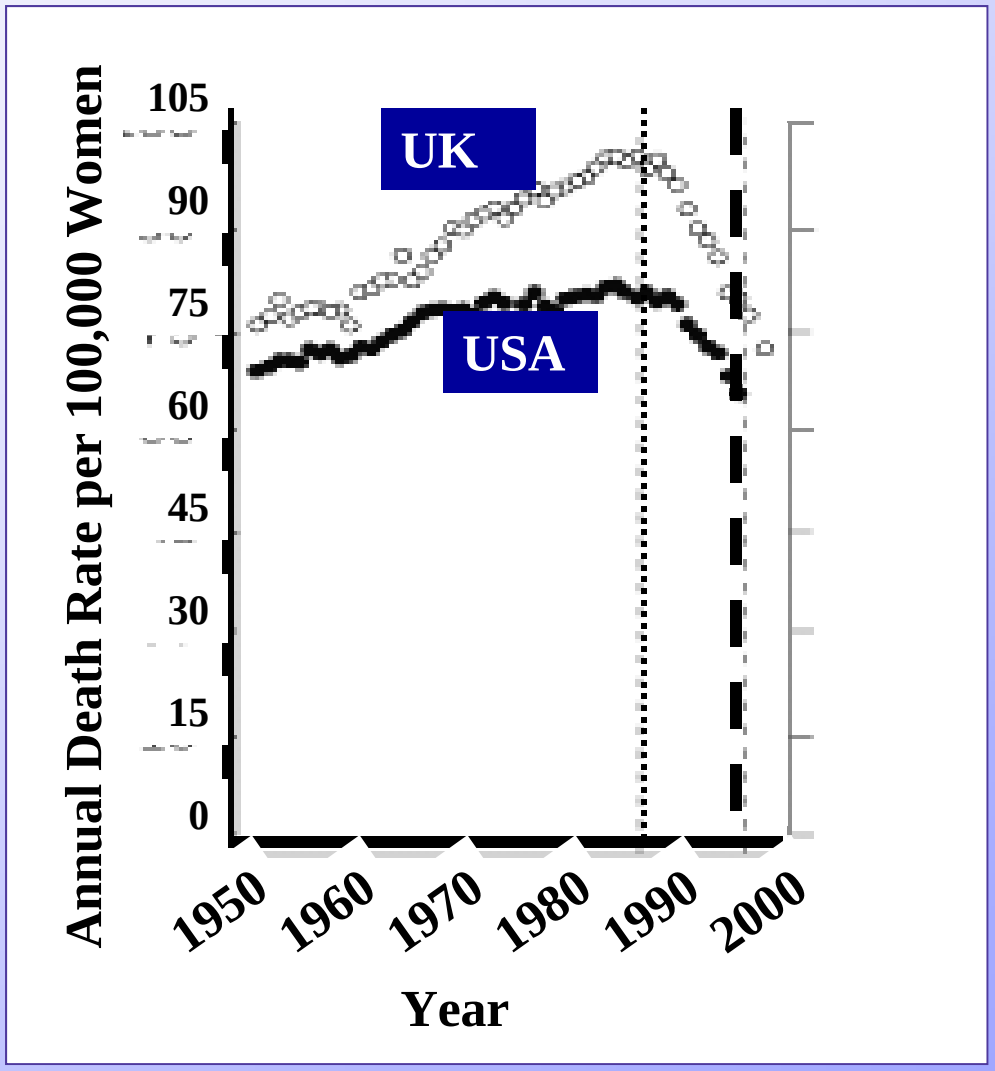
Breast Cancer Stem cells: **NCAB 2/07/06**

