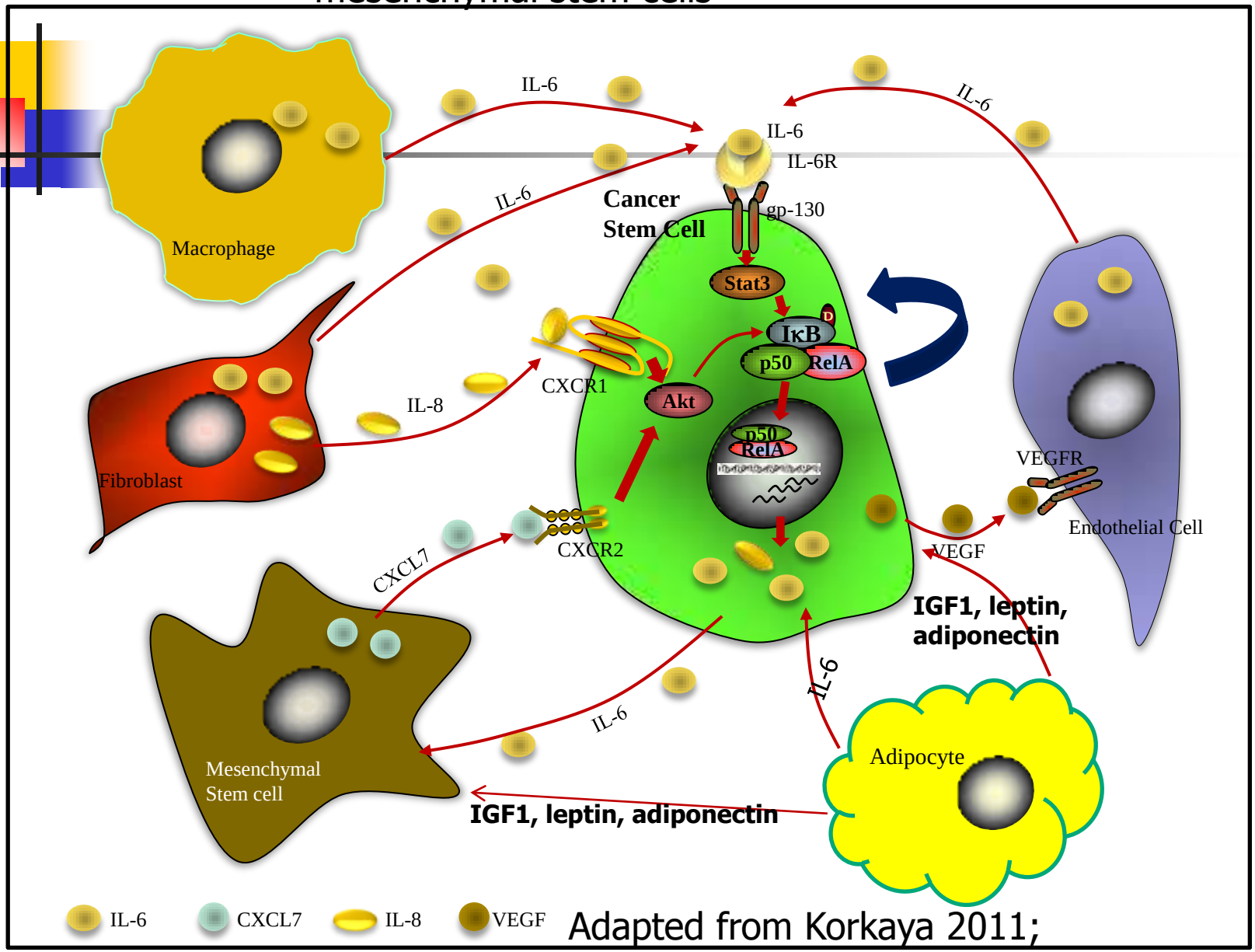
Adapted from image by Korkaya 2011

EMT and MET in tumorigenesis, recurrence and metastasis



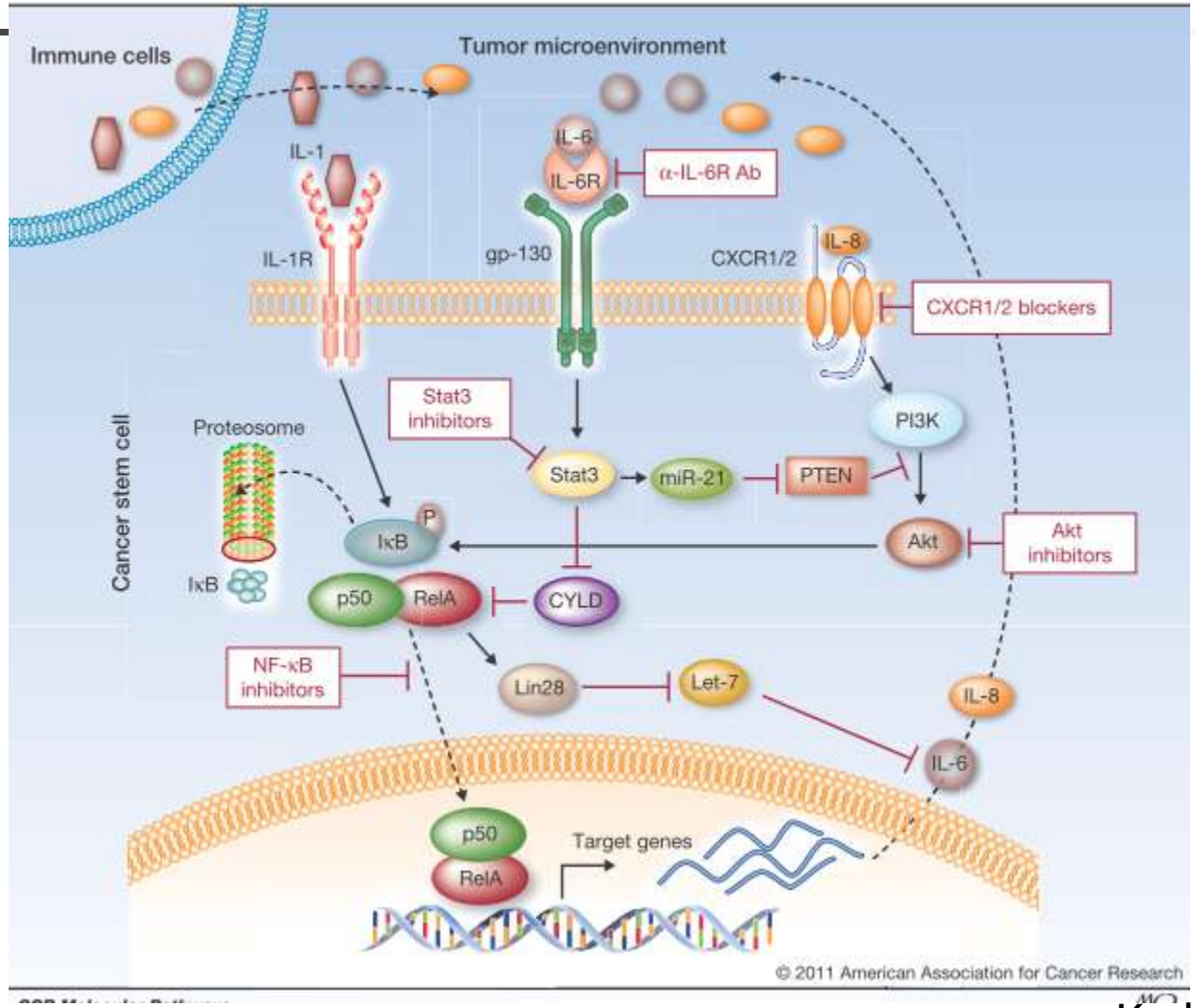
Thompson, Haviv 2011

IGF1, Leptin, adiponectin and IL-6 are prosurvival cytokines for epithelial and mesenchymal stem cells



Adapted from Korkaya 2011; Pochampally 2009, Hursting 2010

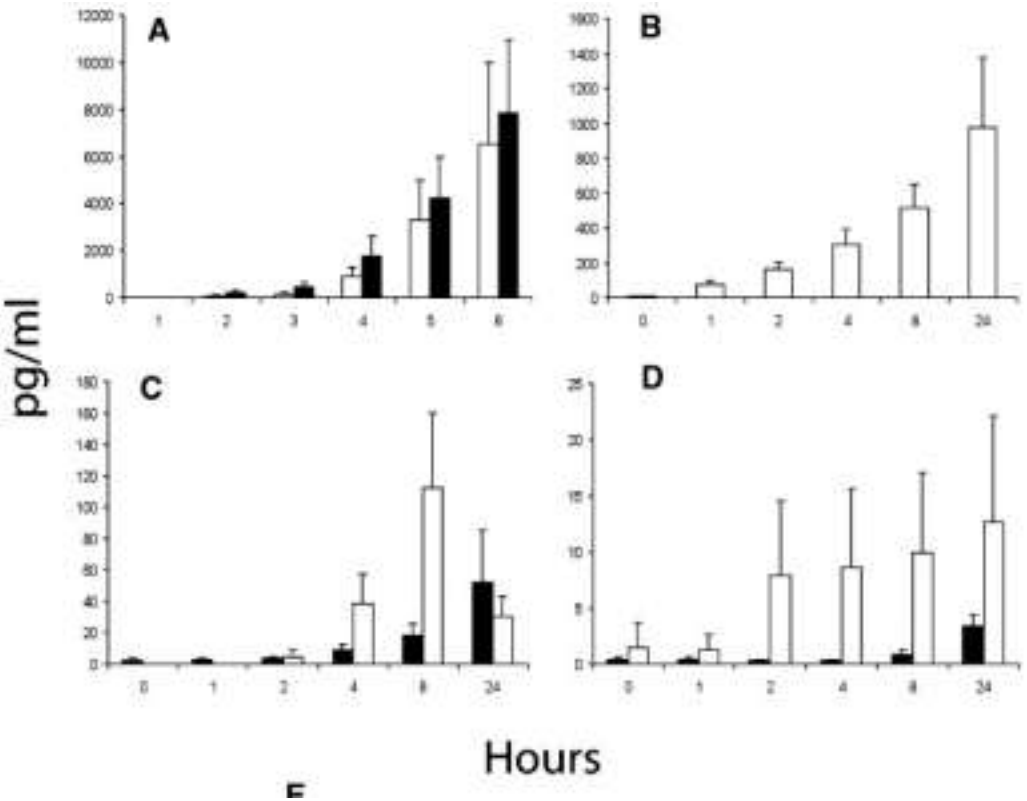
Signaling pathways mediating the effect of the pro-inflammatory state of obesity upon cancer stem cells



Korkaya 2011

