Progress since 2007
Pre-clinical science

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&
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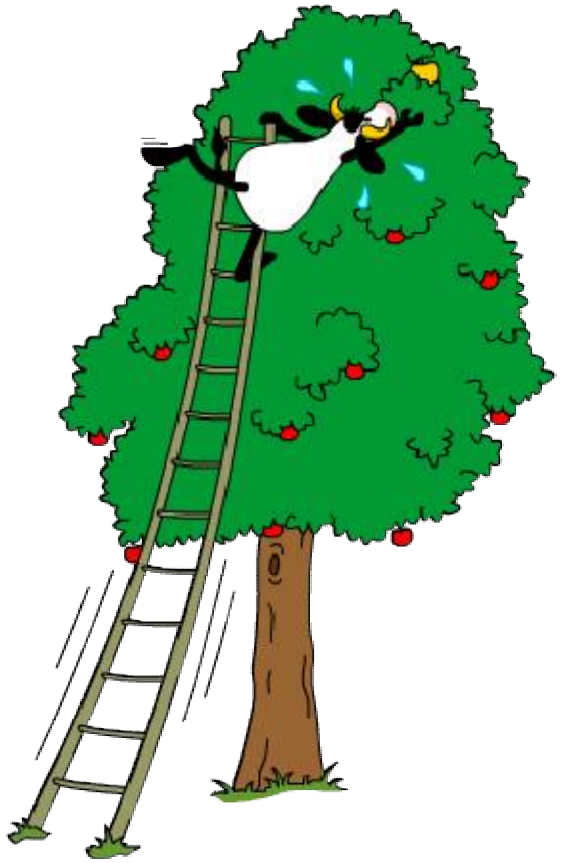
Breast cancer therapeutic targets

Estrogen receptor
HER2

Evolution of breast cancer therapeutic targets



- Estrogen receptor
- HER2

- Subtype specific therapy
- Targeting through synthetic lethality (PARPi for HR defects)

How can you target loss of function?
(BRCA1 mutation, p53, etc)

Synthetic lethality

Science 1997

Integrating Genetic Approaches into the Discovery of Anticancer Drugs

Leland H. Hartwell, Philippe Szankasi, Christopher J. Roberts, Andrew W. Murray, Stephen H. Friend*

The discovery of anticancer drugs is now driven by the numerous molecular alterations identified in tumor cells over the past decade. To exploit these alterations, it is necessary to understand how they define a molecular context that allows increased sensitivity to particular compounds. Traditional genetic approaches together with the new wealth of genomic information for both human and model organisms open up strategies by which drugs can be profiled for their ability to selectively kill cells in a molecular context that matches those found in tumors. Similarly, it may be possible to identify and validate new targets for drugs that would selectively kill tumor cells with a particular molecular context. This article outlines some of the ways that yeast genetics can be used to streamline anticancer drug discovery.

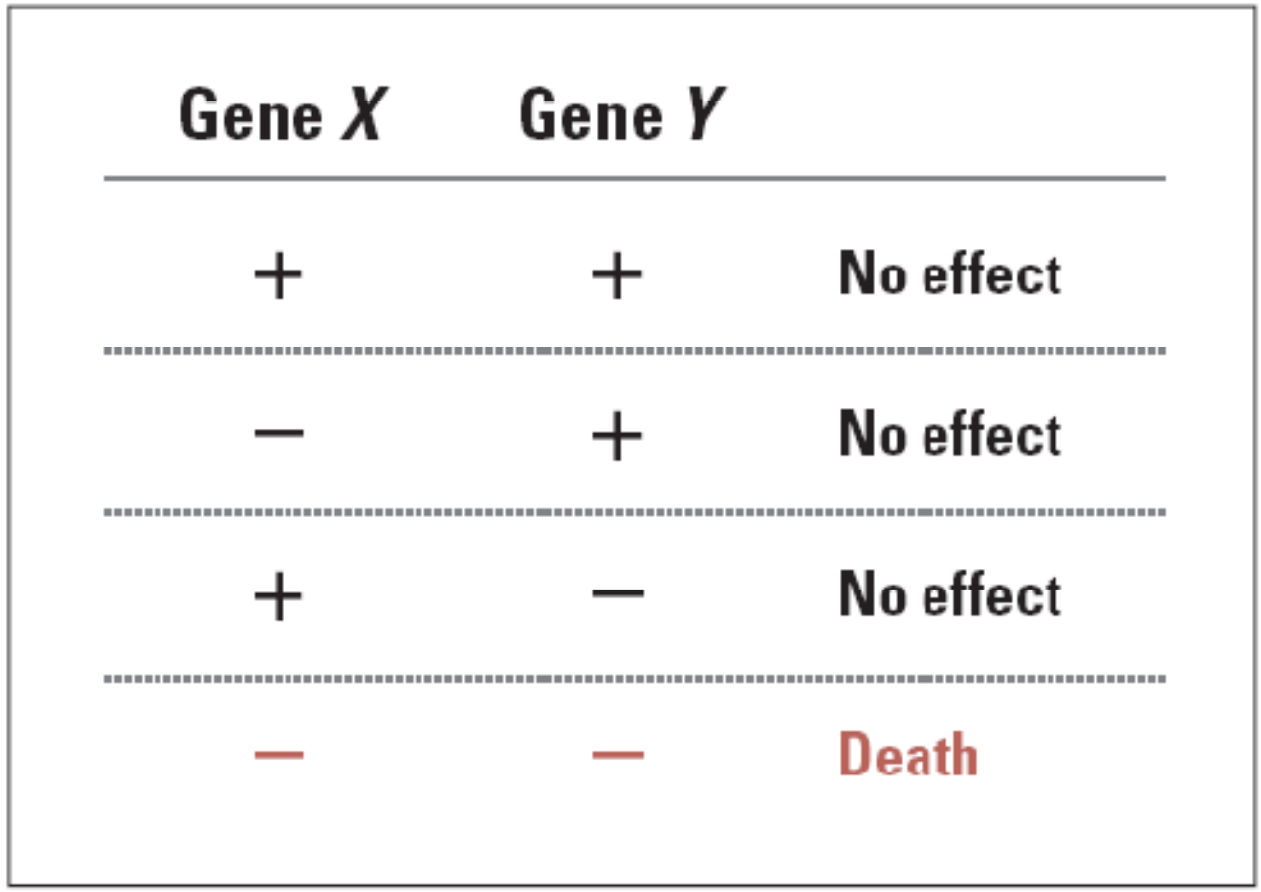
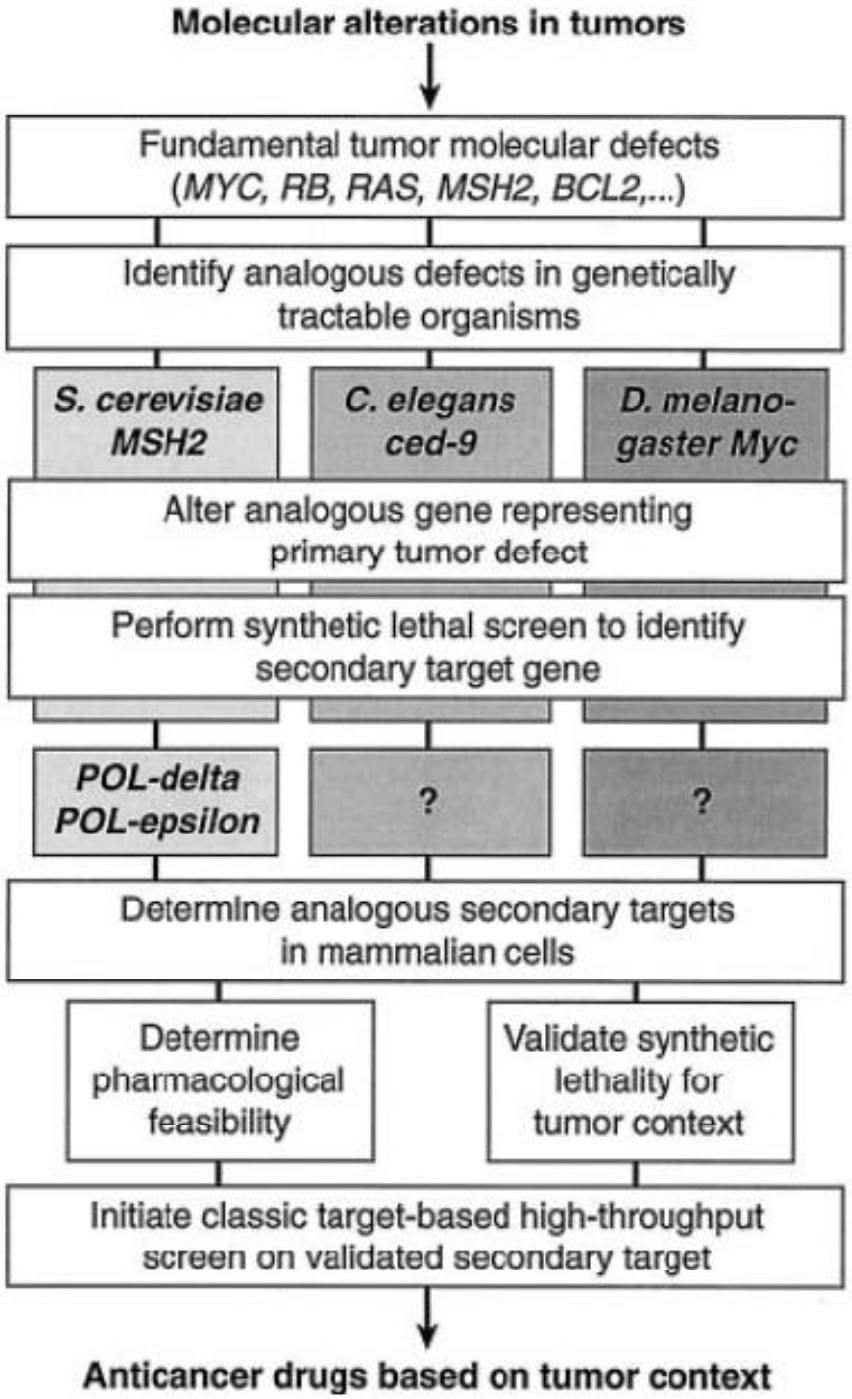


Fig 3. The concept of synthetic lethality. Synthetic lethality occurs when mutation in either of two genes individually has no effect but combining the mutations leads to death.[27] In cancer therapy, this effect implies that inhibiting one of these genes in a context where the other is defective should be selectively lethal to the tumor cells but not toxic to the normal cells, potentially leading to a large therapeutic window.[28]

Table 1. Human genes altered in tumors and their relatives in model genetic systems. Genes that are not structural homologs but act in analogous pathways (such as human *p53* and *S. cerevisiae RAD9*) are shown in brackets. *Saccharomyces cerevisiae* genes are designated with superscript Sc, *S. pombe* with Sp, *C. elegans* with Ce, and *D. melanogaster* with Dm. Because of space limitations, this is only a representative list of genes mutated in tumors that have genetic analogs in model systems. Comprehensive lists of model system genes analogous to human genes mutated in tumors can be found in the references listed herein and in (*34*).

Function	Human genes	Model system analogs: Structural homologs or related biological roles
DNA damage checkpoint	*p53*	[*RAD9*^{Sc}, *rad1*$^{+Sp}$]
	ATM	*MEC1*^{Sc}, *TEL1*^{Sc}, *rad3*$^{+Sp}$, *mei-41*^{Dm}
DNA mismatch repair	*MSH2, MLH1*	*MSH2*^{Sc}, *MLH1*^{Sc}
Nucleotide excision repair	*XP-A, XP-B*	*RAD14*^{Sc}, *RAD25*^{Sc}
O^6-methylguanine reversal	*MGMT*	*MGT1*^{Sc}
Double-strand break repair	*BRCA2, BRCA1*	[*RAD51*^{Sc}, *RAD54*^{Sc}]
DNA helicase	*BLM*	*SGS1*^{Sc}, *rqh1*$^{+Sp}$
Growth factor signaling	*PAS*	*RAS1*^{Sc}, *RAS2*^{Sc}, *let-60*^{Ce}
	NF1	*IRA1*^{Sc}, *IRA2*^{Sc}
	MYC	*dMyc*^{Dm}
	PTH	*patched*^{Dm}
Cell cycle control	Cyclin D, Cyclin E	*CLN1*^{Sc}, *CLN2*^{Sc}, Cyclin D^{Dm}, Cyclin E^{Dm}
	p27^{kip1}	[*SIC1*^{Sc}]
	Pb	*Rbf*^{Dm}
Apoptosis	*BCL-2*	*ced-9*^{Ce}