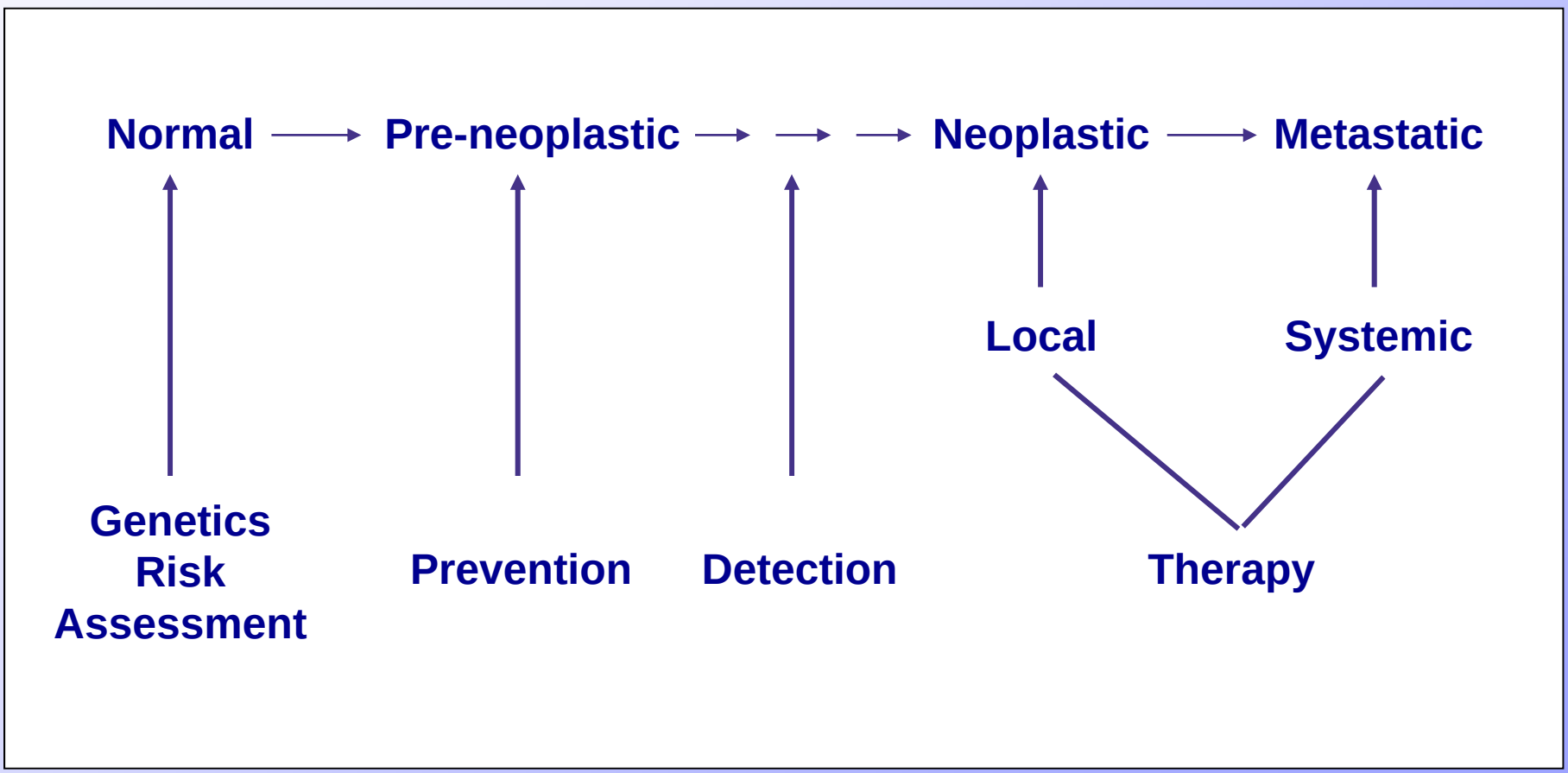
Implications for Prevention and Therapy

Recent decrease in UK and USA breast cancer mortality at ages 5069 years



Peto et al. Lancet 355:1822, 2000

Breast Cancer Development



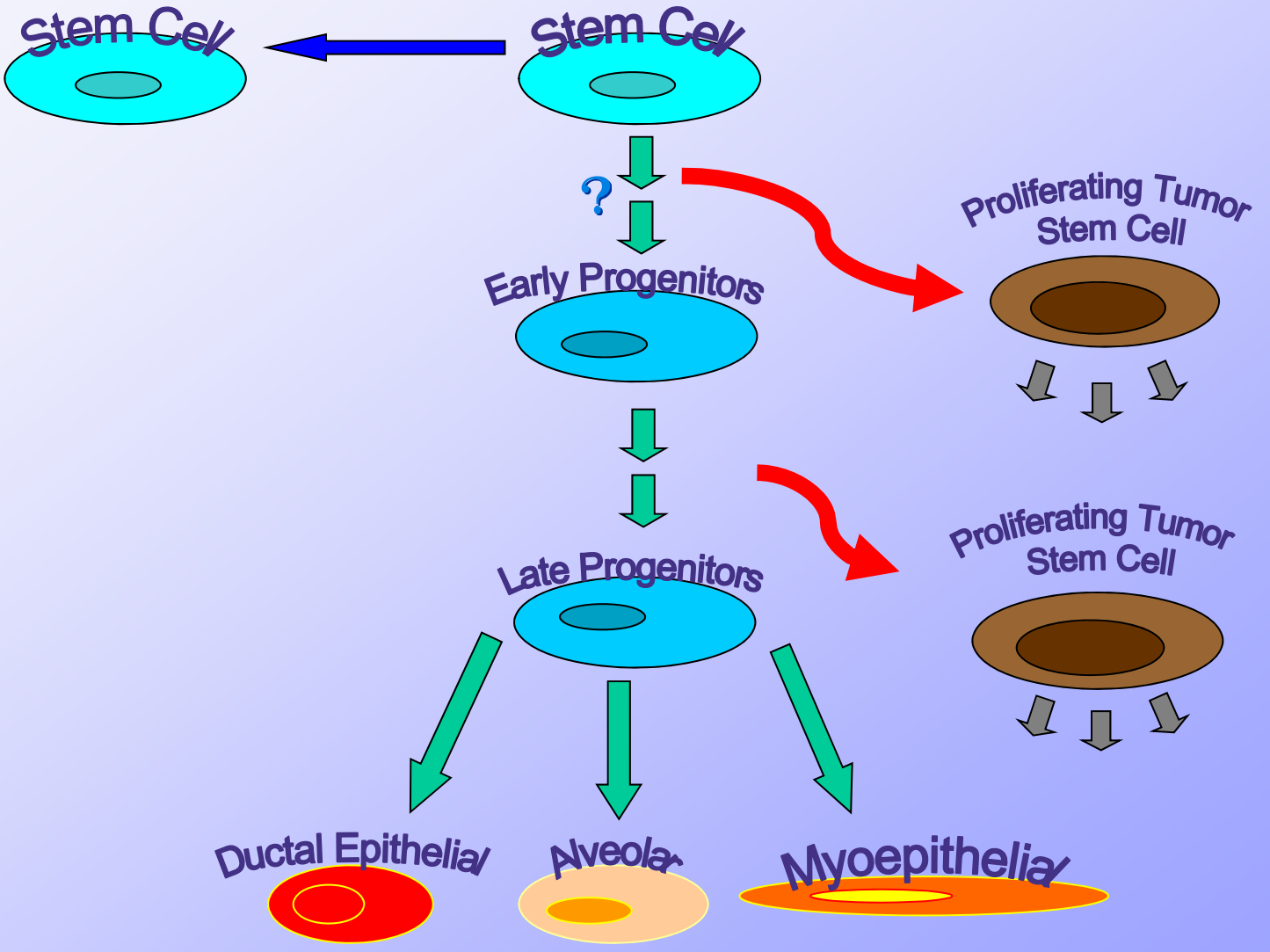
CANCER STEM CELL HYPOTHESIS

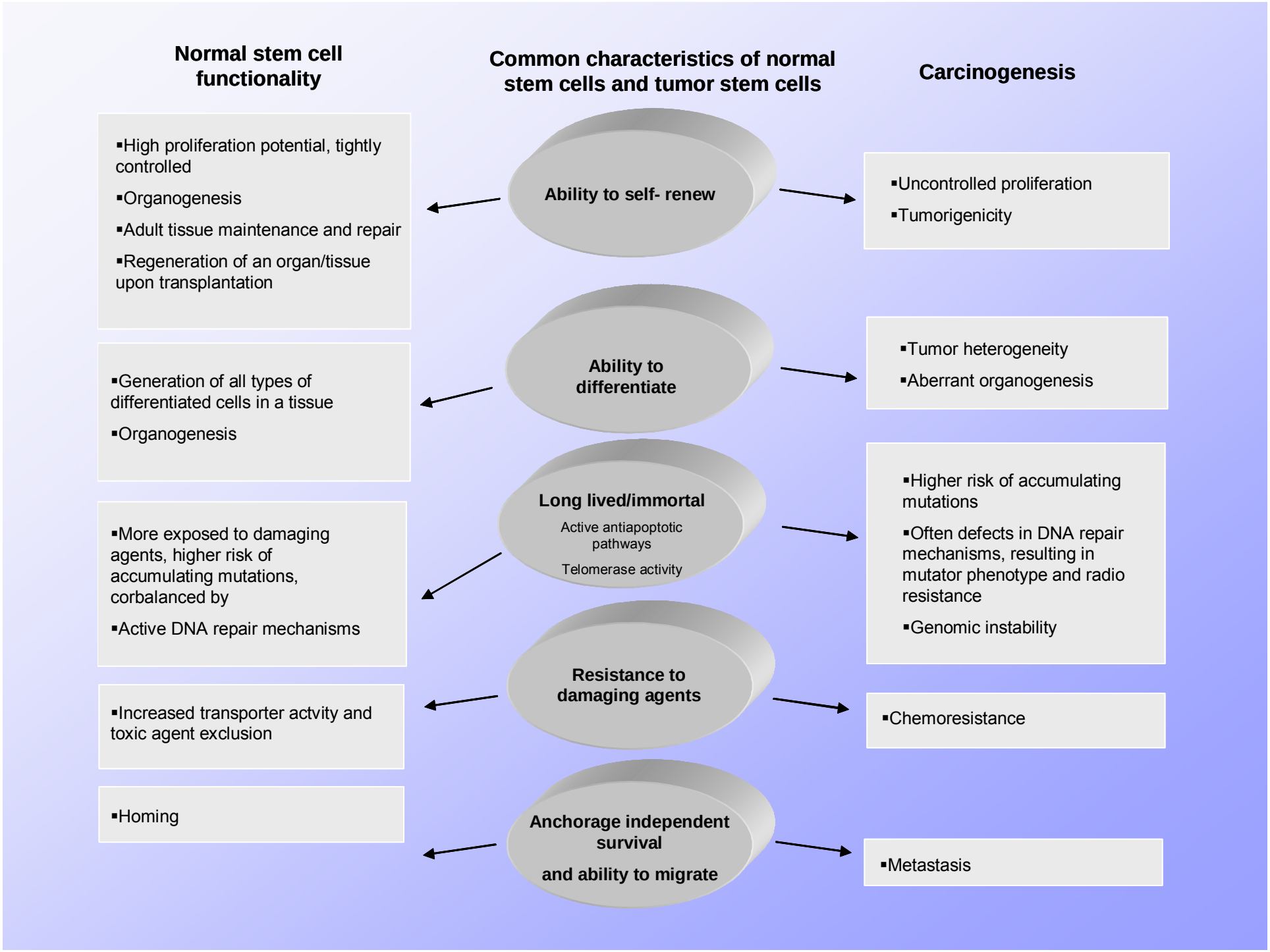
- Cancers Arise From Tissue Stem Or Progenitor Cells
- Cancers Are “Driven” By Cells With Stem Cell Properties