Proinflammatory, proangiogenic and hematopoetic cytokines secreted by human adipose derived stem cells

IL6, IL8



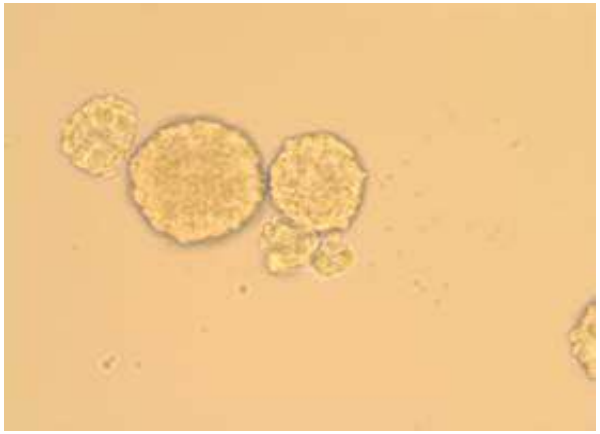
M CSF

GM CSF, TNF

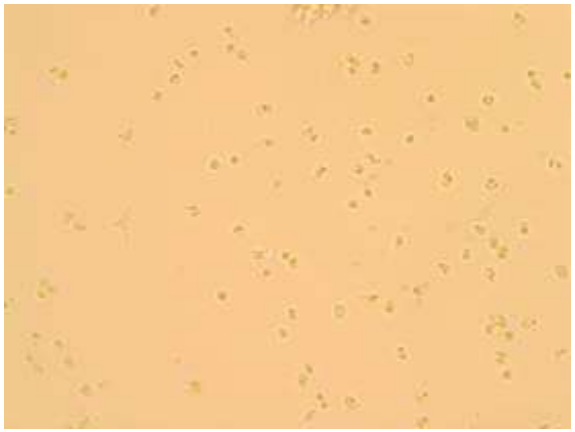
IL7, 11

Kilroy, Gimble 2007

The Human Stem Cell Model and Cancer Biology



DMSO control



10 μM curcumin

- A screening system for cancer treatment/risk reductive intervention efficacy
- Assay for mechanism, microRNA, profiling, protein sequencing, toxicant effects, nutrient/toxicant interactions
- In vivo biomarker of efficacy