Requires model system in which genes can be easily silenced

Human

↓

Yeast model

↓

Identify SL target

↓

Identify human counterpart

↓

Screen drug

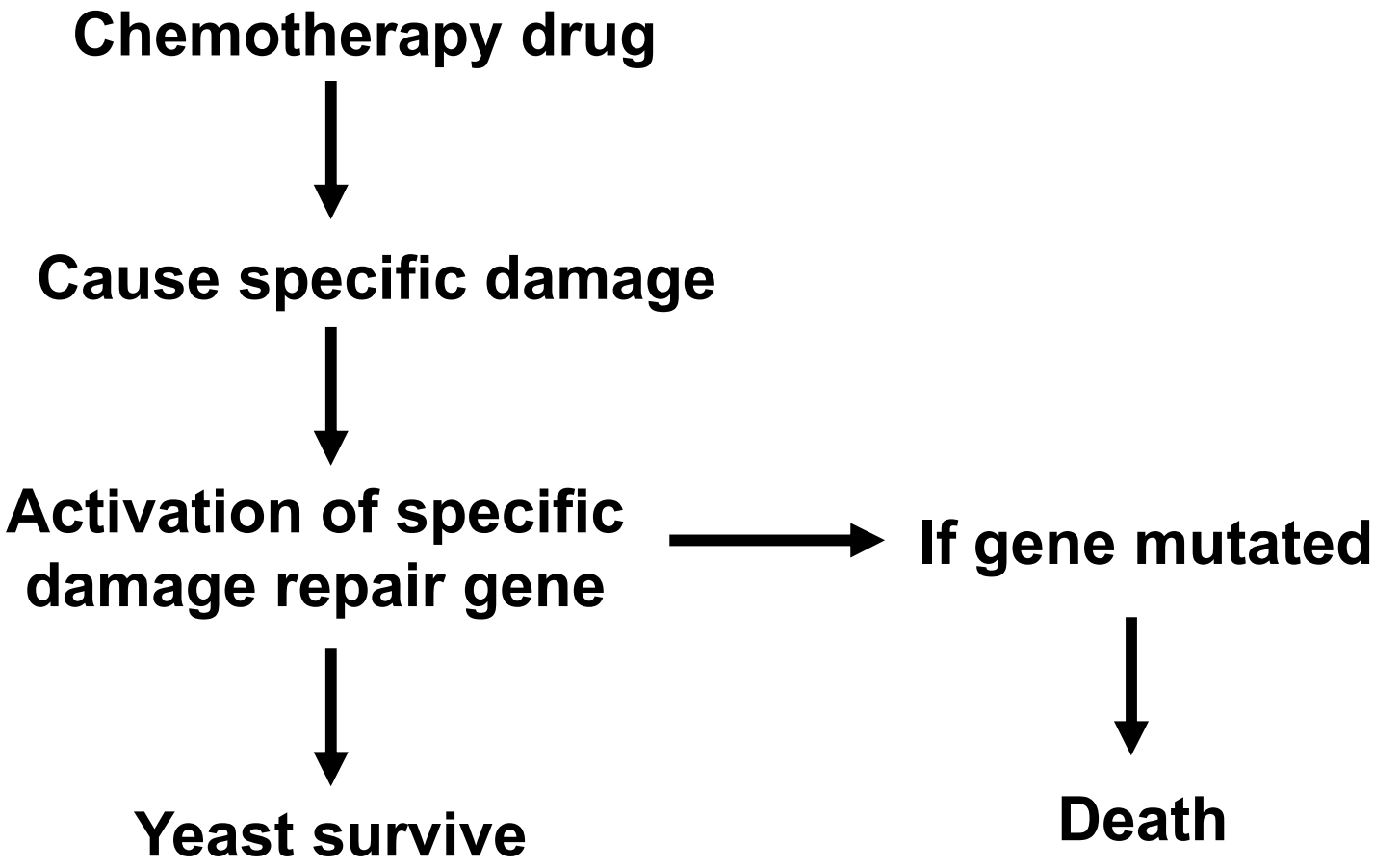
Synthetic lethality screening to identify chemotherapeutic targets

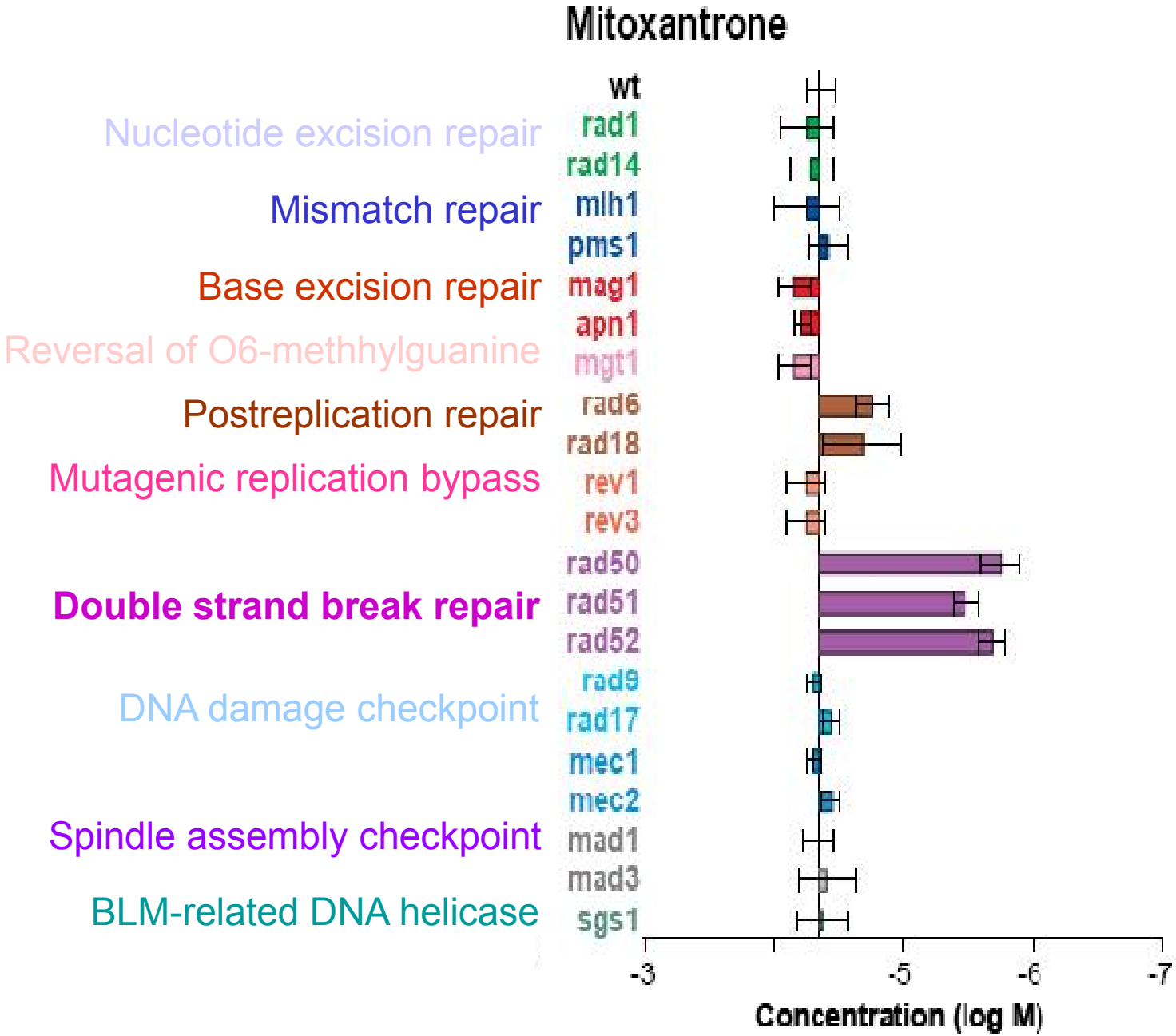
(Seattle Project - Hartwell and Friend)

Simon et al, Cancer Research, 60:328, 2000

- Screening of sensitivity of panel of isogenic yeast strains with selective mutations in DNA repair or cell cycle checkpoint function to 23 chemotherapeutic agents approved by FDA

Synthetic lethality screening to identify chemotherapy targets



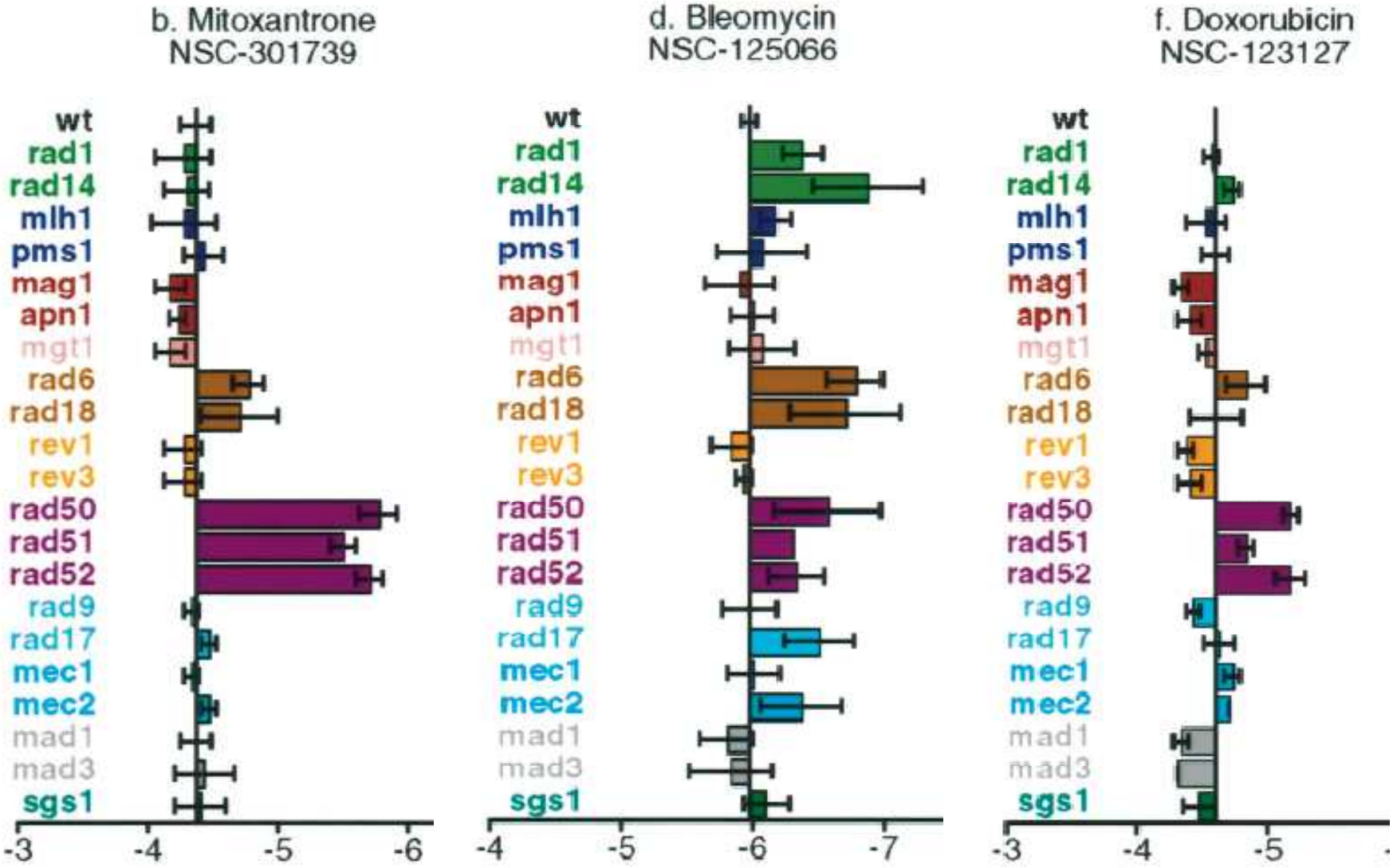

Mitoxantrone
Nucleotide excision repair
Mismatch repair
Base excision repair
Reversal of O6-methhylguanine
Postreplication repair
Mutagenic replication bypass
Double strand break repair
DNA damage checkpoint
Spindle assembly checkpoint
BLM-related DNA helicase
wt
rad1
rad14
mlh1
pms1
mag1
apn1
mgt1
rad6
rad18
rev1
rev3
rad50
rad51
rad52
rad9
rad17
mec1
mec2
mad1
mad3
sgs1
-3
-5
-6
-7
Concentration (log M)

Synthetic lethality screening

- 3 types of agents identified
  - **Selective agents**
    - cisplatin, cytarabine phosphate, camptothecin sodium, mitoxantrone, and idarubicin
  - **Broadly selective agents**
    - mitomycin C, thiotepa, lomustine, carmustine, streptozotocin, mechlorethamine, bleomycin,hydroxyurea, and X-rays
  - **Non-selective agents**
    - methotrexate, trimetrexate, fluorouracil, fluorodeoxyuridine, pentostatin, dacarbazine, actinomycin D, daunorubicin, and doxorubicin
    - Daunorubicin, doxorubicin, and actinomycin D, for example, are capable of generating free radicals, which target membranes in addition to DNA

Many chemotherapeutic agents are non-selective

Simon et al, Cancer Research, 60:328, 2000



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JOURNAL OF CLINICAL ONCOLOGY

BIOLOGY OF NEOPLASIA

A Synthetic Lethal Therapeutic Approach: Poly(ADP) Ribose Polymerase Inhibitors for the Treatment of Cancers Deficient in DNA Double-Strand Break Repair

