

Division of Cancer Biology

Cancer Health Disparities Summit 2007

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July 18, 2007

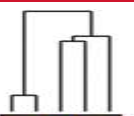
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The Division of Cancer Biology supports

investigator-initiated

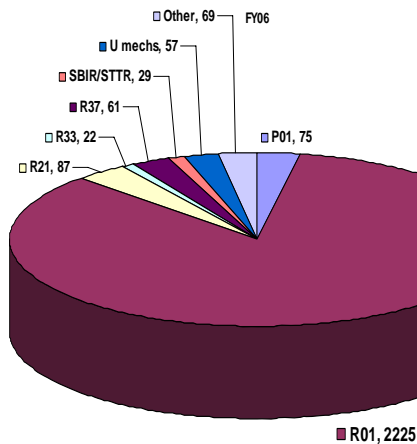
basic research on the biology of cancer,

**across the initiation, progression,
metastasis continuum**



**Scientific Portfolio
RPG (FY06)**

Funded Awards



2625 awards = \$870M

Applications

Type	Applications Received	Funded	Dollars
R01	4,132	289	\$63.84
P01	98	5	\$7.07M
R21	380	39	\$6.45M
Other	360	59	\$1.88M
Total	4,997	342	\$79.24M

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Health Disparities Research

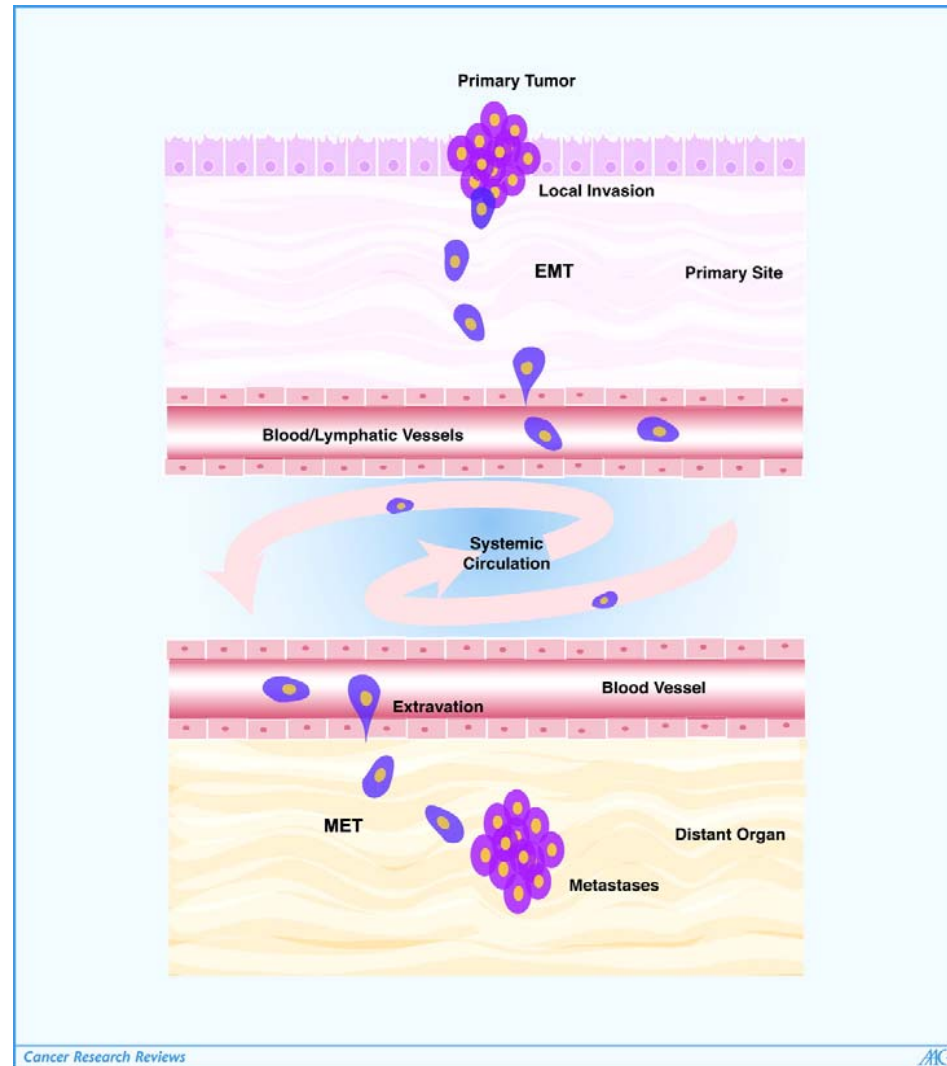
- **22% of NCI's basic research grants address cancers that disproportionately affect different racial and ethnic minority populations**
- **NCI researchers investigate the molecular and cellular basis of these diseases and the distinctions among different populations**
- **Among these cancers are: breast, colon, lung, prostate, stomach, liver and cervical cancer**