Kakarala, 2010

Regulation of stem cell self renewal and clonal expansion

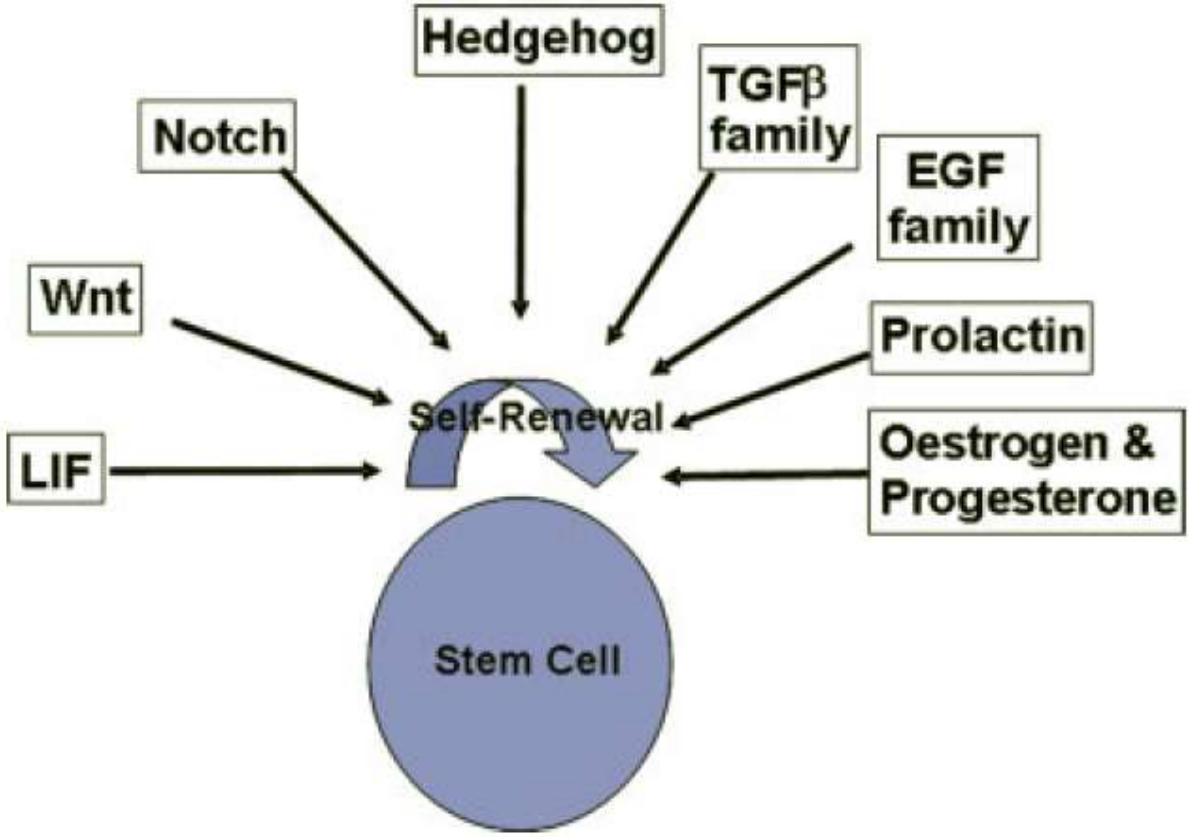


Figure 1. Proposed pathways involved in breast epithelial stem cell self-renewal

Curcumin's Anticarcinogenesis Mechanisms

Constitutive activation of transcription factors

-AP -1, NFκB

-Tumor Suppressor Genes

Modulation of Signaling

- Wnt/β catenin

-Notch

-Hedgehog

Overexpression of

-Oncogenes

-Her 2

-Growth factors eg. EGF, PDGF