Alan Ashworth

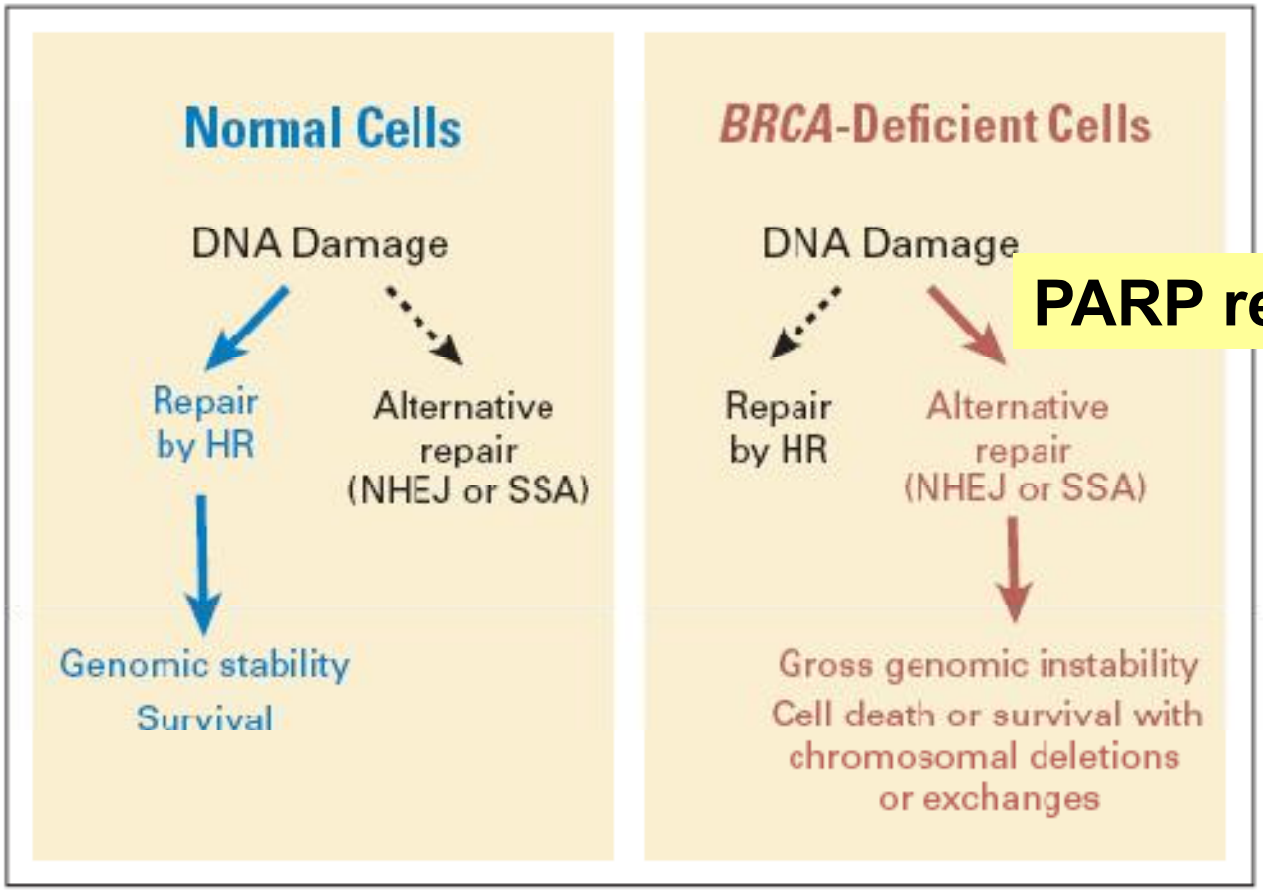
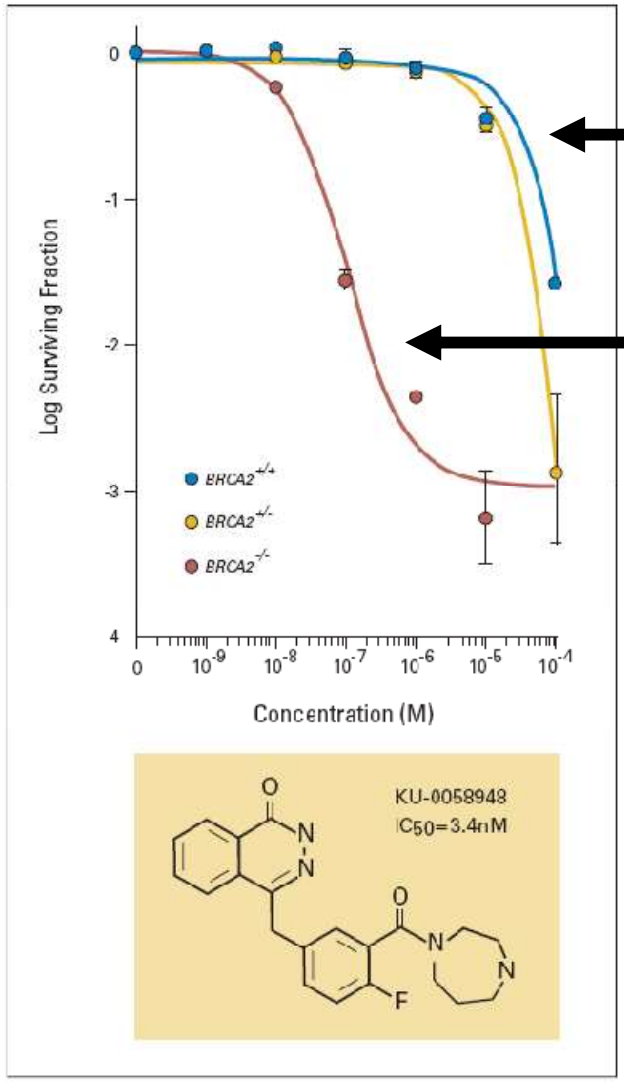


Fig 1. Loss of functional BRCA1 or BRCA2 affects the choice of DNA double-strand break (DSB) repair pathway. DNA DSBs are repaired in normal cells, in part, by homologous recombination (HR) -based mechanisms. Functional BRCA1 and BRCA2 proteins are required for efficient repair by HR and genomic stability. In the absence of BRCA1 or BRCA2, alternative repair pathways, such as nonhomologous end-joining (NHEJ) and single-strand annealing (SSA), are used, leading to cell death or survival with genomic damage.

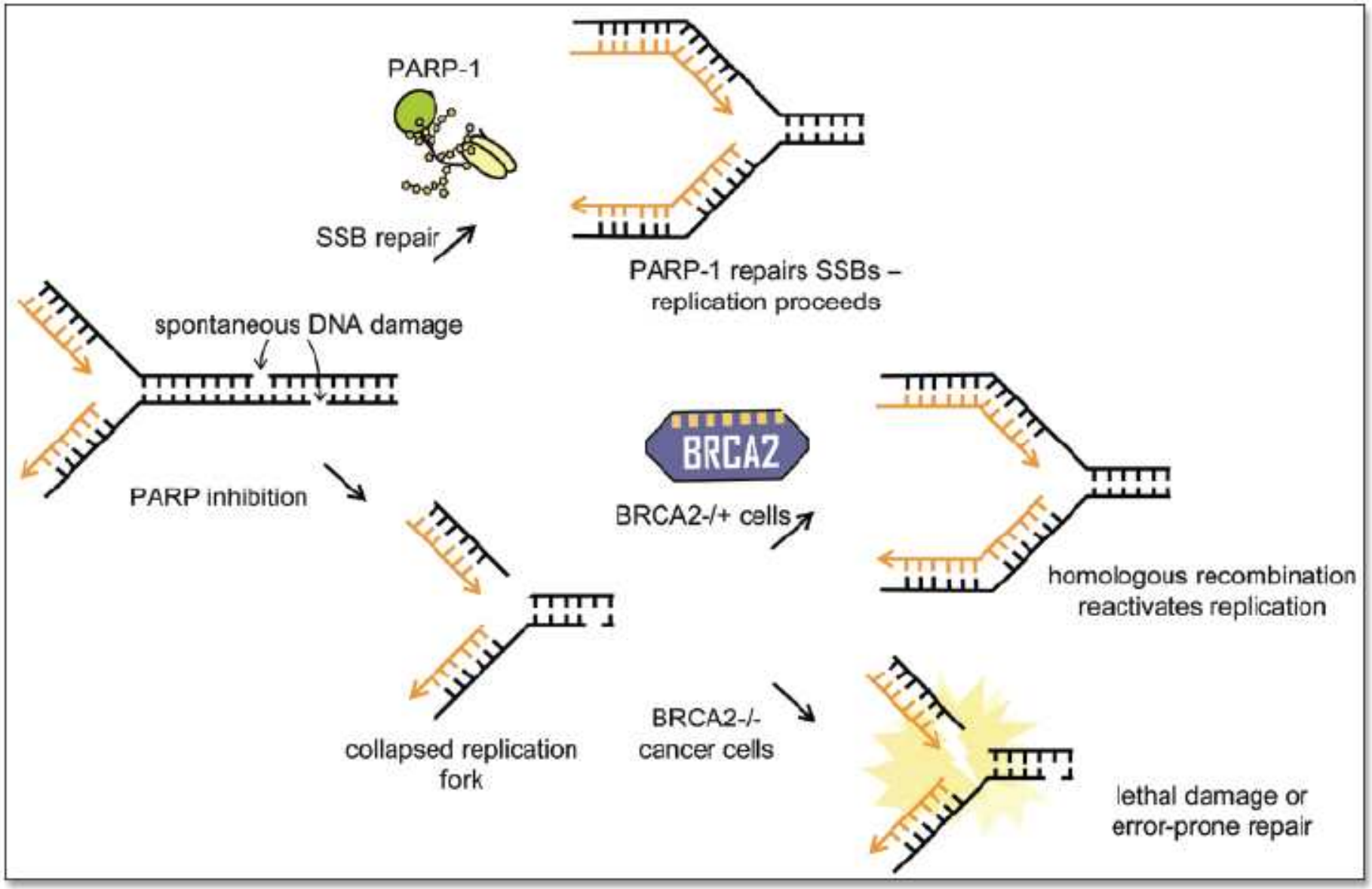
Inhibition of PARP1 selectively kills BRCA deficient cells