Characteristics of Stem Cells

- Self Renewal
- Multi-Lineage Differentiation

Development of the Mammary Gland and Mammary Tumors

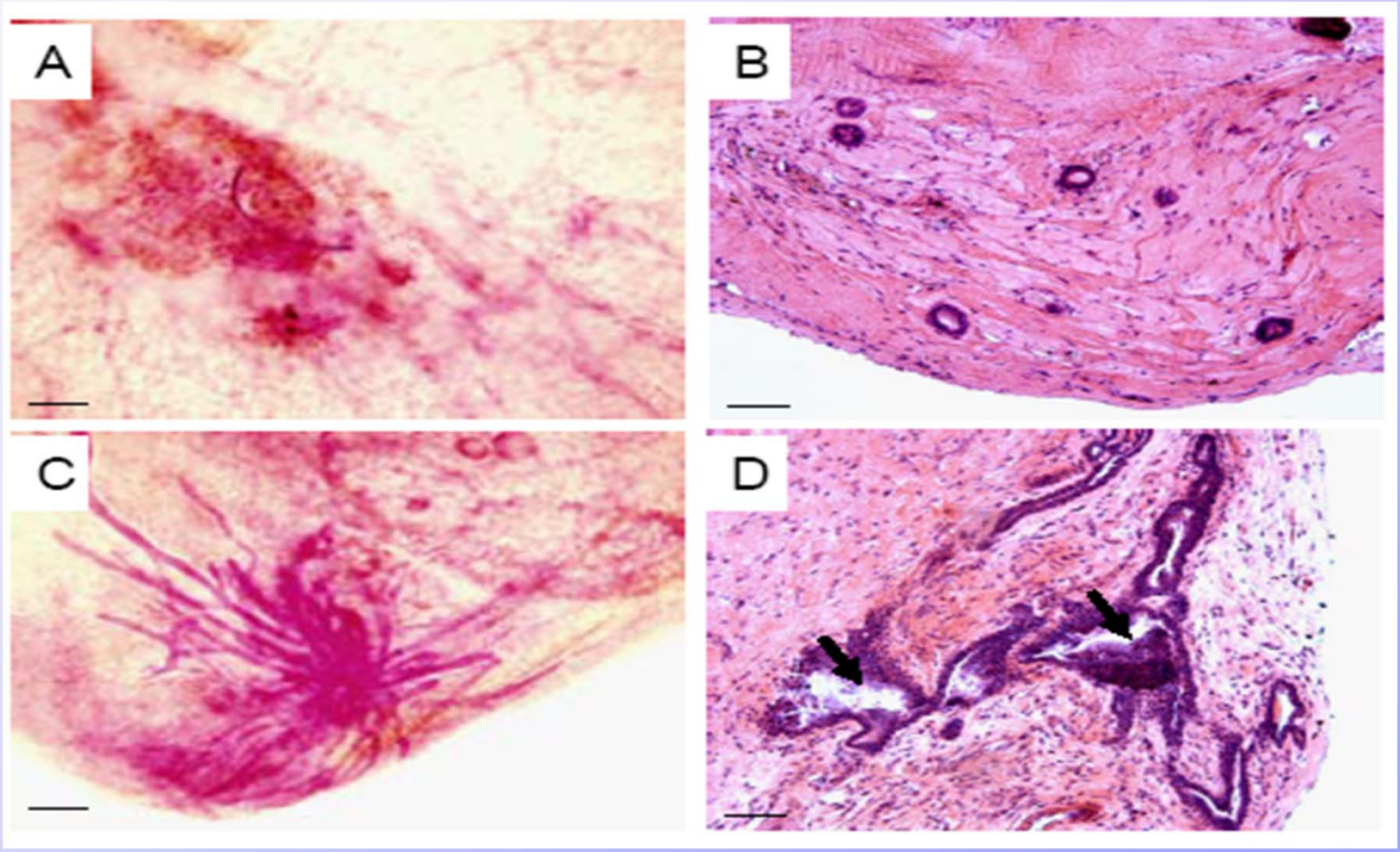



Normal stem cell functionality
Common characteristics of normal stem cells and tumor stem cells
Carcinogenesis
▪High proliferation potential, tightly controlled
▪Organogenesis
▪Adult tissue maintenance and repair
▪Regeneration of an organ/tissue upon transplantation
Ability to self- renew
▪Uncontrolled proliferation
▪Tumorigenicity
▪Generation of all types of differentiated cells in a tissue
▪Organogenesis
Ability to differentiate
▪Tumor heterogeneity
▪Aberrant organogenesis
▪More exposed to damaging agents, higher risk of accumulating mutations, corbalanced by
▪Active DNA repair mechanisms
Long lived/immortal
Active antiapoptotic pathways
Telomerase activity
▪Higher risk of accumulating mutations
▪Often defects in DNA repair mechanisms, resulting in mutator phenotype and radio resistance
▪Genomic instability
▪Increased transporter actvity and toxic agent exclusion
Resistance to damaging agents
▪Chemoresistance
▪Homing
Anchorage independent survival
and ability to migrate
▪Metastasis

Pathways Involved in Stem Cell Self Renewal and Cancer

- Notch
- Hedgehog
- Bmi-1
- Wnt

Hedgehog Target Gli-2 Promotes Ductal Hyperplasia



CANCER STEM CELL HYPOTHESIS

- Cancers Arise From Tissue Stem Or Progenitor Cells
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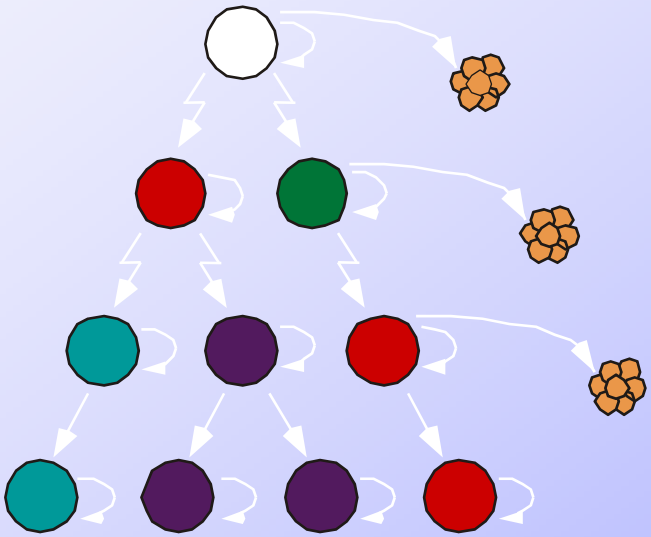
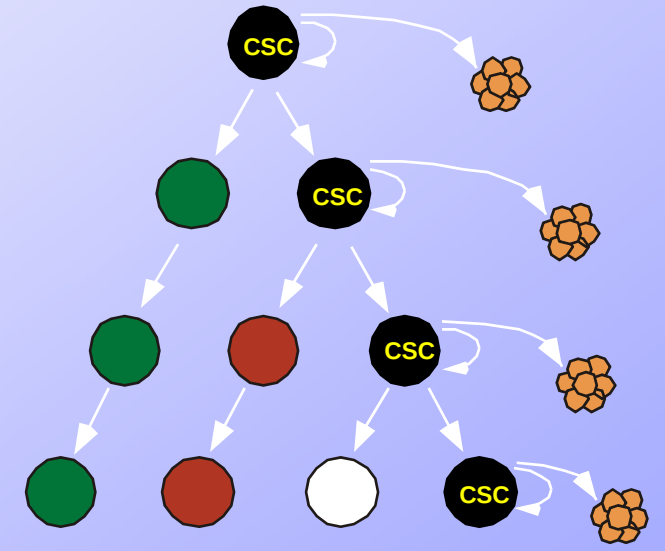
Models of Tumor Heterogenity