-Survival factors eg. Survivin, bcl 2, bcl-xl

-Cyclin D1

Overexpression of

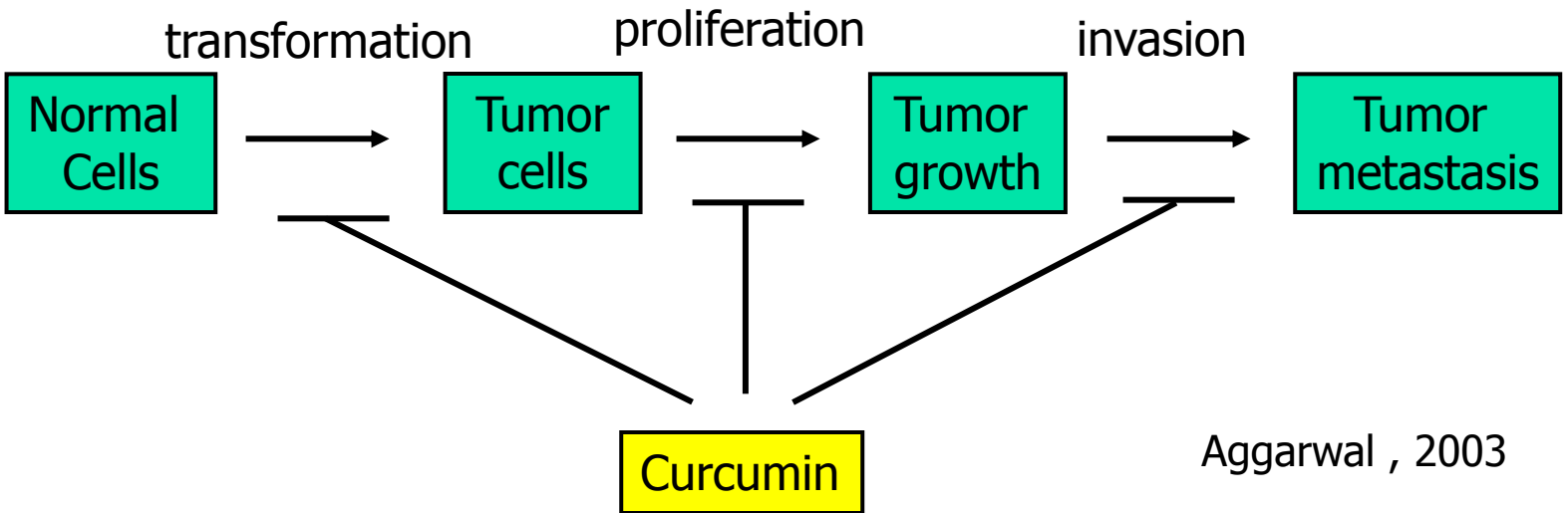
-MMPs

-Cox 2

-adhesion molecules

-chemokines

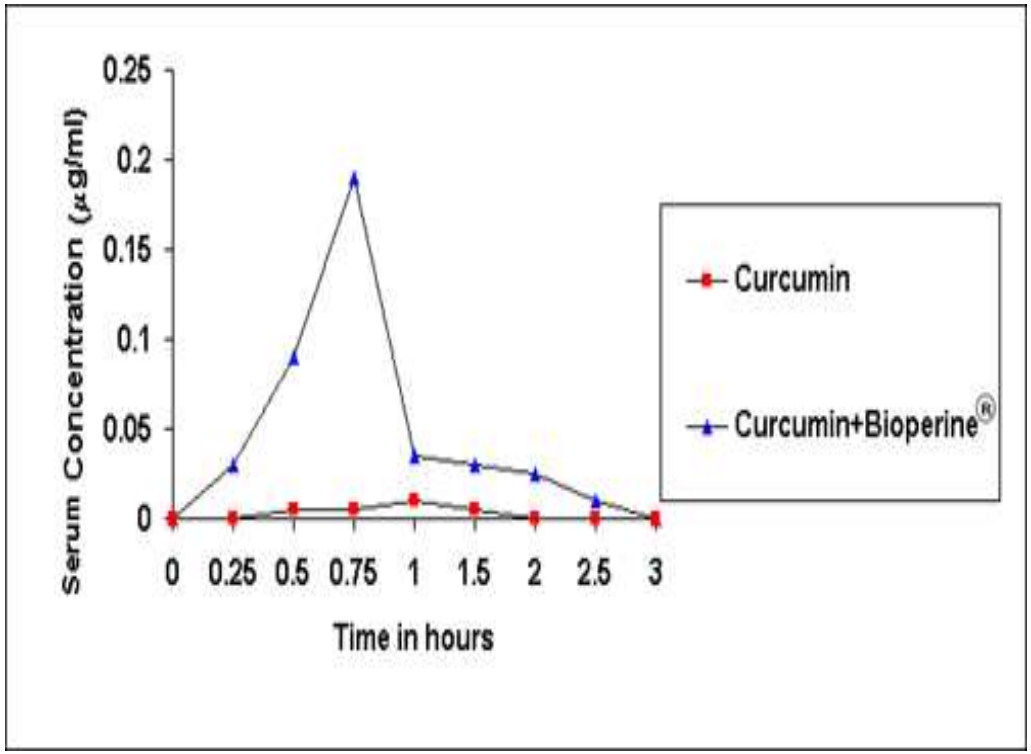
-TNF



Aggarwal , 2003

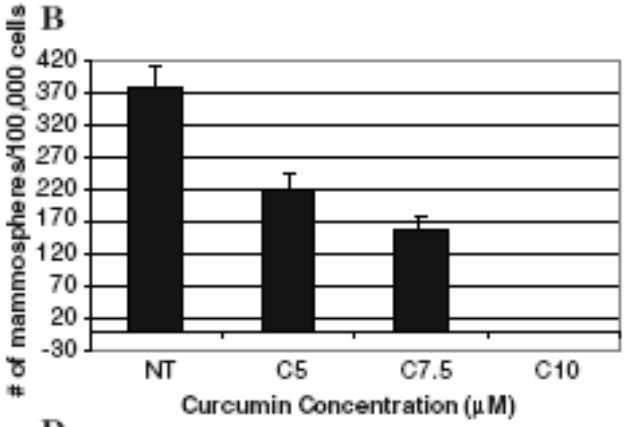
Piperine

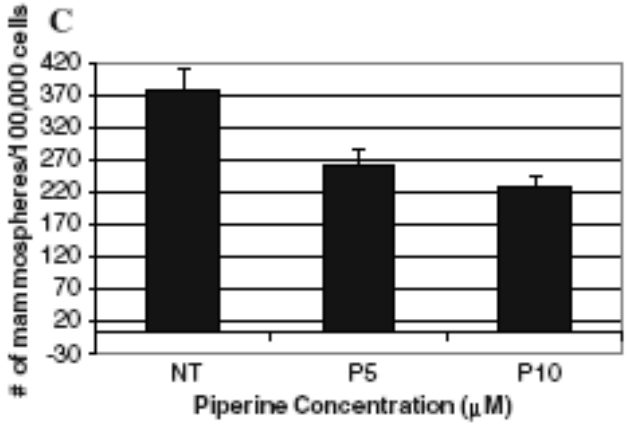
- Isolate of piper nigrum and piper longum or black pepper/ hot peppers
- Inhibits
  - P-glycoprotein drug efflux
  - First pass enzymes, CYP 3A4
  - Intestinal conjugation
  - NFkB