Wild type

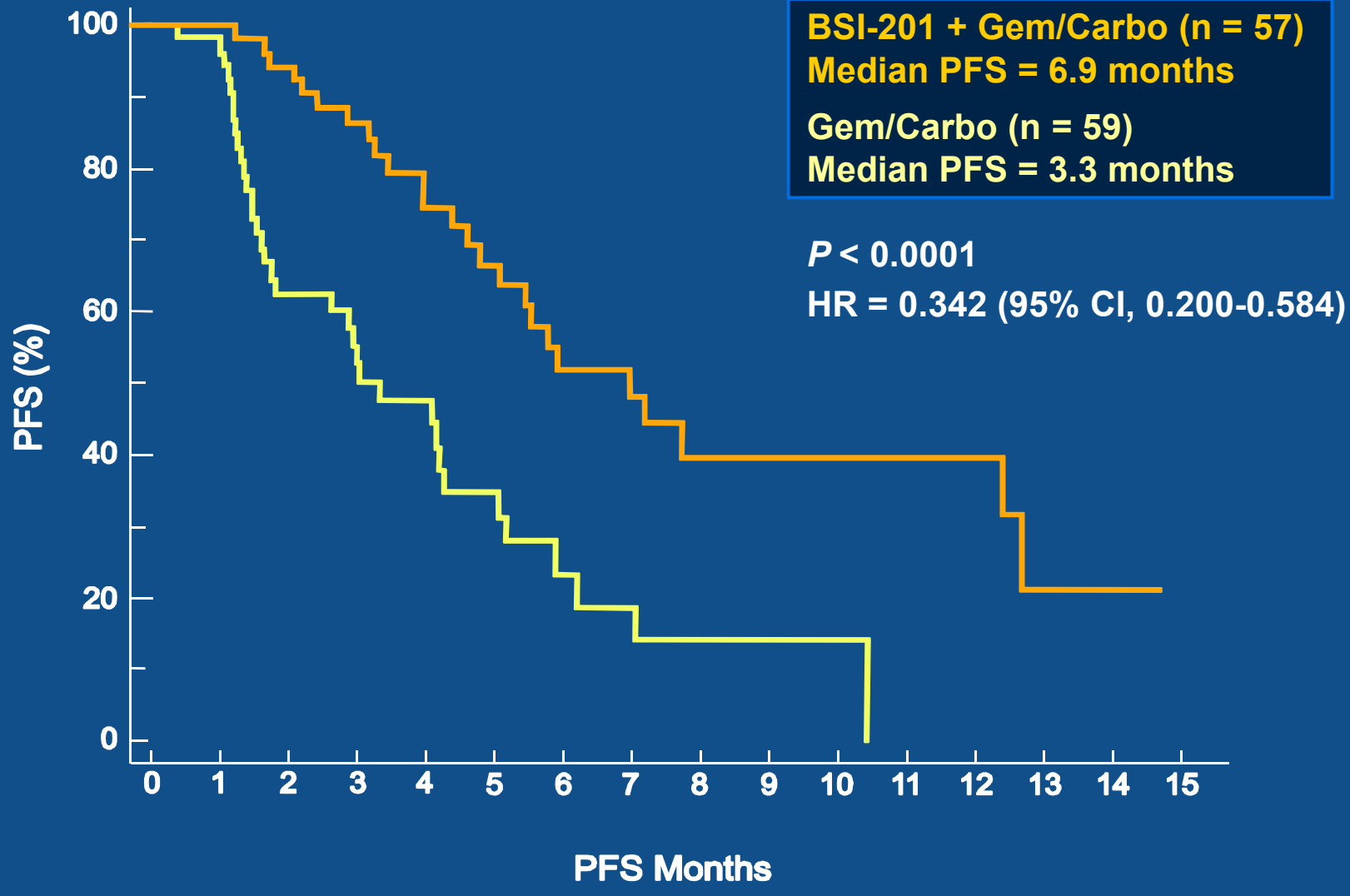
BRCA deficient

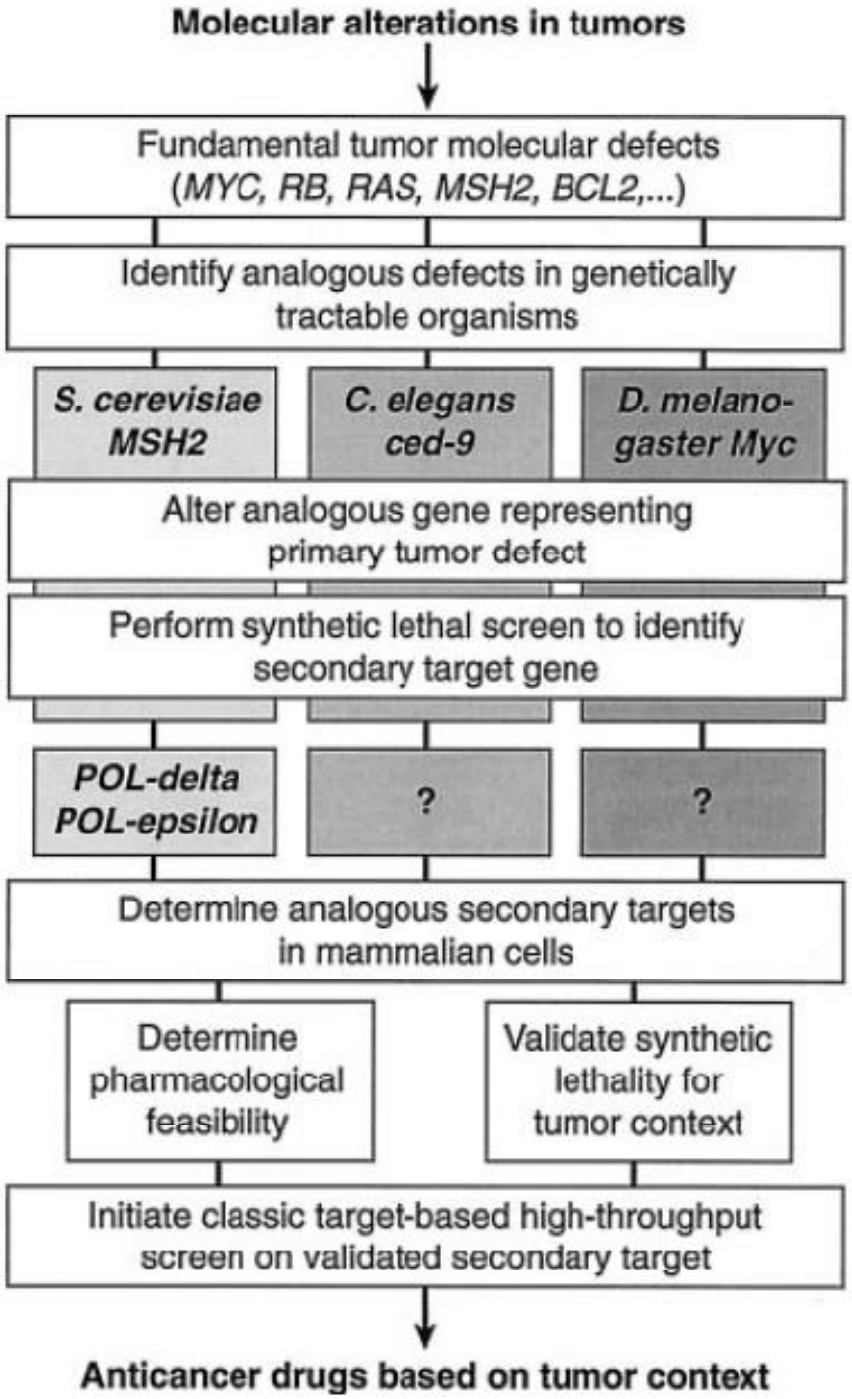
Fig 4. *BRCA2* mutant cells are exquisitely sensitive to a potent PARP inhibitor.[36] Clonogenic survival curves of *BRCA2* wild-type, heterozygous, and deficient cells after treatment with the poly(ADP) ribose polymerase inhibitor KU0058948.[37] *BRCA2*-deficient cells are more than 1,000-fold more sensitive than wild-type or heterozygous cells to KU0058948.


PARP-1
SSB repair
PARP-1 repairs SSBs –
replication proceeds
spontaneous DNA damage
PARP inhibition
BRCA2
BRCA2-/+ cells
homologous recombination
reactivates replication
collapsed replication
fork
BRCA2-/-
cancer cells
lethal damage or
error-prone repair

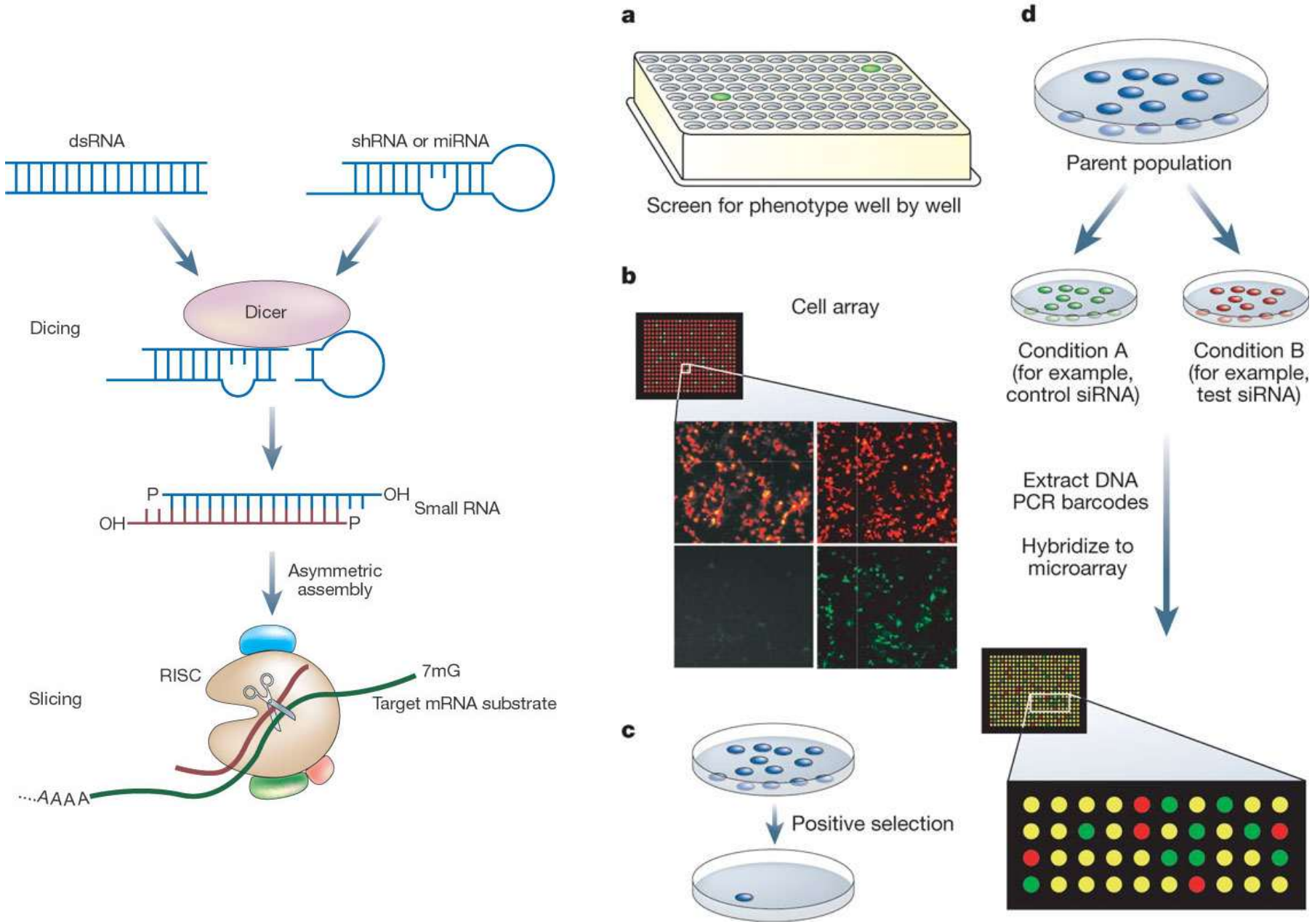
BRCAness = defects in DNA double strand break (DSB) repair pathway

Progression-Free Survival





Now this can be achieved in cancer cell lines with RNA interference


dsRNA
shRNA or miRNA
Dicing
Dicer
P
OH
OH
P
Small RNA
Asymmetric assembly
RISC
Slicing
7mG
Target mRNA substrate
····AAAA
a
Screen for phenotype well by well
b
Cell array
c
Positive selection
d
Parent population
Condition A (for example, control siRNA)
Condition B (for example, test siRNA)
Extract DNA PCR barcodes
Hybridize to microarray

MOLECULAR AND CELLULAR BIOLOGY, Dec. 2006, p. 9377–9386 Vol. 26, No. 24
0270-7306/06/$08.00+0 doi:10.1128/MCB.01229-06

Small Interfering RNA Screens Reveal Enhanced Cisplatin Cytotoxicity in Tumor Cells Having both BRCA Network and TP53 Disruptions[▽‡]

Steven R. Bartz,[1]†* Zhan Zhang,[1]† Julja Burchard,[1] Maki Imakura,[1] Melissa Martin,[1] Anthony Palmieri,[1] Rachel Needham,[1] Jie Guo,[1] Marcia Gordon,[1] Namjin Chung,[2] Paul Warrener,[1] Aimee L. Jackson,[1] Michael Carleton,[1] Melissa Oatley,[2] Louis Locco,[2] Francesca Santini,[2] Todd Smith,[2] Priya Kunapuli,[2] Marc Ferrer,[2] Berta Strulovici,[2] Stephen H. Friend,[3,4] and Peter S. Linsley[1]

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RNA interference strategy to identify key determinant of treatment response

Cancer Cell
Report

A Functional Genetic Approach Identifies the PI3K Pathway as a Major Determinant of Trastuzumab Resistance in Breast Cancer

Katrien Berns,[1,6] Hugo M. Horlings,[2,6] Bryan T. Hennessy,[5] Mandy Madiredjo,[1] E. Marielle Hijmans,[1] Karin Beelen,[3] Sabine C. Linn,[3] Ana Maria Gonzalez-Angulo,[5] Katherine Stemke-Hale,[5] Michael Hauptmann,[4] Roderick L. Beijersbergen,[1] Gordon B. Mills,[5] Marc J. van de Vijver,[2] and René Bernards[1,*]