Stochastic model



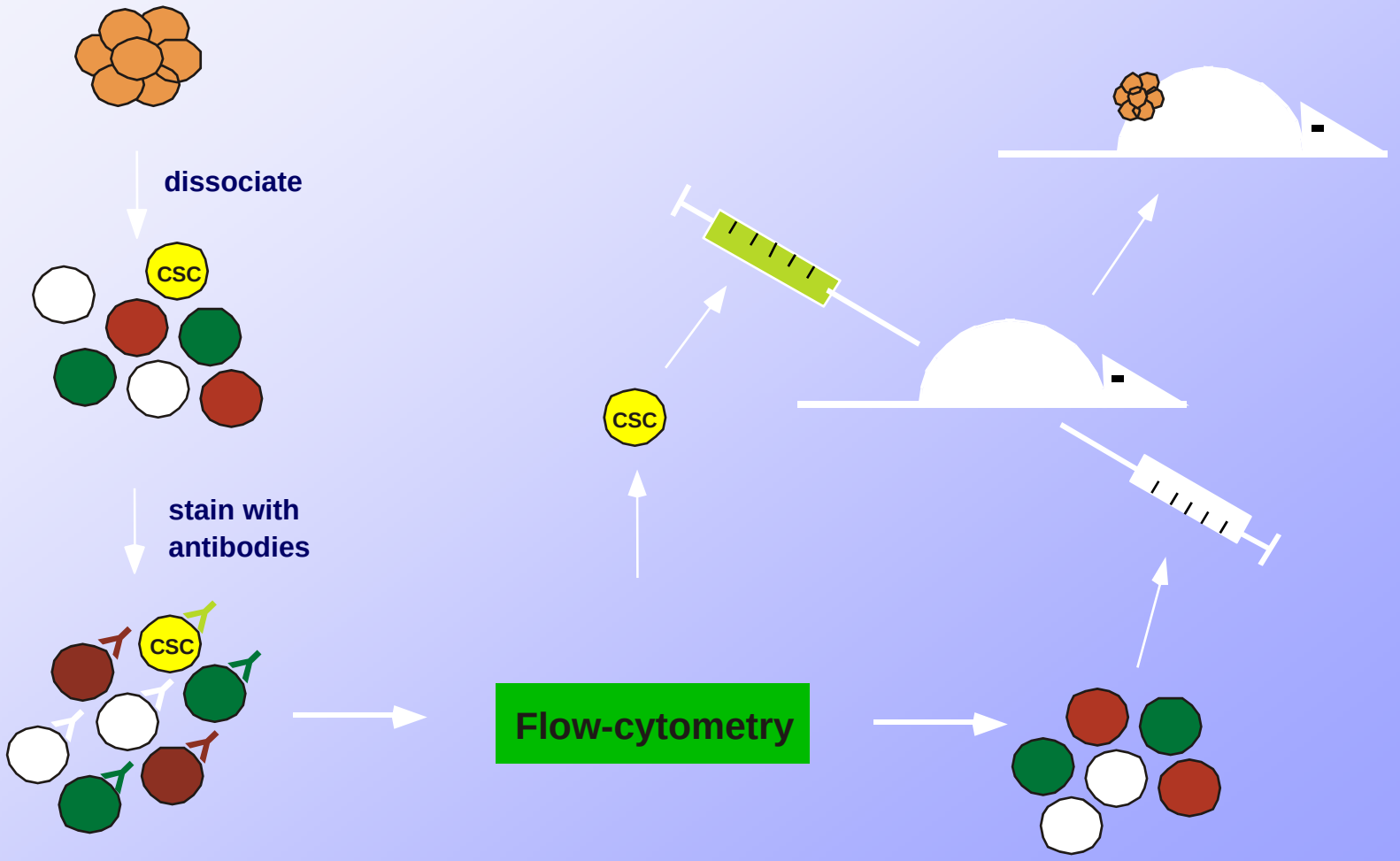
Cancer cells are heterogeneous, but most cells can proliferate extensively and form new tumors.

Cancer stem cell model



Cancer cells are heterogeneous, and only rare cancer stem cells have the ability to proliferate extensively and form new tumors.

The Isolation of Human Cancer Stem Cells



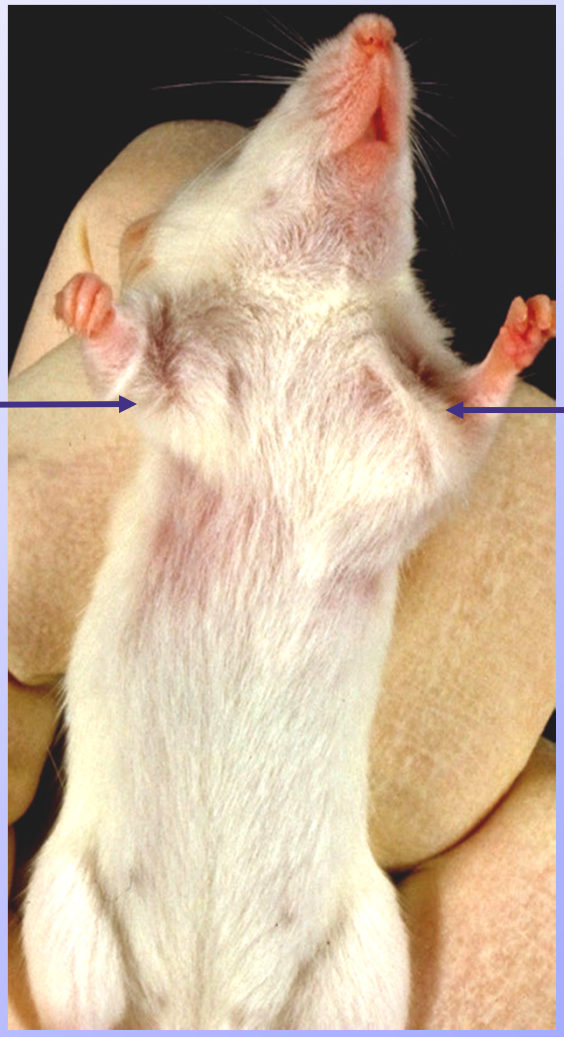
Tumorigenicity of Cancer Cell Subsets

Cells / injection	$5x10^5$	10^5	$5x10^4$	$2x10^4$	10^4	$5x10^3$	10^3	200
Unsorted (T1)	4/4	4/4	6/6	-	2/6	-	0/6	-
B38+CD44+CD24+	-	-	-	0/5	0/5	0/5	0/5	-
B38+CD44+CD24-	-	-	-	5/5	5/5	5/5	5/5	-
ESA+CD44+CD24-	-	-	-	-	-	-	8/8	4/4
Unsorted (T2)	4/4	4/4	4/4	-	1/6	-	0/6	-
B38+CD44+CD24+	-	-	-	0/5	0/5	0/5	0/5	-
B38+CD44+CD24-	-	-	-	5/5	5/5	5/5	5/5	-

Tumor 1 was derived from a metastatic pleural effusion and Tumor 2 was derived from a primary breast tumor.