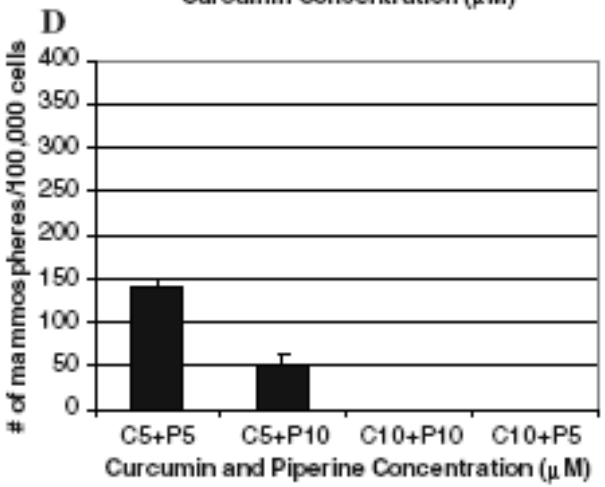


Shoba 1998

Targeting Breast Stem Cells with the Cancer Preventive Compounds Curcumin and Piperine (1 spheres)

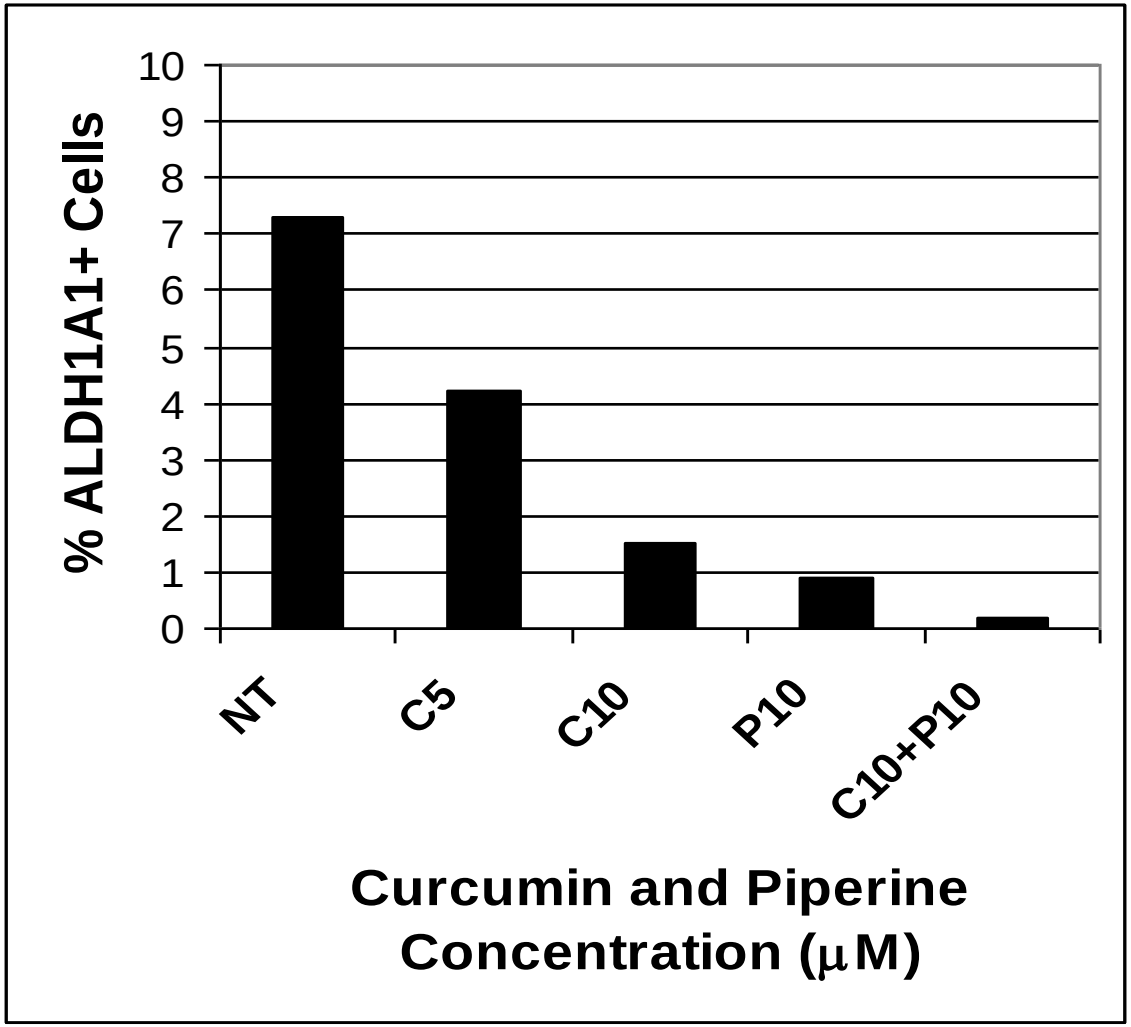




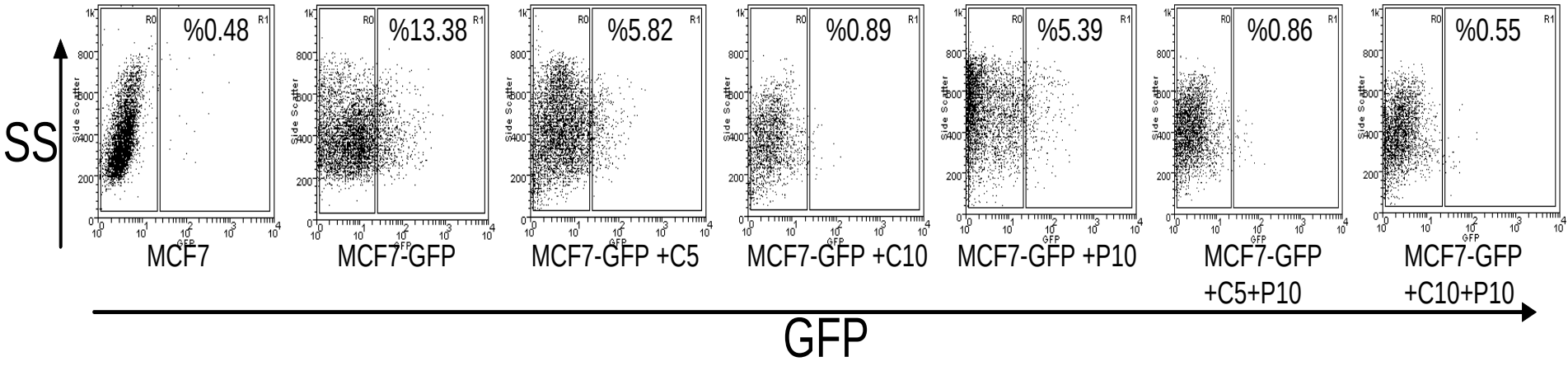


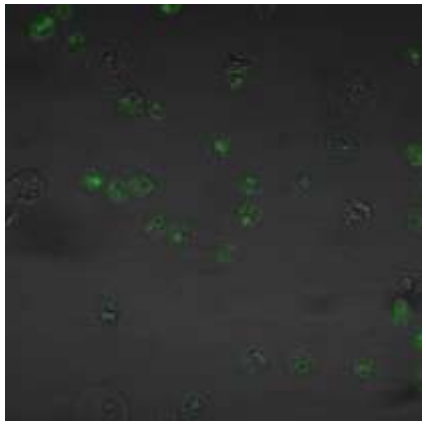