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[2]Division of Experimental Therapy
[3]Division of Medical Oncology
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The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
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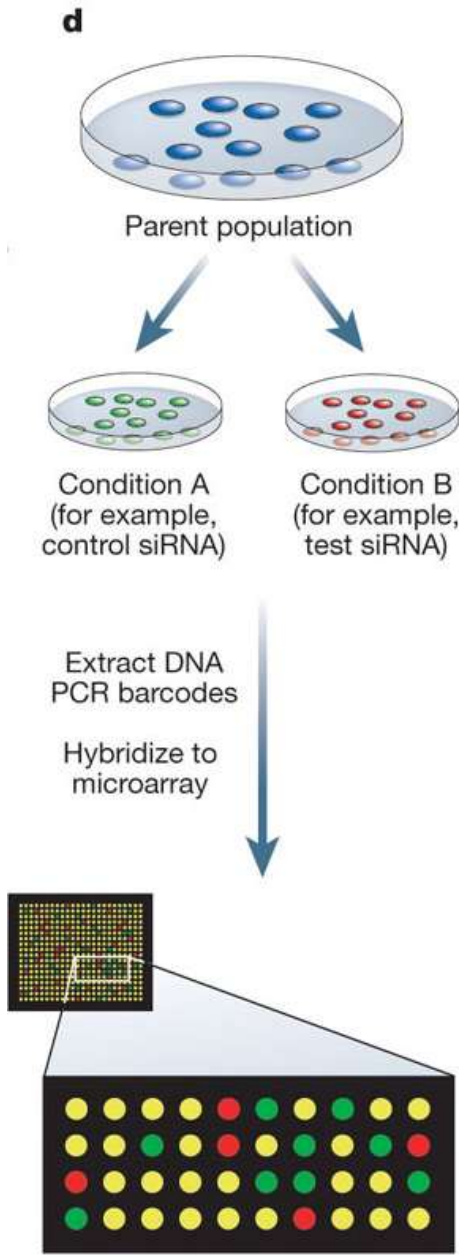
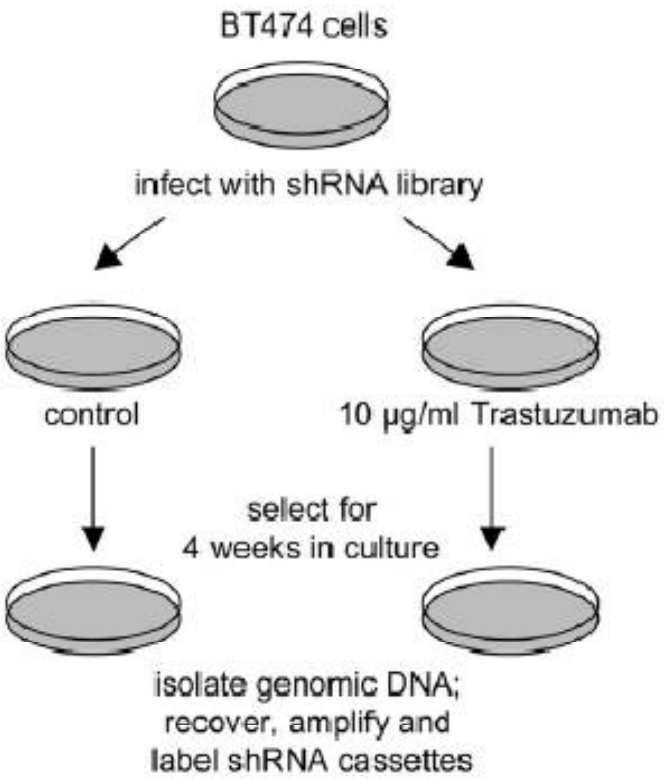
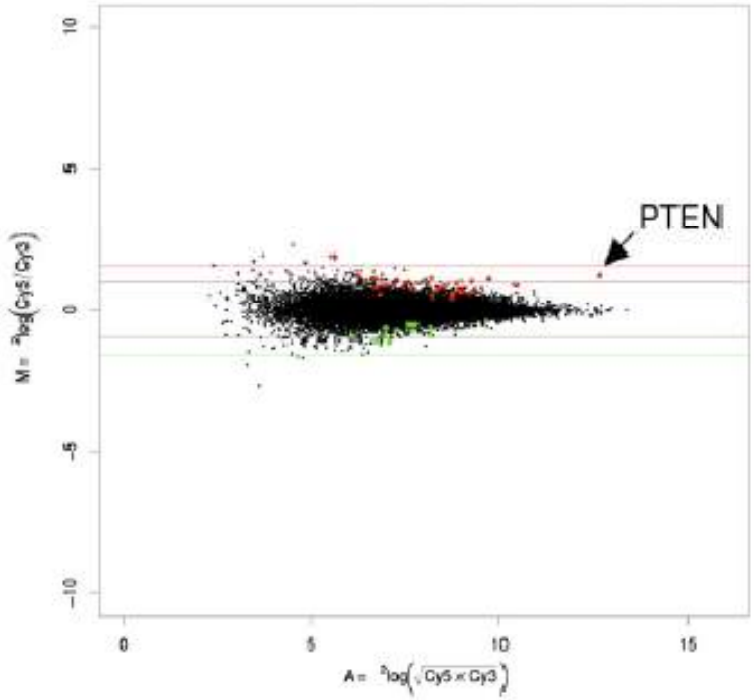
[6]These authors contributed equally to this work.
*Correspondence: r.bernards@nki.nl
DOI 10.1016/j.ccr.2007.08.030

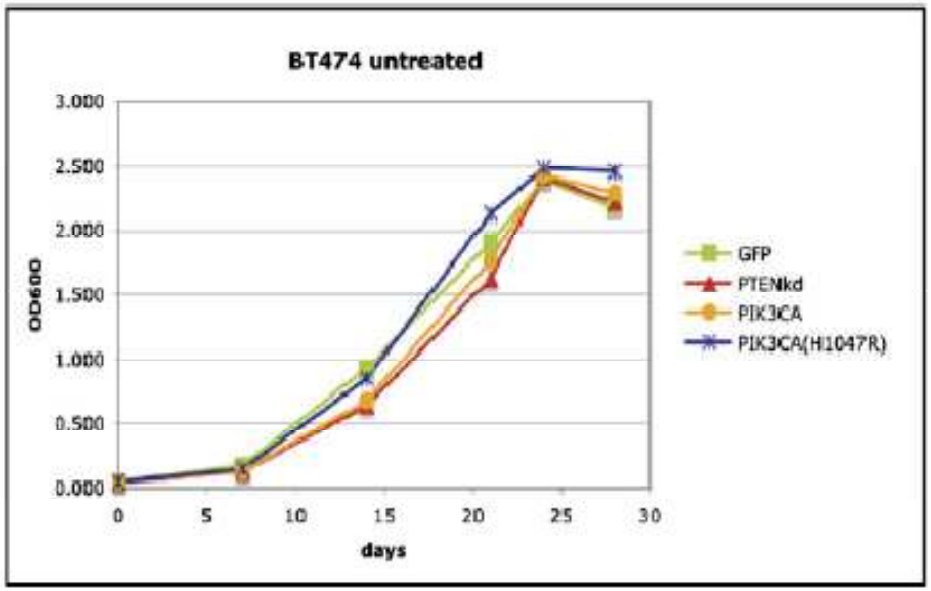

d
Parent population
Condition A
(for example,
control siRNA)
Condition B
(for example,
test siRNA)
Extract DNA
PCR barcodes
Hybridize to
microarray

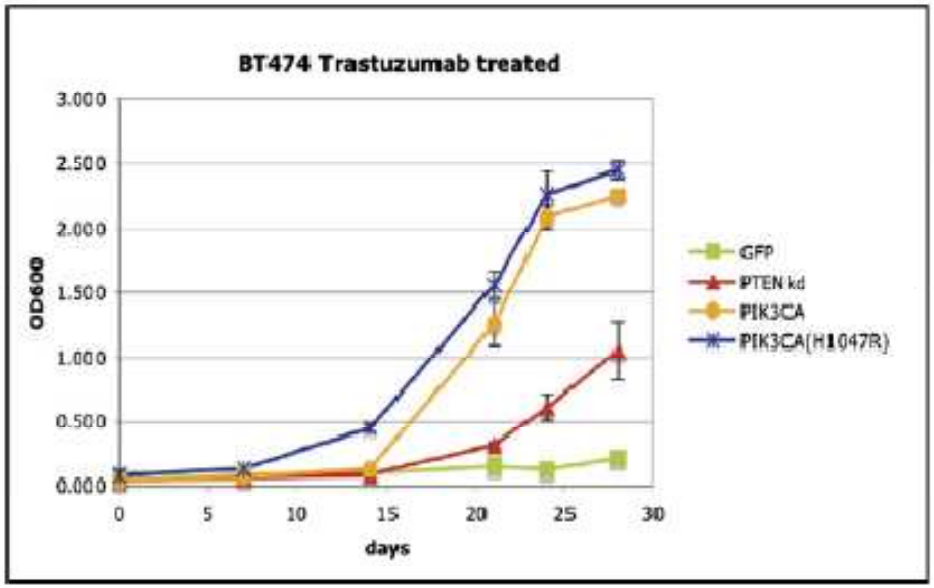

BT474 cells
infect with shRNA library
control
10 µg/ml Trastuzumab
select for
4 weeks in culture
isolate genomic DNA;
recover, amplify and
label shRNA cassettes

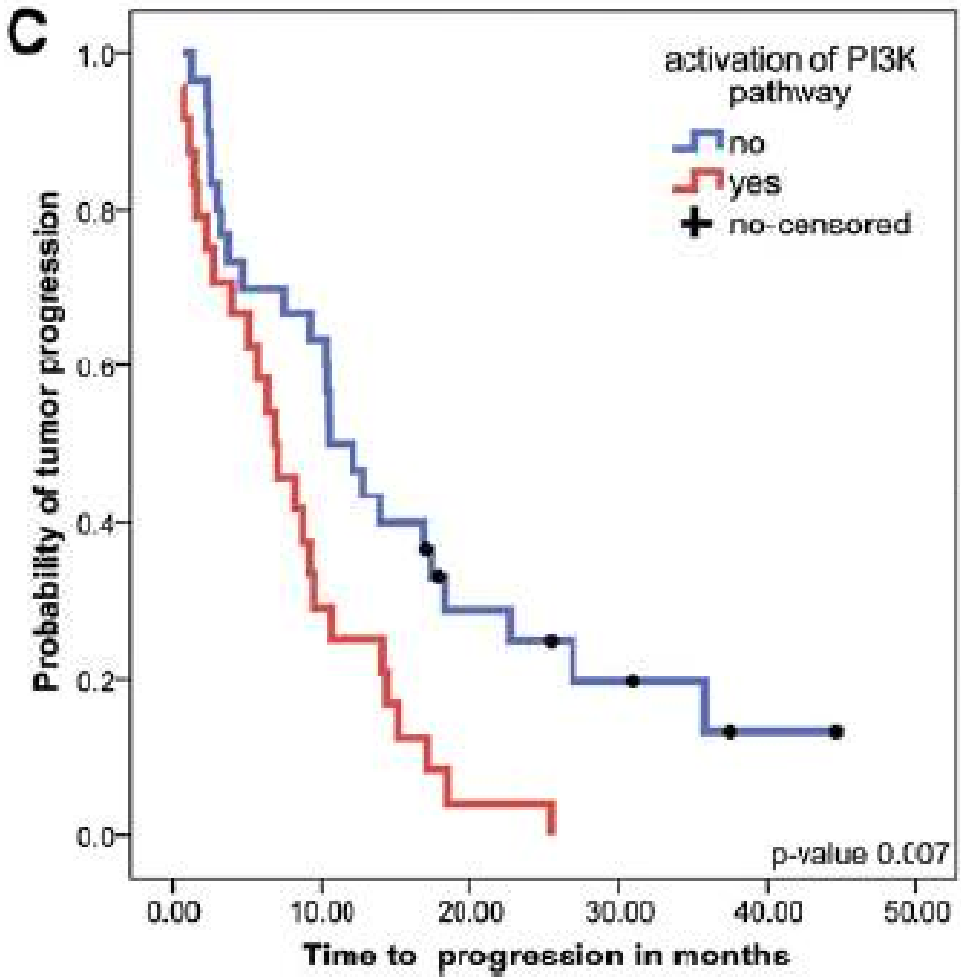
C


PTEN
10
5
0
−5
−10
0
5
10
15

PTEN loss or PIK3CA activation confers resistance to trastuzumab






C
activation of PI3K pathway
no
yes
no-censored
Probability of tumor progression
1.0
0.8
0.6
0.4
0.2
0.0
p-value 0.007
0.00
10.00
20.00
30.00
40.00
50.00
Time to progression in months

Cancer Cell
Article

Identification of CDK10 as an Important Determinant of Resistance to Endocrine Therapy for Breast Cancer

Elizabeth Iorns,[1] Nicholas C. Turner,[1] Richard Elliott,[1] Nelofer Syed,[1] Ornella Garrone,[2] Milena Gasco,[2] Andrew N.J. Tutt,[1,3] Tim Crook,[1] Christopher J. Lord,[1,*] and Alan Ashworth[1,*]
[1]The Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research, Fulham Road, London SW3 6JB, UK
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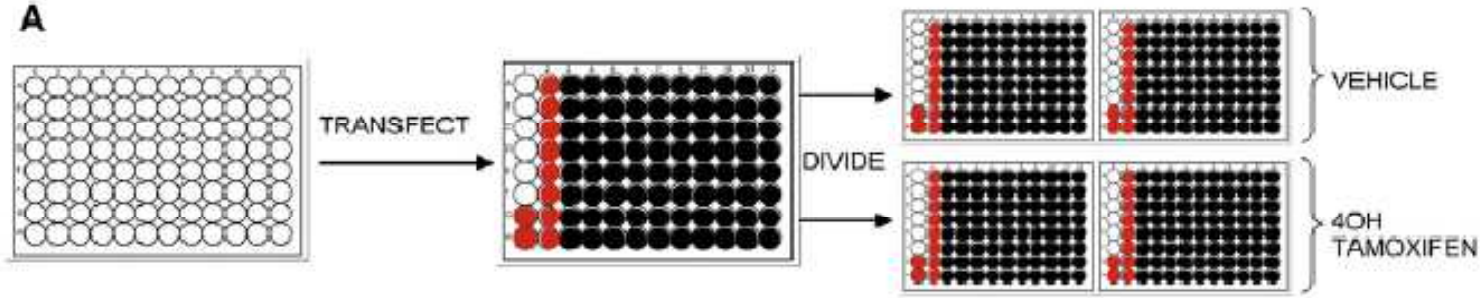
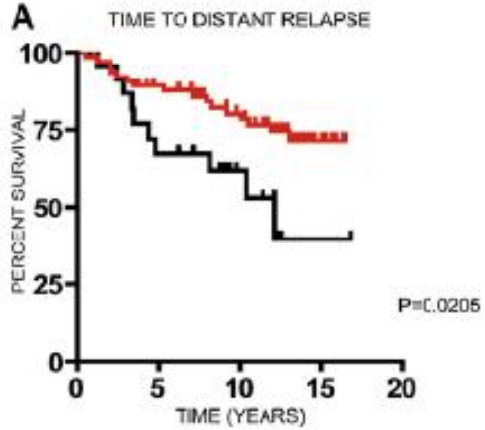
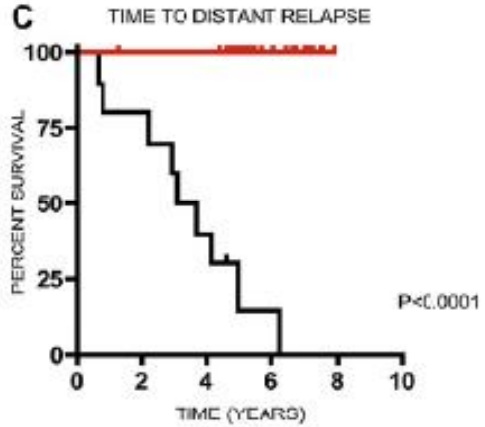
*Correspondence: chris.lord@icr.ac.uk (C.J.L.), alan.ashworth@icr.ac.uk (A.A.)
DOI 10.1016/j.ccr.2008.01.001