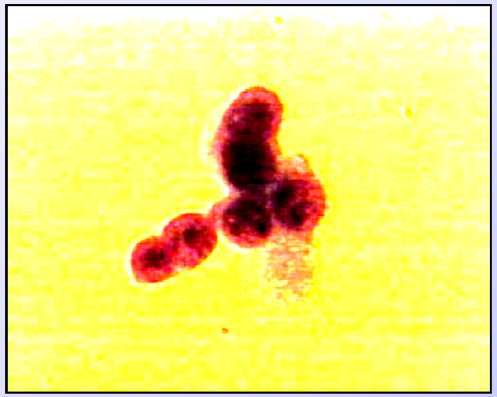
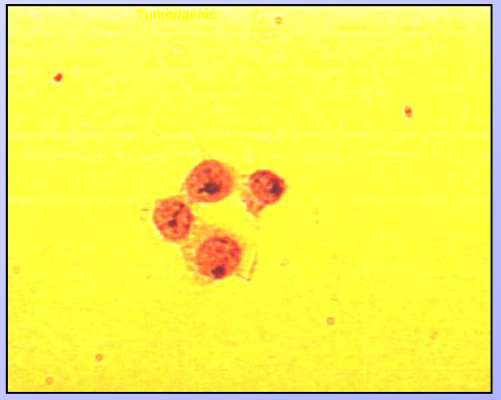
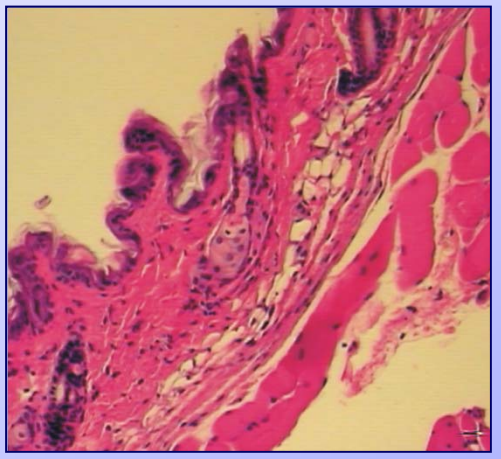
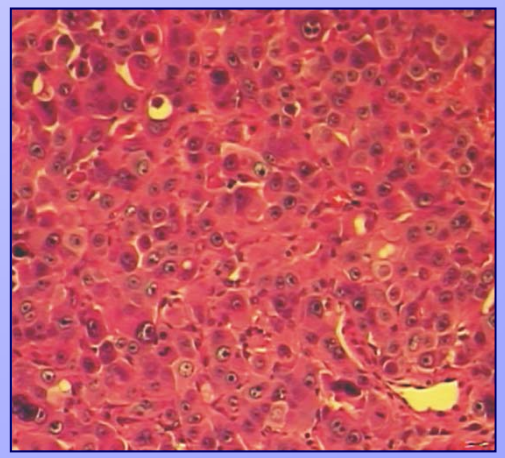
Tumor Formation by Human Breast Cancer Cells in Mouse Model

CD44+;B38.1+
CD24+

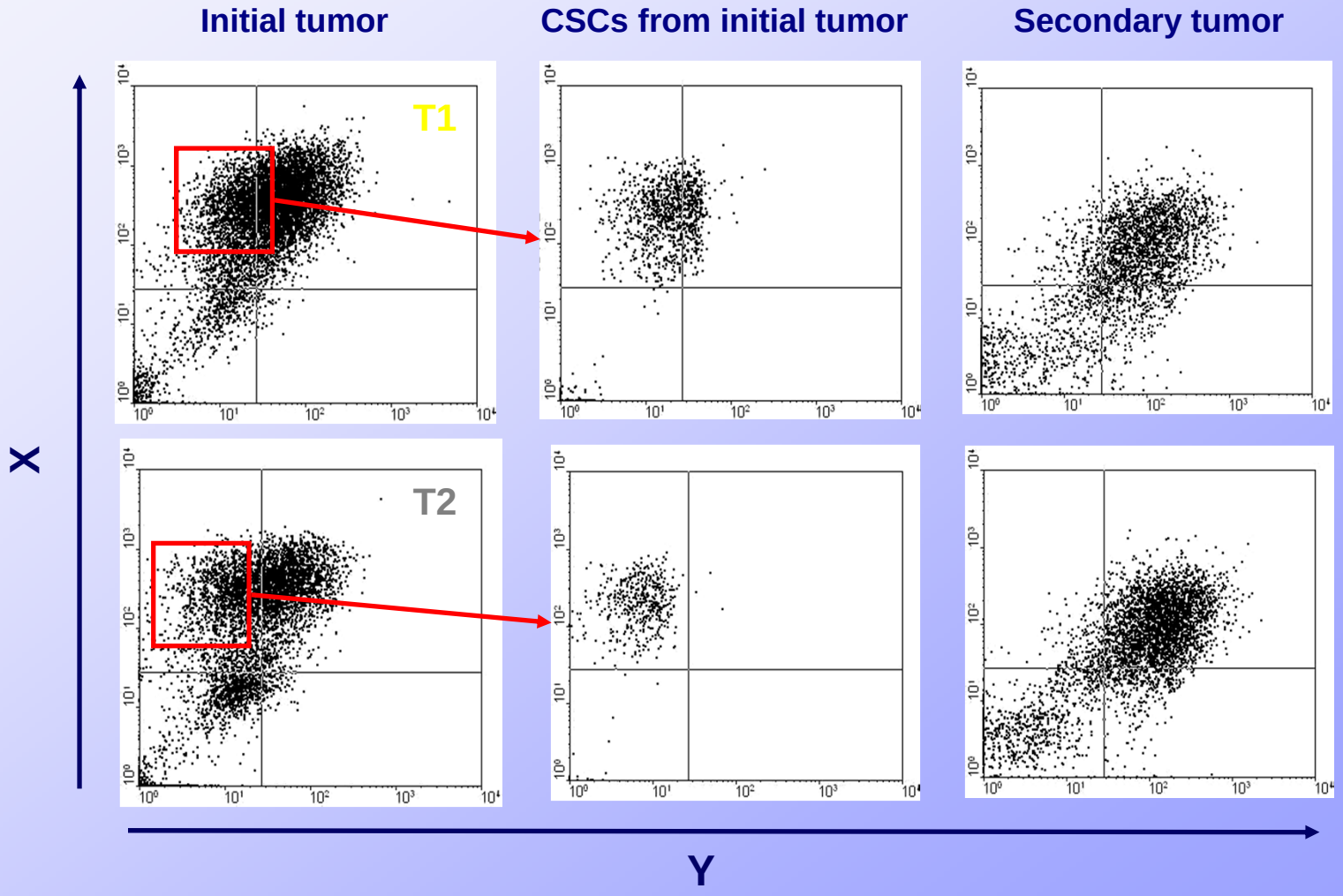


CD44+;B38.1+
CD24-

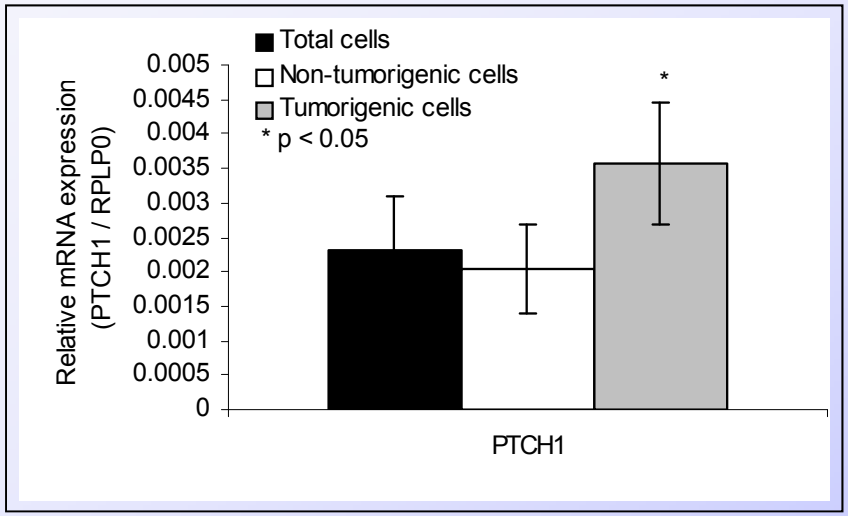
Both Non-Tumorigenic Cancer Cells and Cancer Stem Cells have a Malignant Appearance, but Only Stem Cells Give Rise to New Tumors