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Breast Cancer	% Positive
• ER/PR positive	70-75
• erbB2 positive	20-25
• ER Negative	10-15*

* Higher in African Americans

Embryonic Transcription Factors & EMT Essential for Metastasis



Robert Weinberg

Breast Cancer Metastasis: Reactivation of Embryonic Transcription Factors → EMT

Transcription Factor Tumor Type

Twist

Lobular ER positive

Goosecoid

Ductal ER+ or erb2↑

FoxC2

Basal ER/PR/her2 negative

Cell 117: 927, 2004

PNAS 103: 18969, 2006

HBC: Basal-like Non-basal-like

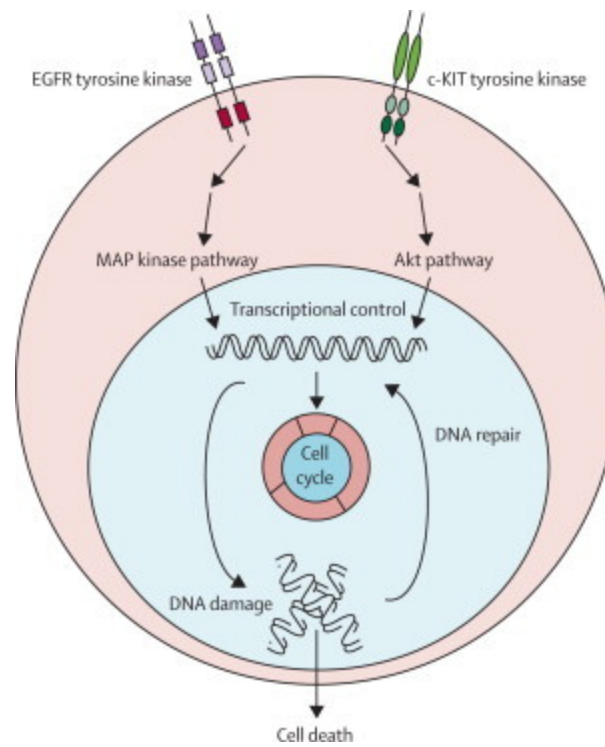
• ER	14% +ve	78
• erbB2	0	26
• Keratin5/6	62	14
• EGFR	57	8
• p53 mutation	82	13
• Cyclin E	80	6
• Vimentin	94	8

ER Negative Breast Cancer

- **Poorly differentiated w/ Central necrosis**
- **Higher proliferation rate (mechanism ?)**
- **Viscera and brain: dominant sites of metastasis**
- **LOH 5q14 (100% vs. 0% in non-basal)**
harbors DNA repair genes and tumor suppressor genes (Rad50, Rad17, APC, MSH3, XRCC4)
- **6p21-p25 amplification** (harbors many oncogenes – Notch4, DEK, E2F3, PIM-1, CCND3)
- **Higher gene copy number ; 2-3 times higher SNPs**

Cleator, Heller & Coombes, "Triple negative breast cancer: therapeutic options. *Lancet Oncol* 8:235-244, 2007

Overexpression of EGFR and c-KIT, high proliferative rate; ↑MAPK and AKT signaling, high rate of DNA aberration, and possibly DNA repair pathways, p53 mutations, phenotypically similar to BRCA1-associated cancers.



Division of Cancer Biology: part of an NCI-wide Think Tank on ER Negative Breast Cancer (Nov 2007)

- **The current state-of-the-art in cancer biology and clinical management**
- **Identification of challenges and research opportunities**
- **Eventual goal: Initiative to support research: impact on treatment, diagnosis and/or prevention**

ER-negative Breast Cancer Think Tank: Examples of Scientific issues

- Pathways that drive proliferation ?
- Are these tumors more susceptible to agents that cause (a) interstrand and DS breaks? and (b) inhibition of already defective DNA repair by e.g., poly ADP ribose polymerase ?
- BRCA-1 status (methylated or silenced?)
- Subclasses of ER negative (molecular heterogeneity)