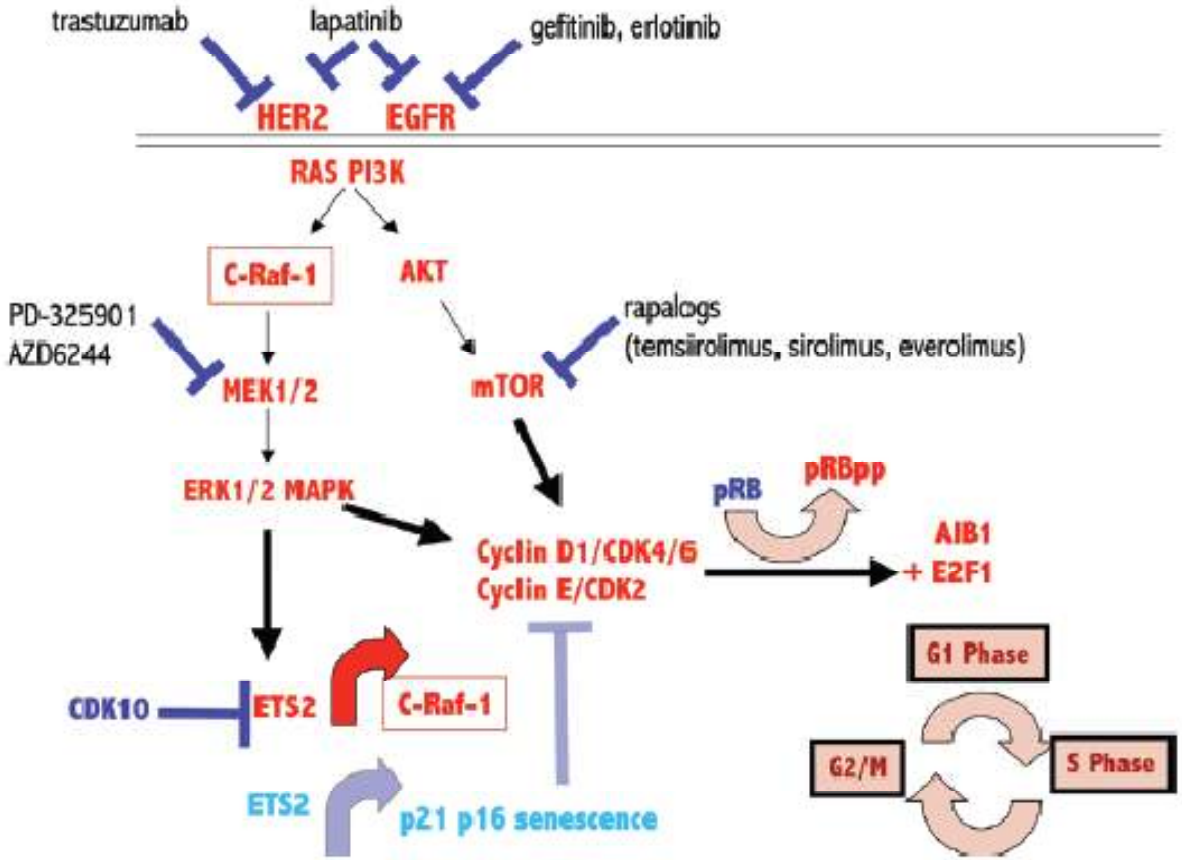

A
TRANSFECT
DIVIDE
VEHICLE
4OH
TAMOXIFEN


A
TIME TO DISTANT RELAPSE
PERCENT SURVIVAL
100
75
50
25
0
0
5
10
15
20
TIME (YEARS)
P=0.0205

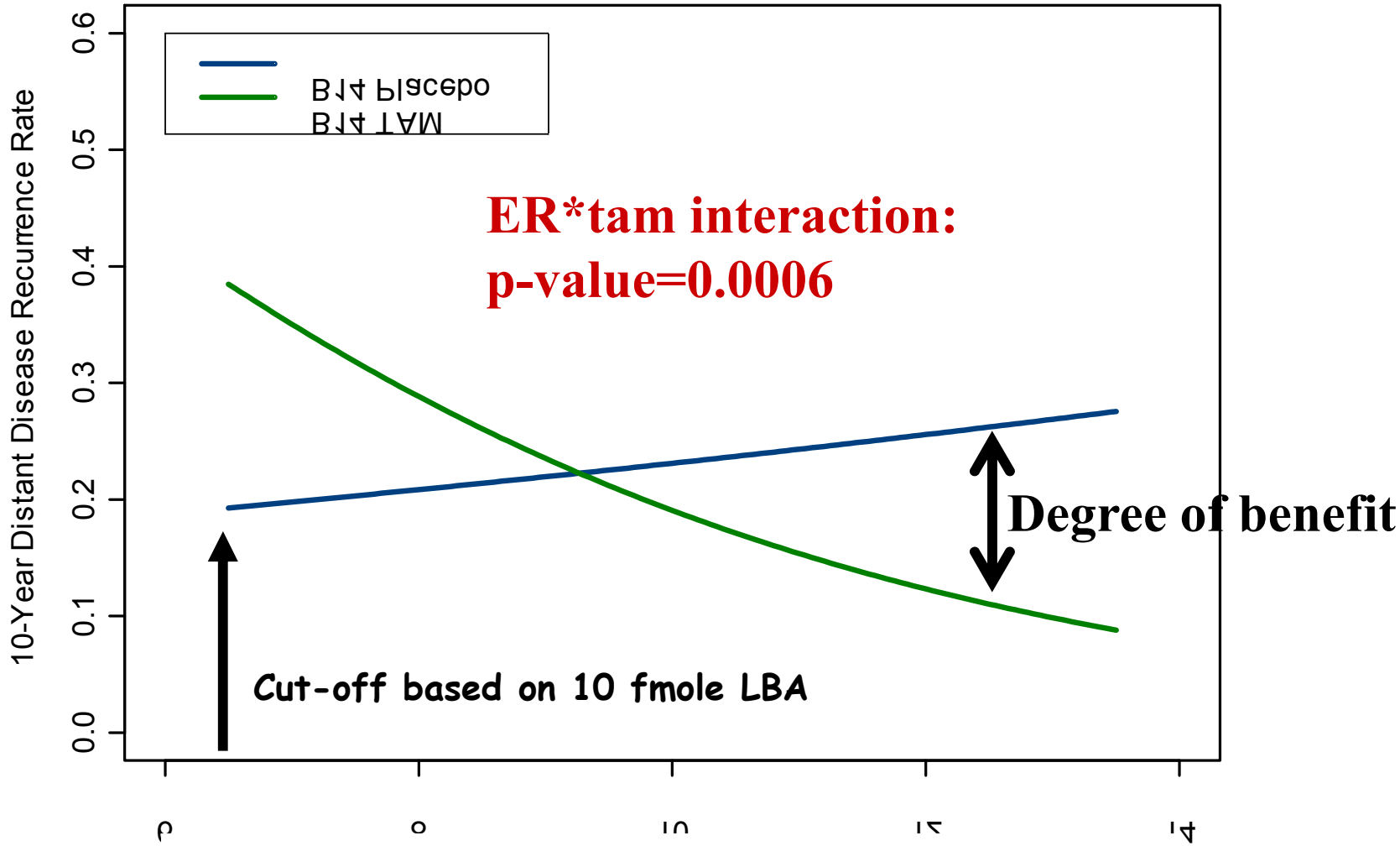

C
TIME TO DISTANT RELAPSE
PERCENT SURVIVAL
100
75
50
25
0
0
2
4
6
8
10
TIME (YEARS)
P<0.0001

Unraveling the Complexity of Endocrine Resistance in Breast Cancer by Functional Genomics

Charles Swanton[1,2,*] and Julian Downward[1,*]
[1]Cancer Research UK London Research Institute, Signal Transduction Laboratory, 44 Lincoln's Inn Fields, London WC2A 3PX, UK
[2]Royal Marsden Hospital, Department of Medicine, Fulham Road, London SW3 6JJ, UK
*Correspondence: swanton@cancer.org.uk (C.S.); downward@cancer.org.uk (J.D.)
DOI 10.1016/j.ccr.2008.01.021