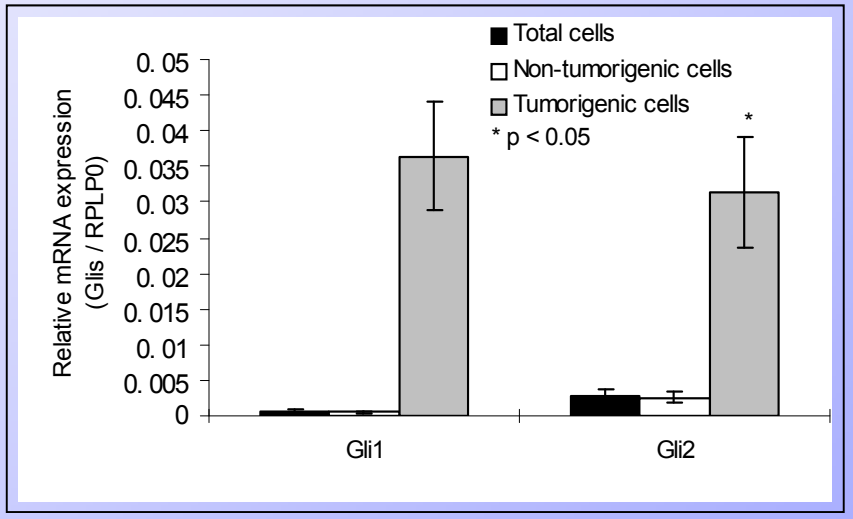
	Non-tumorigenic cells	Cancer stem cells
Isolated human breast cancer cells		
Injection sites in the mice		

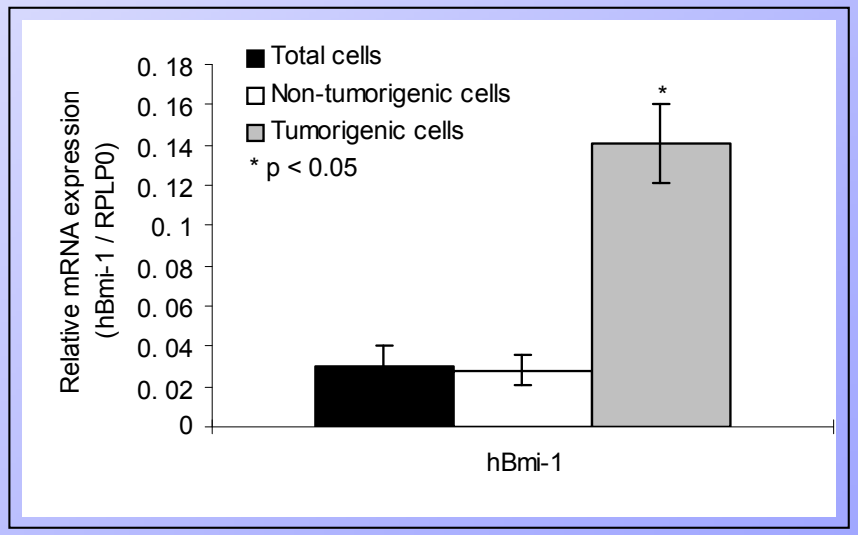
Breast Cancer Stem Cells give rise to Phenotypically Diverse Tumors after Transplantation