Kakarala et al, Breast Cancer Res Treat; 2010, in press.

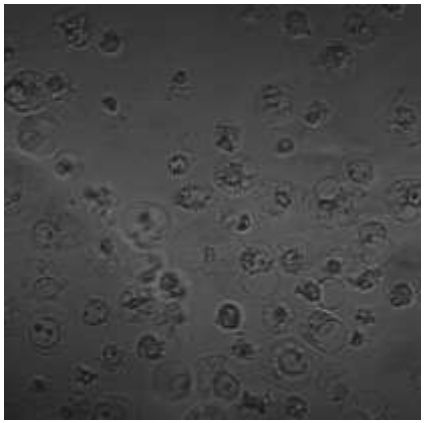
Effect of Curcumin and Piperine on ALDH+ cells (%)



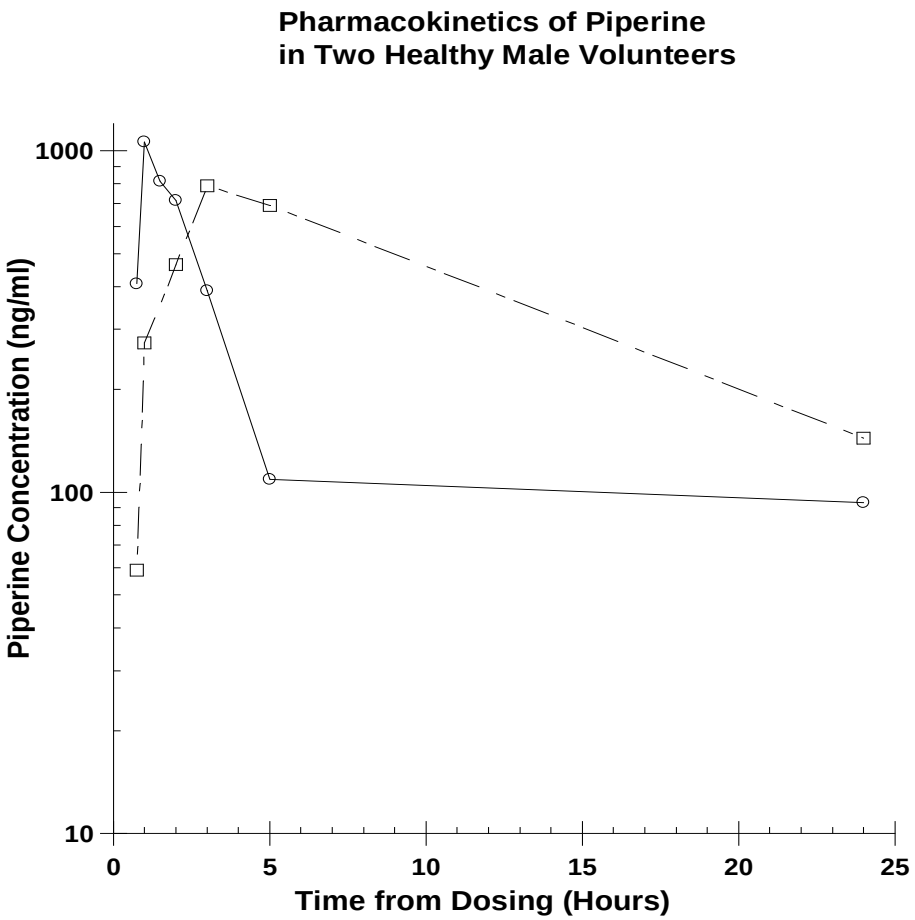
Curcumin/Piperine's Effect on Wnt Signaling