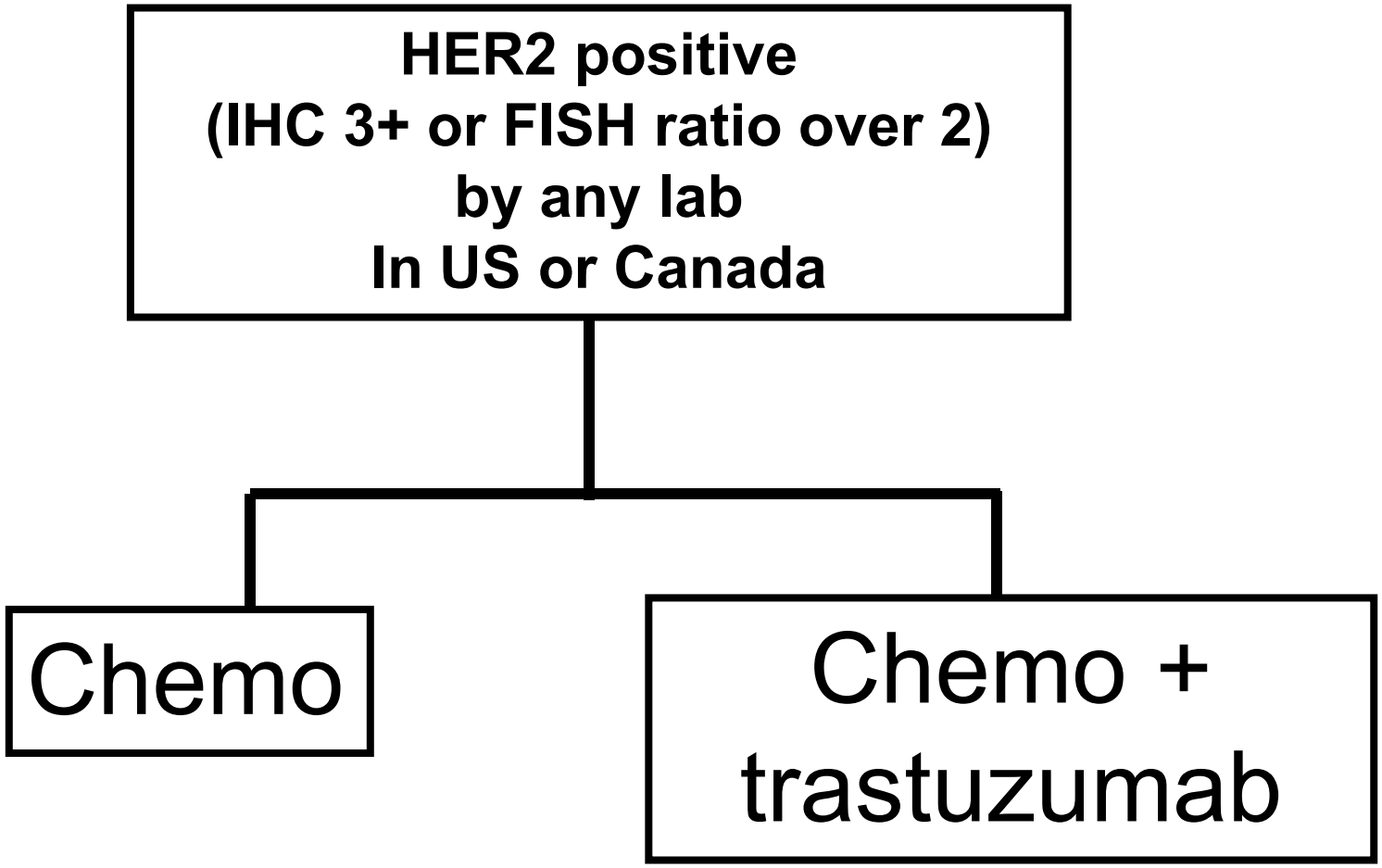


Association of Quantitative ER Expression by QRT-PCR and Tamoxifen Benefit

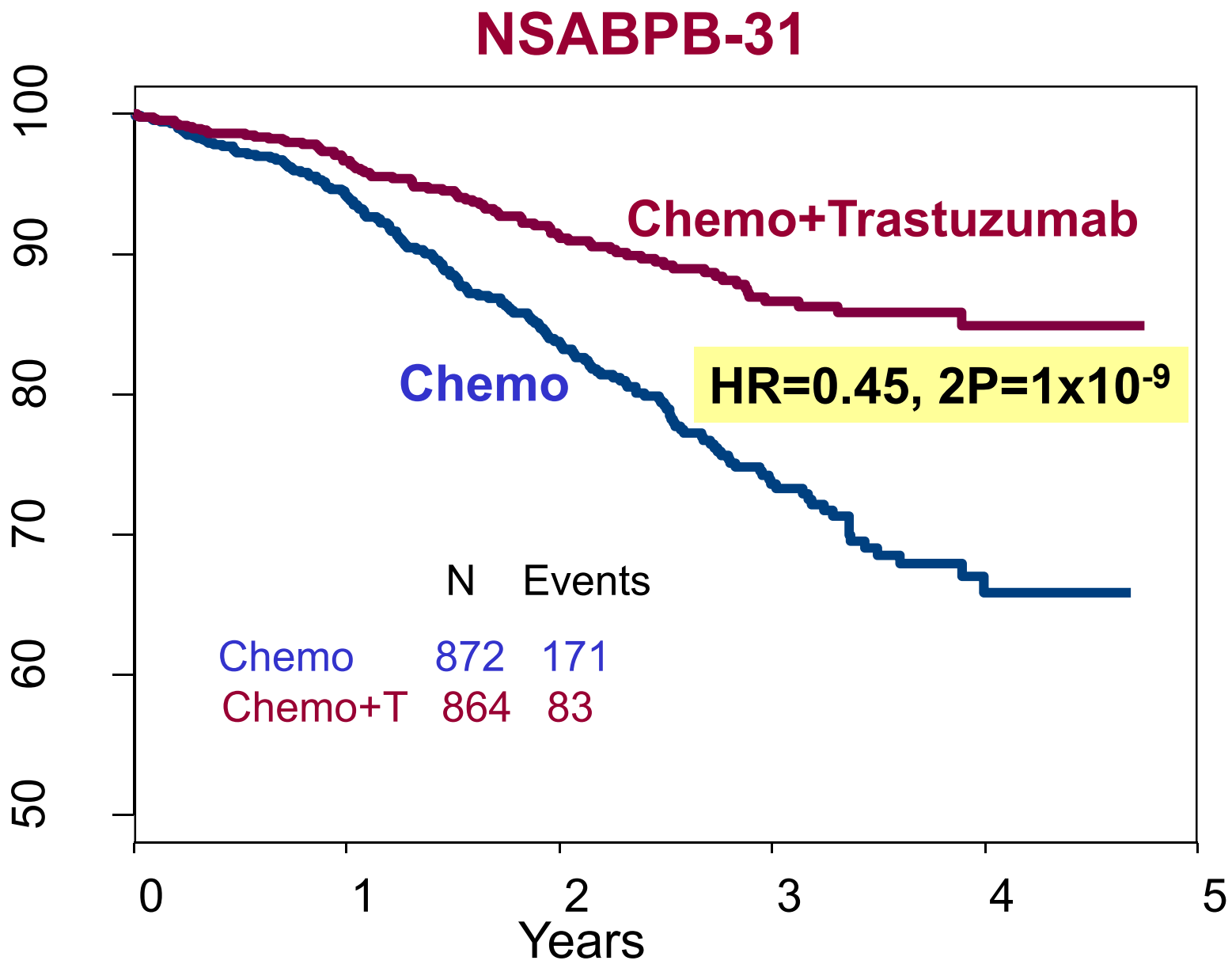


Role of DTC in adjuvant setting

NSABP B31


HER2 positive
(IHC 3+ or FISH ratio over 2)
by any lab
In US or Canada
Chemo
Chemo +
trastuzumab

Impact of adjuvant trastuzumab on Disease-Free Survival

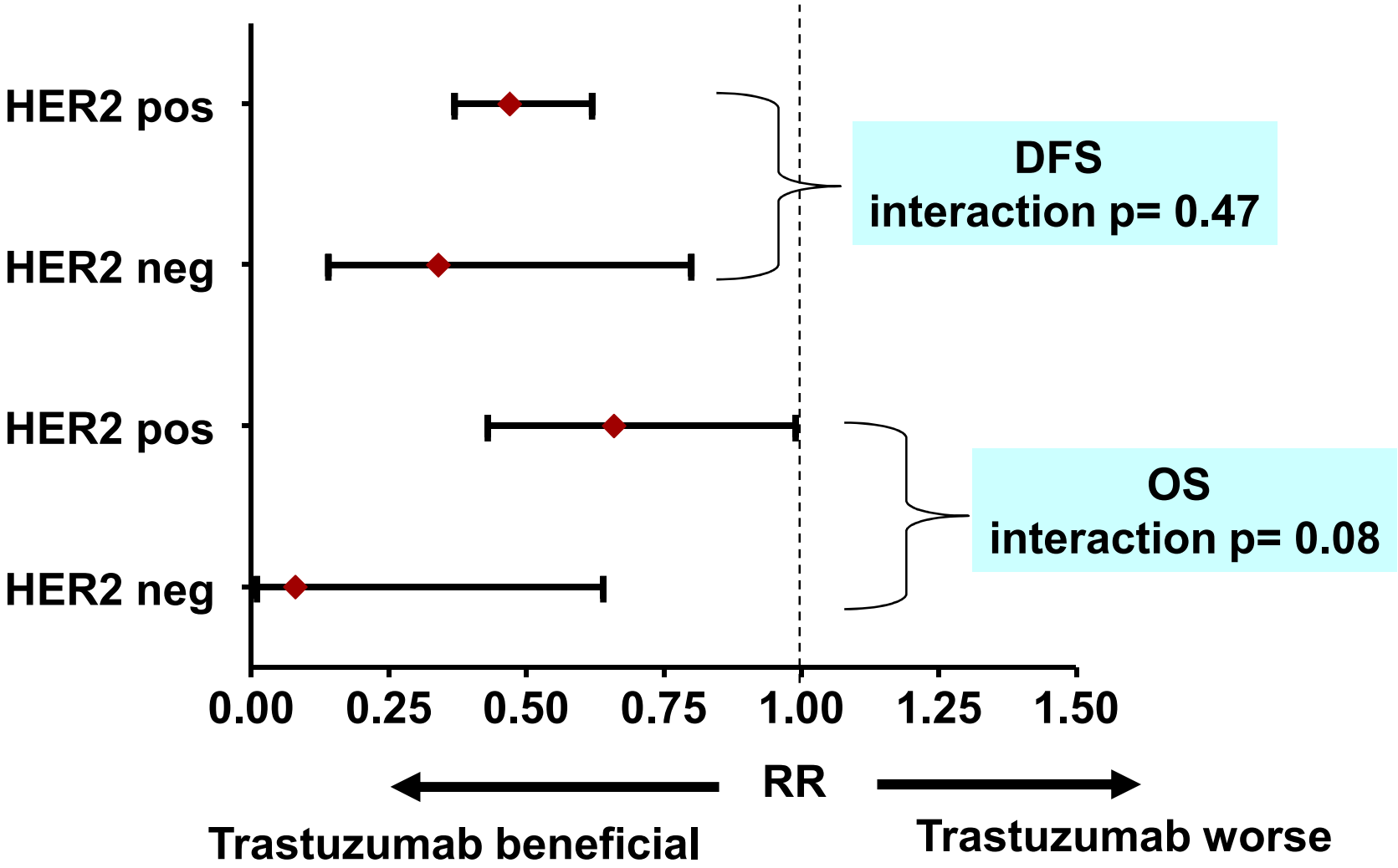


B-31, distribution of cases according to central HER2 assay

	IHC=0	IHC=1	IHC=2	IHC=3	unk
FISH-	25	87	62	31	2
FISH+	9	32	84	1457	6

"Central assay negative"

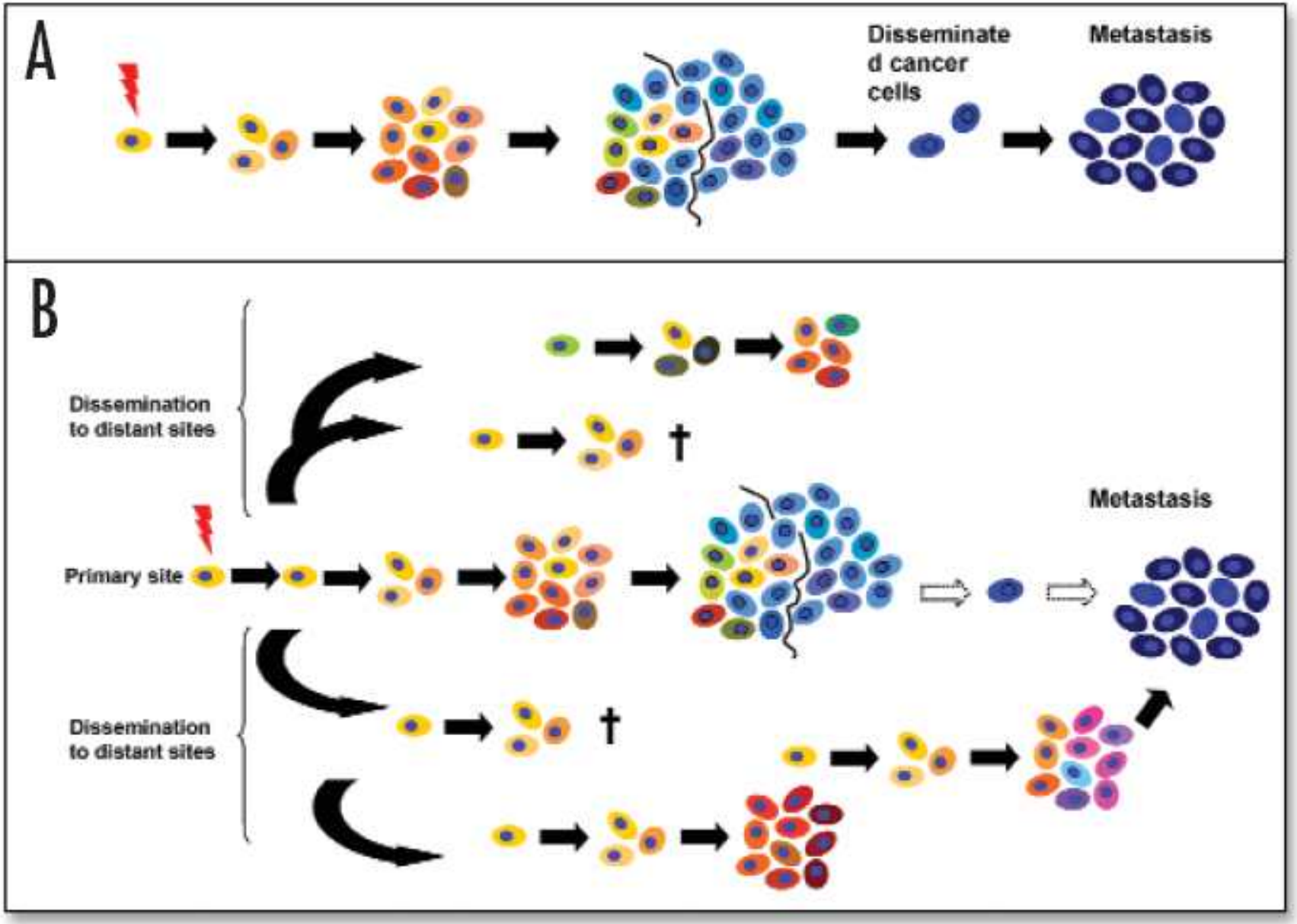
NSABP B31
(Paik et al, NEJM 2009)



Schardt JA, Meyer M, Hartmann CH et al, Cancer Cell, 8:227-239 (2005)