Hedgehog Activation & Bmi-1 Expression in Cancer Stem Cells







Mammary stem cell self-renewal pathways

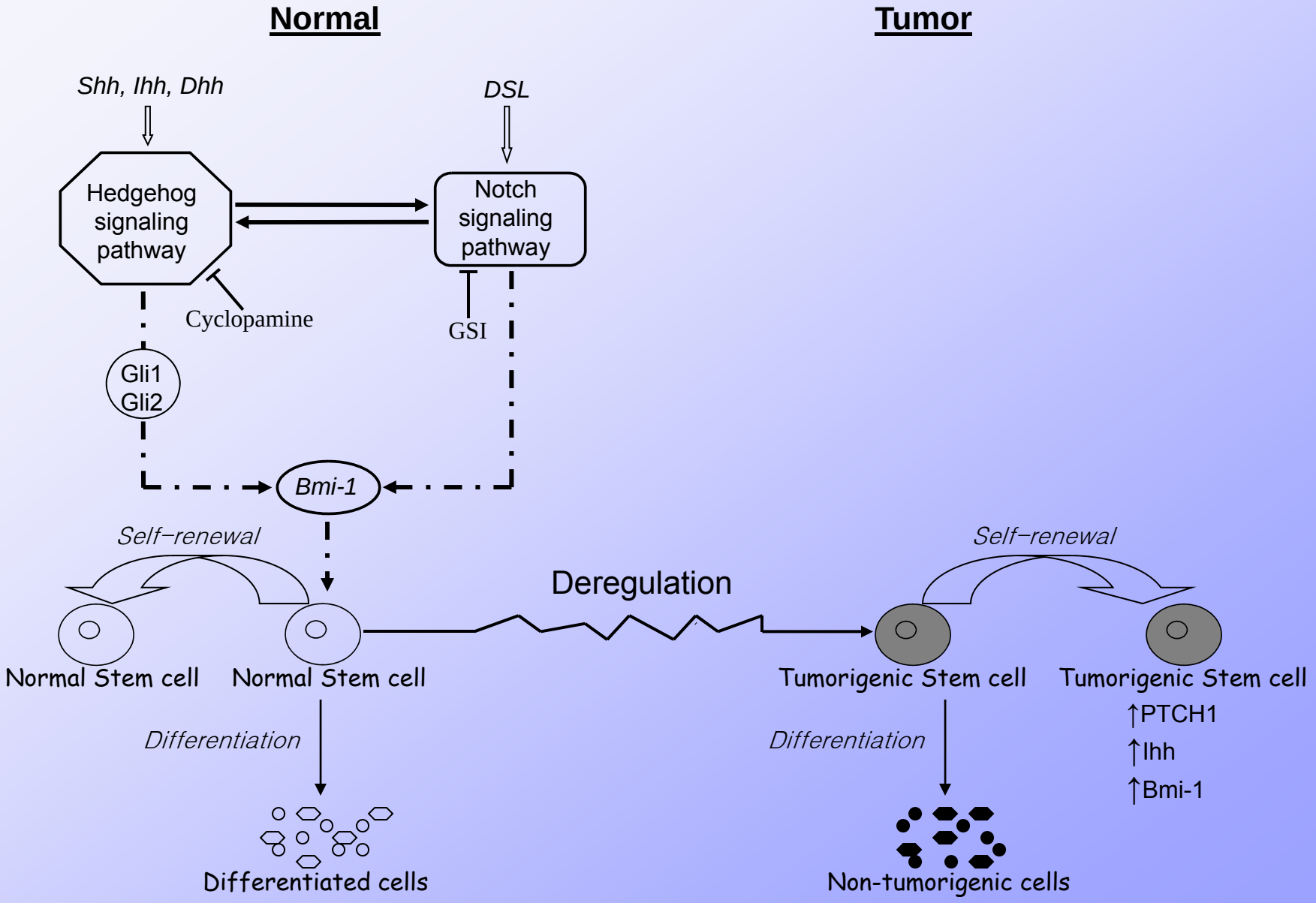
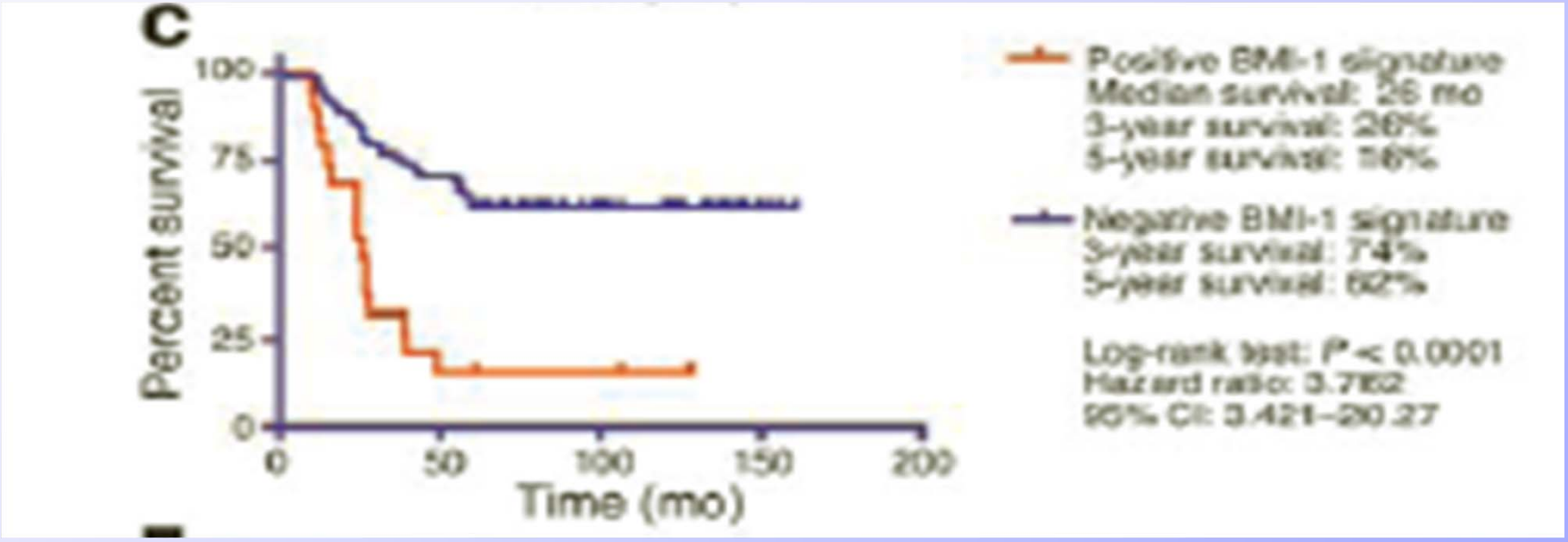


Figure 10

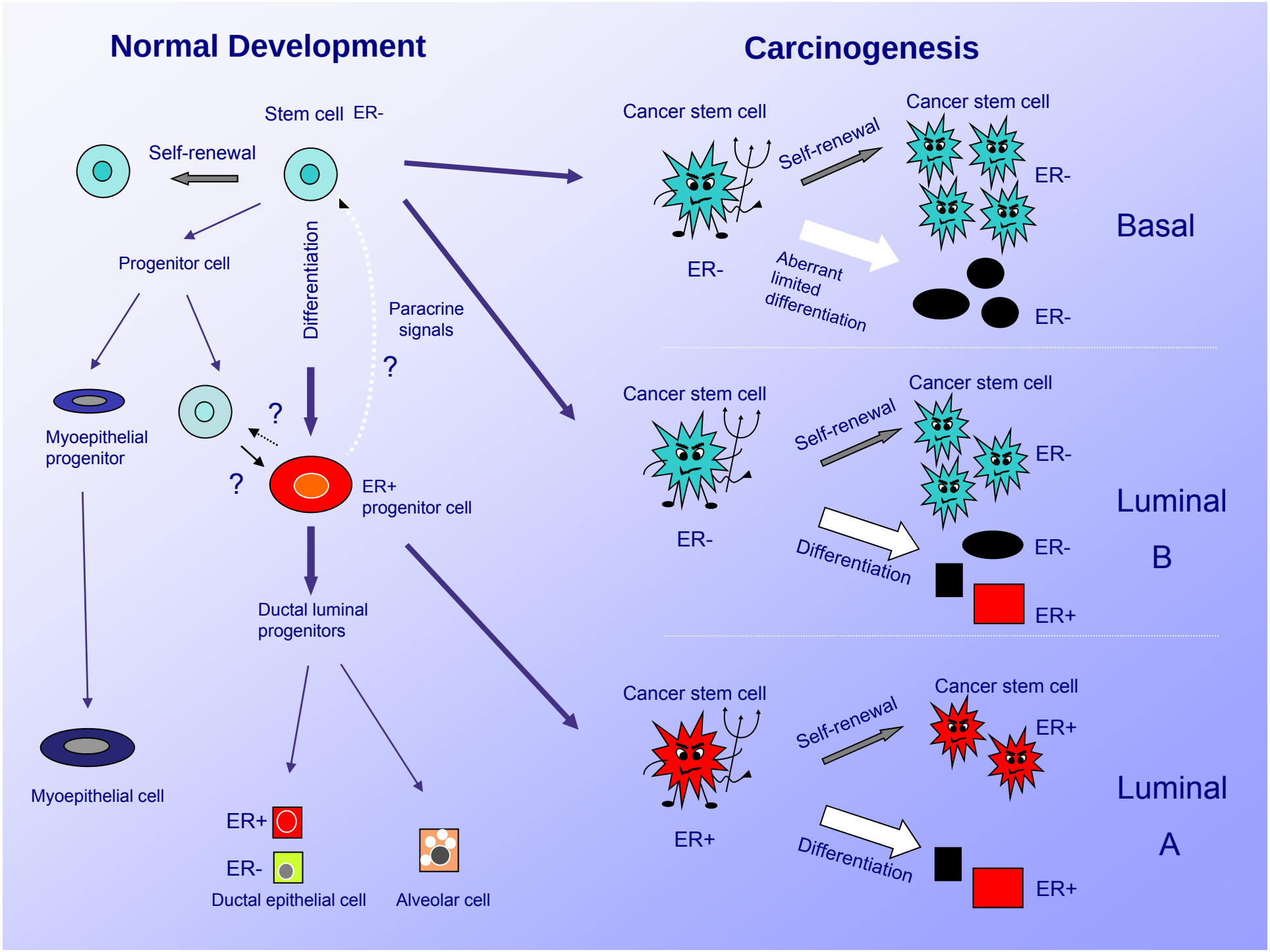


BMI-1 “Stem-Cell” Signature and Patient Survival

Glinsky et al. JCI 115:1503, 2005

Implications of TSC – Profiling / Diagnosis / Prevention

- Cell of origin may determine molecular profile
- Molecular profiling may miss important TSC genes
- Significance of TSC in metastasis
- Identification of TSC in situ may have diagnostic/prognostic value
- Elimination of mutated stem/progenitor cells important prevention strategy