Piperine in human plasma after 50mg oral dose



Kakarala et al. J Ag Food Chem 2010

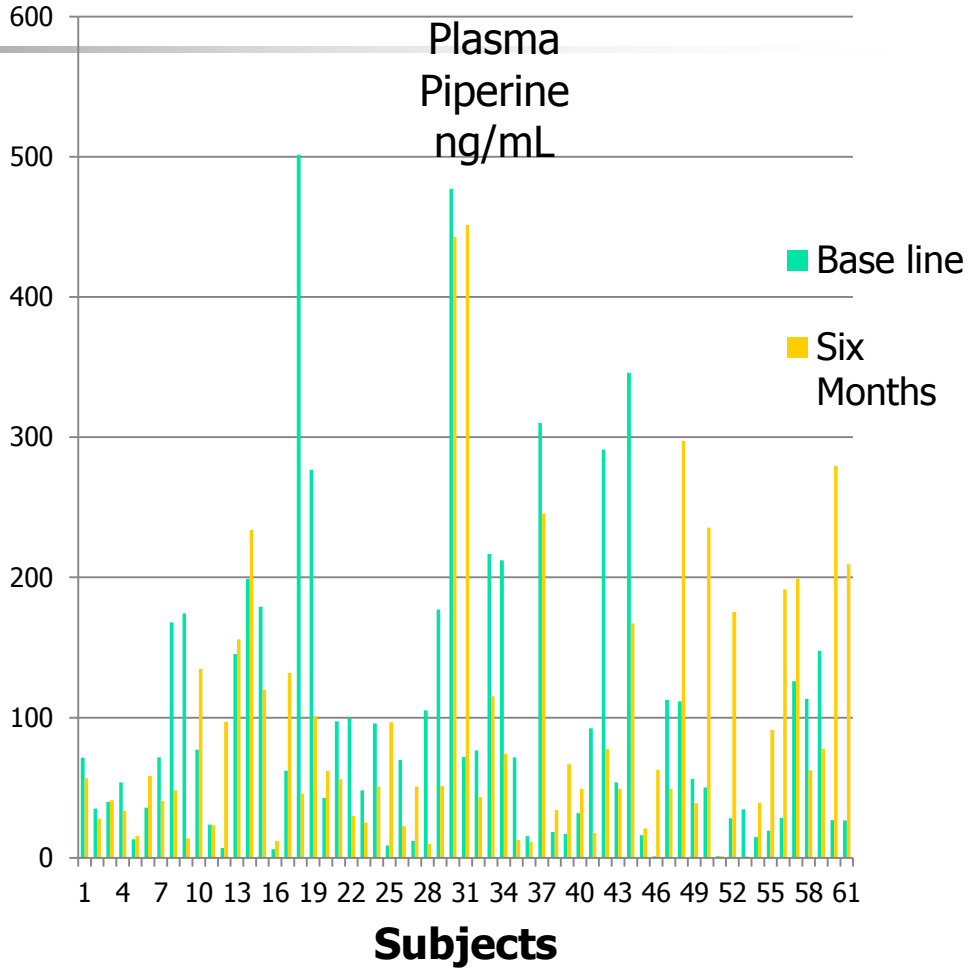
Is dietary piperine bioavailable ?

- 7 day food records, baseline and at 24 wks Mediterranean diet intervention
- Assess sources of piperine, peppers, black pepper, prepared foods, eggs
- Plasma samples to assay for piperine
  - at baseline and
  - at 24 wks

Kakarala, Cheng, Drs Djuric/Brenner

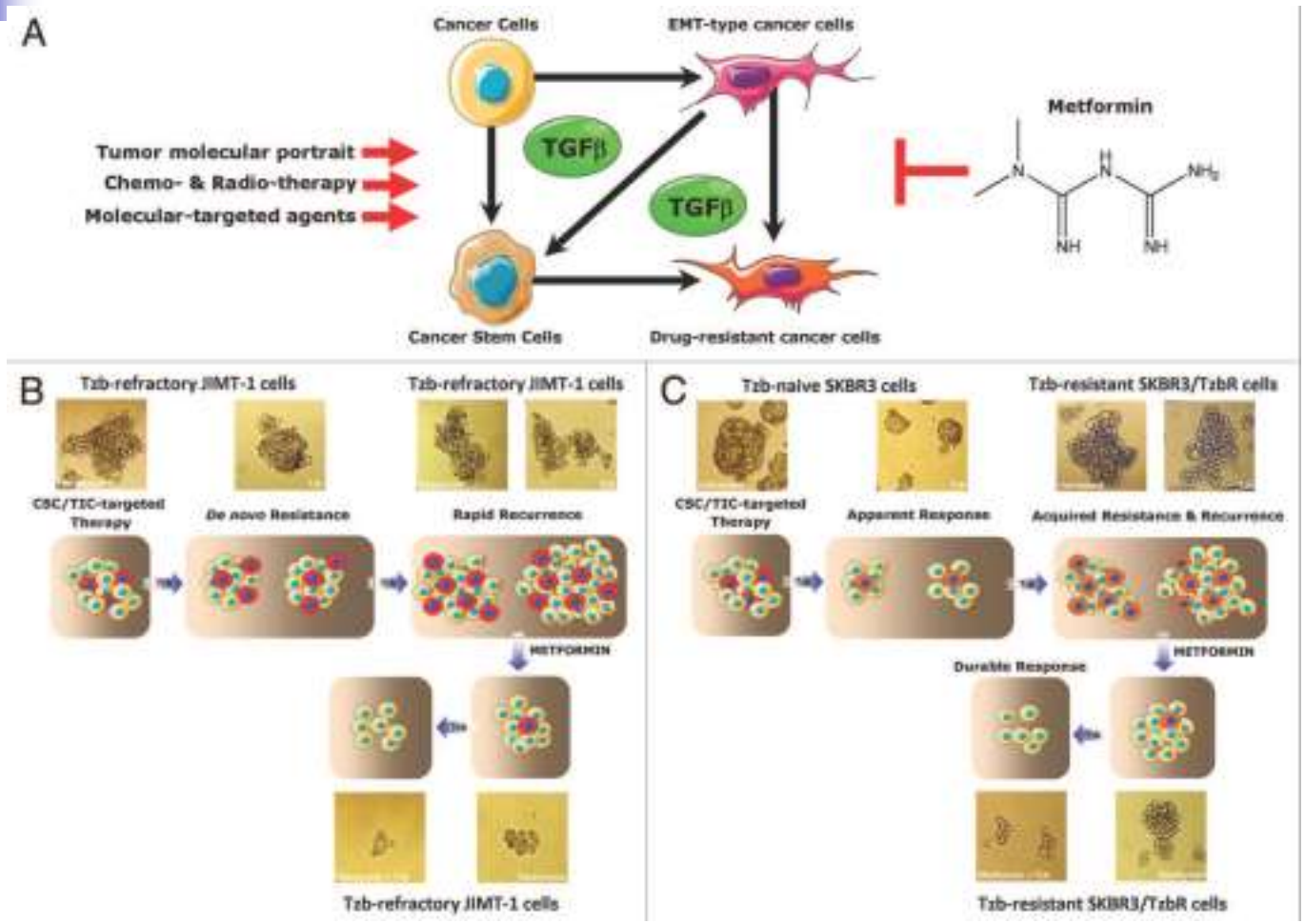
Piperine in human plasma!