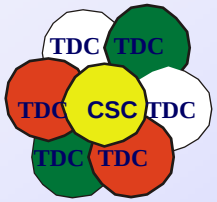

Normal Development
Carcinogenesis
Stem cell ER-
Self-renewal
Progenitor cell
Differentiation
Paracrine signals
?
?
?
Myoepithelial progenitor
ER+ progenitor cell
Ductal luminal progenitors
Myoepithelial cell
ER+
ER-
Ductal epithelial cell
Alveolar cell
Cancer stem cell
Self-renewal
ER-
Aberrant limited differentiation
Cancer stem cell
ER-
ER-
Basal
Cancer stem cell
Self-renewal
ER-
Differentiation
Cancer stem cell
ER-
ER-
ER+
Luminal B
Cancer stem cell
Self-renewal
ER+
Differentiation
Cancer stem cell
ER+
ER+
Luminal A

Cancer Stem Cells: Implications For Metastasis

CSC=Cancer Stem Cell

TDC=Terminally Differentiated Cell

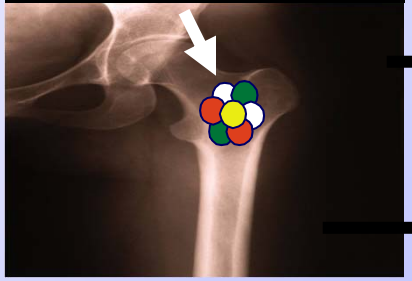
1°
Tumor



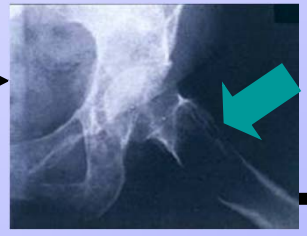
TDC only

No Metastases

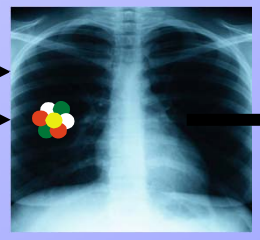
CSC with FULL malignant potential



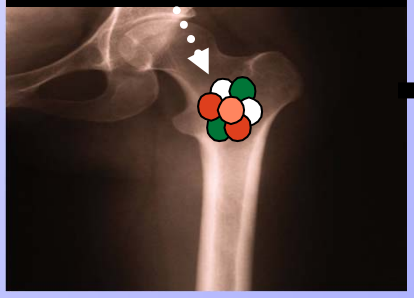
Metastases in months to few years



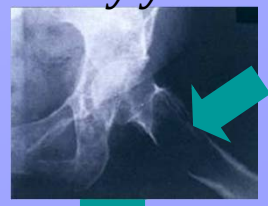
Subsequently to other sites



CSC with PARTIAL malignant potential

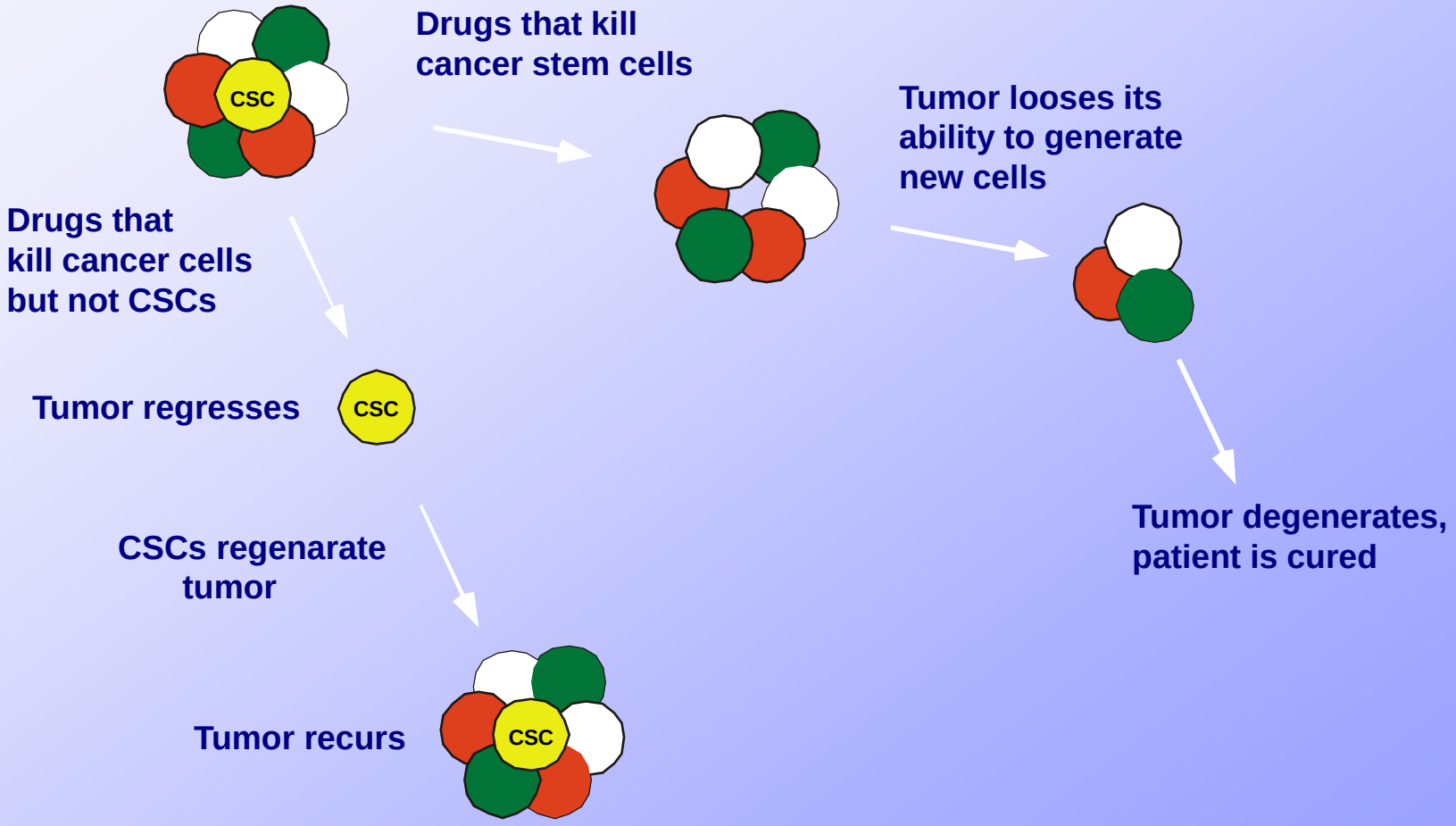


***Dormancy* followed by Metastases after many years:**



Secondary Oncogenic "Hits" and/or Changes in Microenvironment

The Implications of Human Cancer Stem Cells (CSCs) for Treatment



Implications of TSC Therapeutics

- Tumor regression inadequate endpoint
  - Preclinical models
  - Phase II clinical trials
- TSC may be resistant to therapy (apoptosis)
- Effective therapies should target TSC while sparing normal cells
- Genes in TSC self-renewal pathway may provide new therapeutic targets

Evidence for “ Stem Cells” in Human Cancer

- Breast Cancer
- Leukemia
- Multiple Myeloma
- Brain Cancer
- Lung Cancer
- Prostate Cancer
- Melanoma