- Mediterranean Diet
- 6 mo.s intervention
- 70 subjects, baseline only 9
- Blood drawn after 12 hr. fast
- Piperine detectable in all but 3 blood samples!!
- Range 6-500 ng/mL
- Mean 100.22 ng/mL, baseline 94.04 ng/mL, 6 mo.s
- No intervention effect



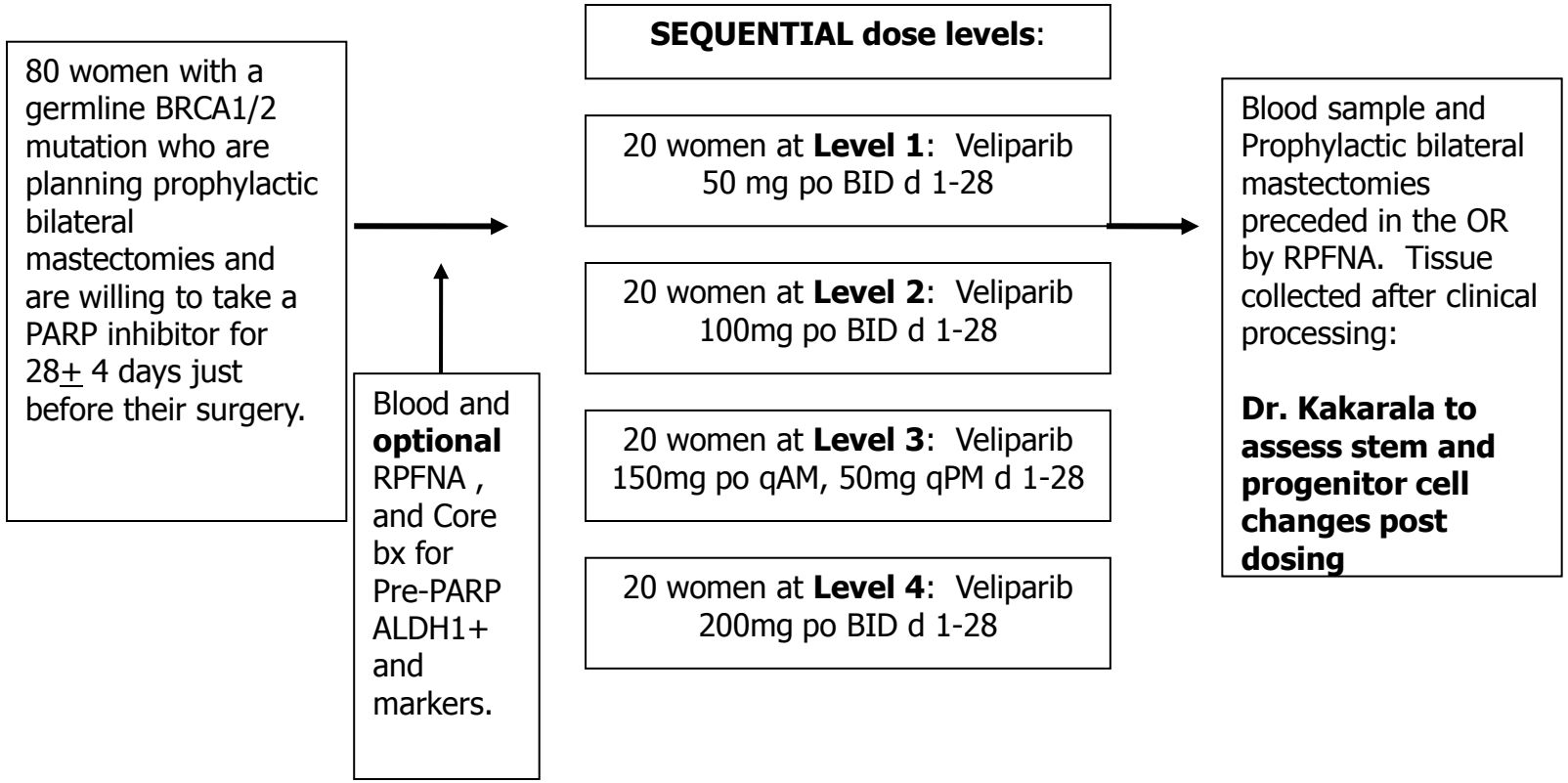
Kakarala, Cheng, Dubey, Djuric, Brenner

Metformin, TGF β and EMT Induction of tumor suppressor Let 7 and suppression of miRNA 181a



Cufi, Menendez 2010, 2011

Assessing stem cell changes as biomarkers in human clinical trials eg. PARP inhibition in women with BRCA1/2 mutations



PI: J. Garber, DFCI, Susan G. Komen Foundation

M. Kakarala UM Site PI and Collaborator

Clinical Trial Design to Assess Cancer Stem Cell Endpoints

- Conventional imaging or molecular biomarkers such as Ki67 do not work
- Need large volumes of fresh/frozen tissue for dynamic endpoints
- Profiling potentially powerful tool
- Epigenetics key to assessing environmental/dietary exposure effects
- New tools in development for in situ imaging of individual cells for multiple markers

Funding

Past

- Innovative concepts in stem cell research CC - $50,000
- Trehan Foundation - $75,000
- NIH KL2 – 75% salary 9/07- 1/10
- VA 5/8 appt
- John Thomas Foundation 12/09
- Donations from Coady family

Present

- NIH K07 (9/10) 75% salary x 5 yrs. + 30K/yr research funds
- Komen Foundation Promise grant 20% salary x 5 yrs. + 75K/yr research funds (9/10)
- VA CDA 100 % salary + 65K/yr research funds 9/10 awarded but declined
- EDRN Competitive Renewal 20% salary x 5 yrs. + 50K/yr. research funds (9/10)
- Komen Career Catalyst Award

Acknowledgements

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- Drs. Kathy Cooney, John Carethers, Eric Fearon, Robb Todd, Scott Gitlin, Lisa Newman, Jennifer Griggs, Daniel Hayes, Celina Kleer

- Drs. Sharon Hoerr, Arshad Majid, Judy Garber, Kornelia Polyak, Jenny Chang, Krishna Misra, Rajendra Mehta, Kishore Chaudhry, Sunita Saxena