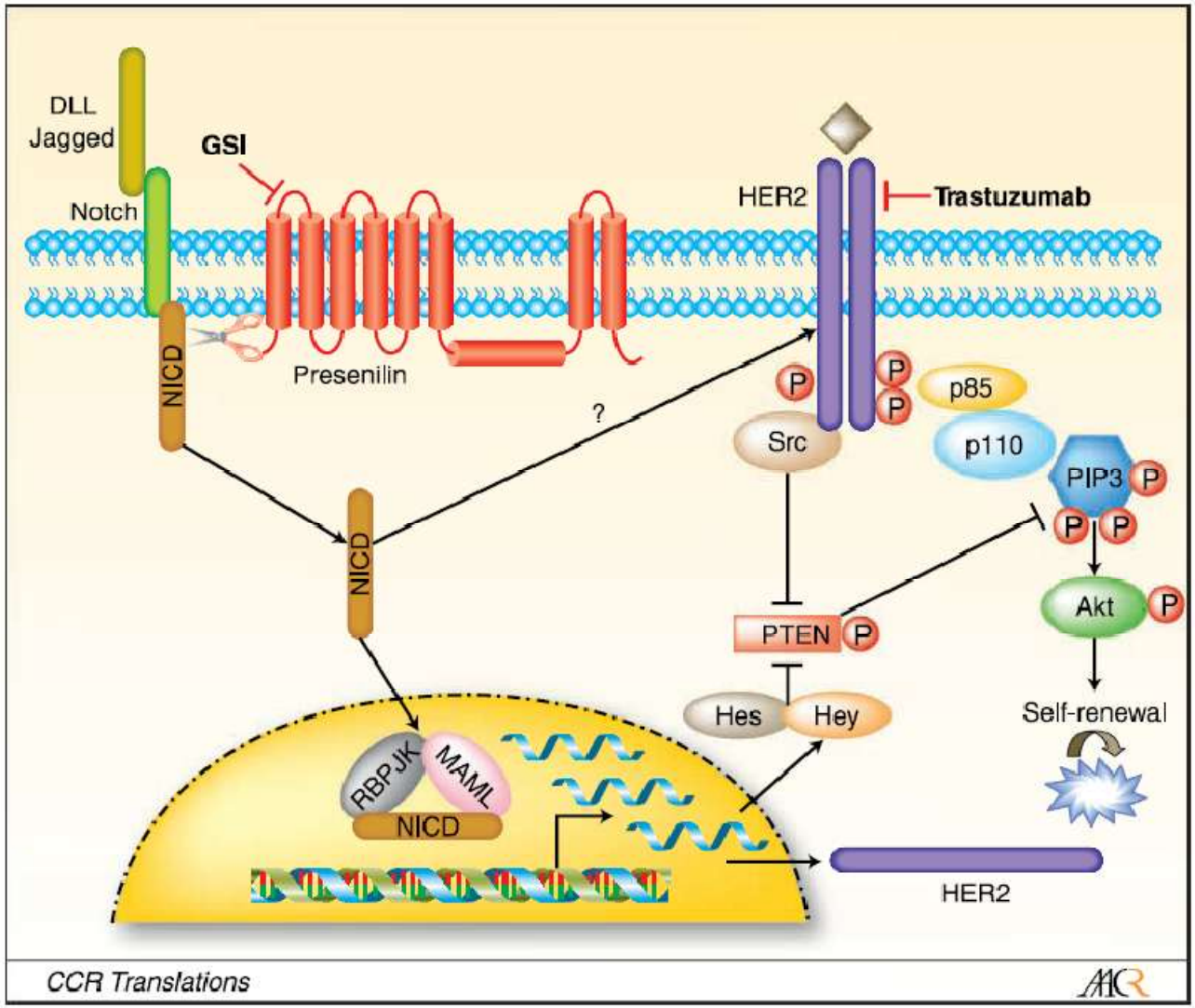
	Primary tumor IHC 3+	Primary tumor IHC<3+
DTC HER2 amplified	1	5
DTC HER2 not-amplifed	10	11

Klein CA, Cell Cycle 3:29-31, 2004

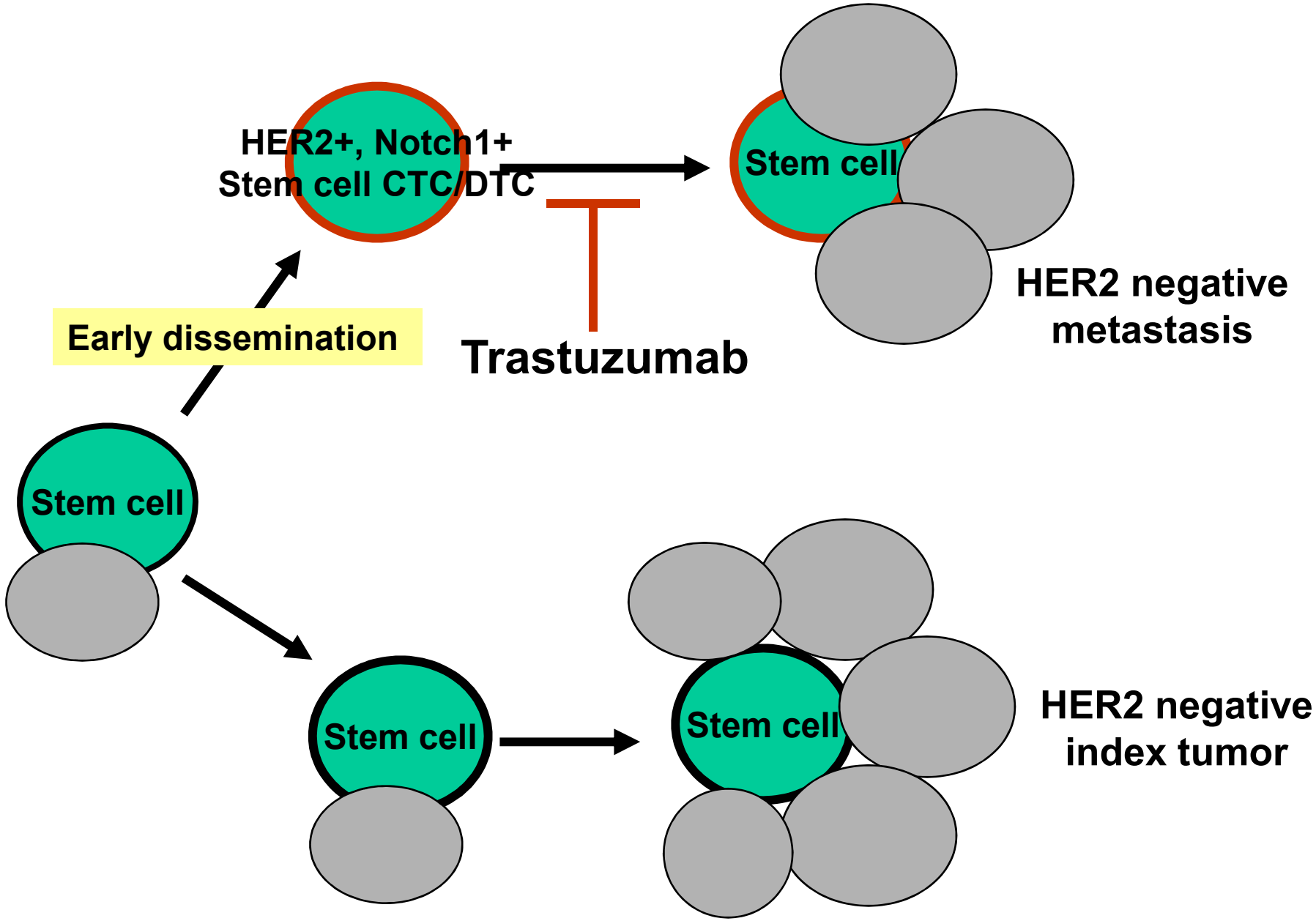


HER2, Notch, and Breast Cancer Stem Cells – Targeting the Axis of Evil

Korkaya and Wicha, CCR 2009



CTC/DTC/Stem Cell hypothesis

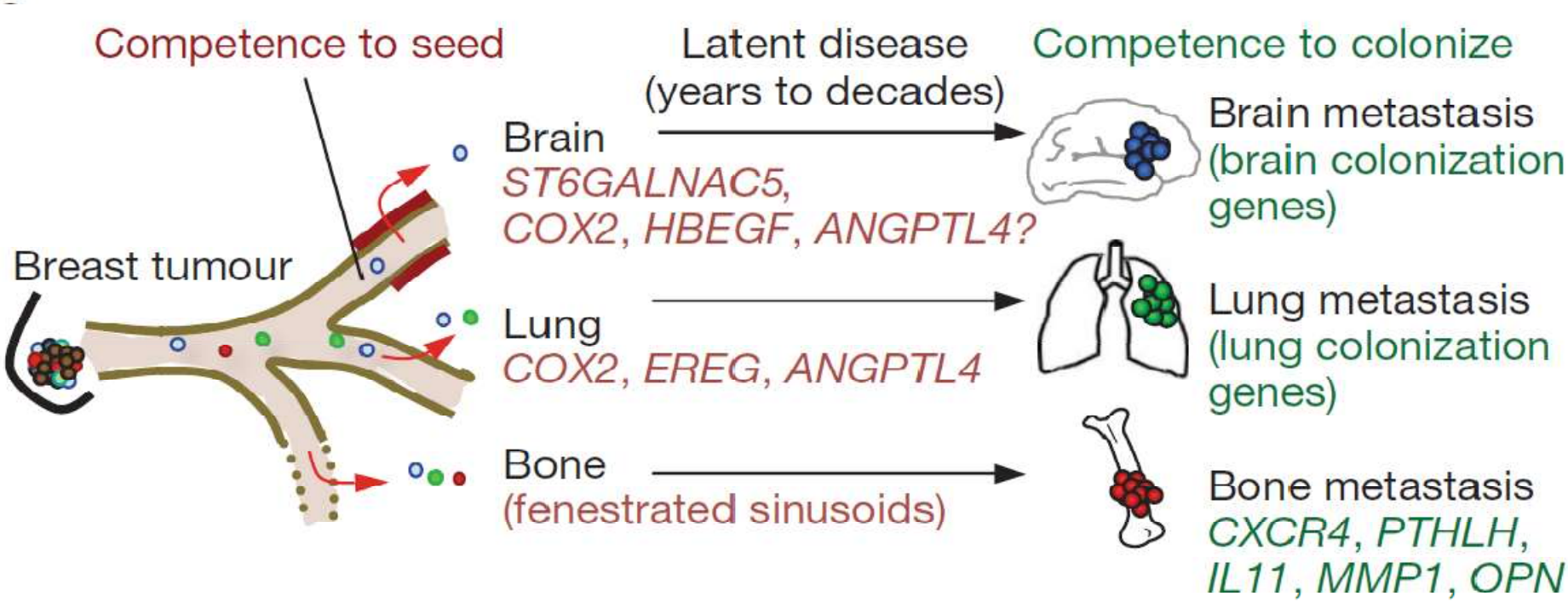


Potential problems of marker development in neoadjuvant setting

Metastatic & Neoadjuvant setting	**Adjuvant setting**
Direct effect on tumor burden	**Many confounding variables** – Bulk disease removed – **Stem cells?** – Base-line risk – Legacy treatment (tamoxifen, chemotherapy) – DTC

Organ specific metastases

(Joan Massagué lab at MSKCC)



Zhang XH et al. Latent bone metastasis in breast cancer tied to Src-dependent survival signals. Cancer Cell 2009;16:67-78.
Padua D et al. TGFbeta primes breast tumors for lung metastasis seeding through angiopoietin-like 4. Cell 2008;133:66-77
Bos PD et al. Genes that mediate breast cancer metastasis to the brain. Nature 2009;459:1005-9.
Korpal M, et al. Imaging transforming growth factor-beta signaling dynamics and therapeutic response in breast cancer bone metastasis. Nat Med 2009;15:960-6.

Vol 459|18 June 2009|doi:10.1038/nature08021 nature

LETTERS

Genes that mediate breast cancer metastasis to the brain

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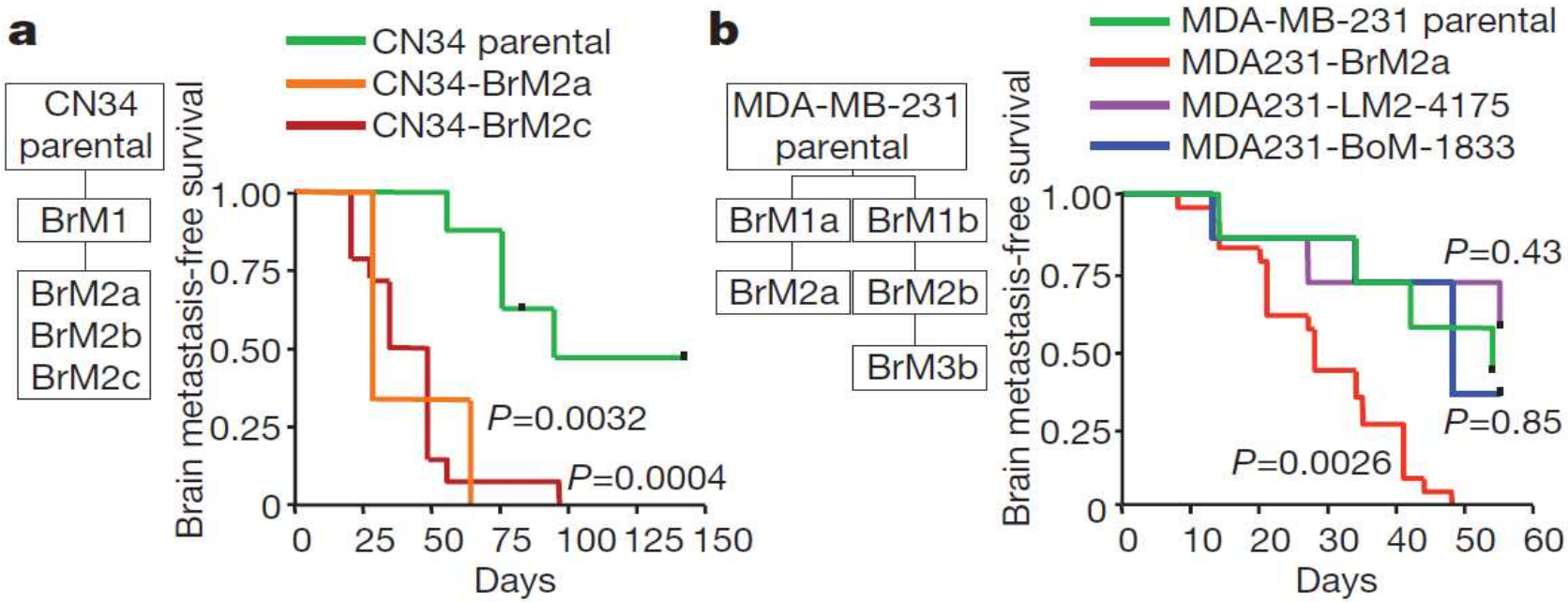
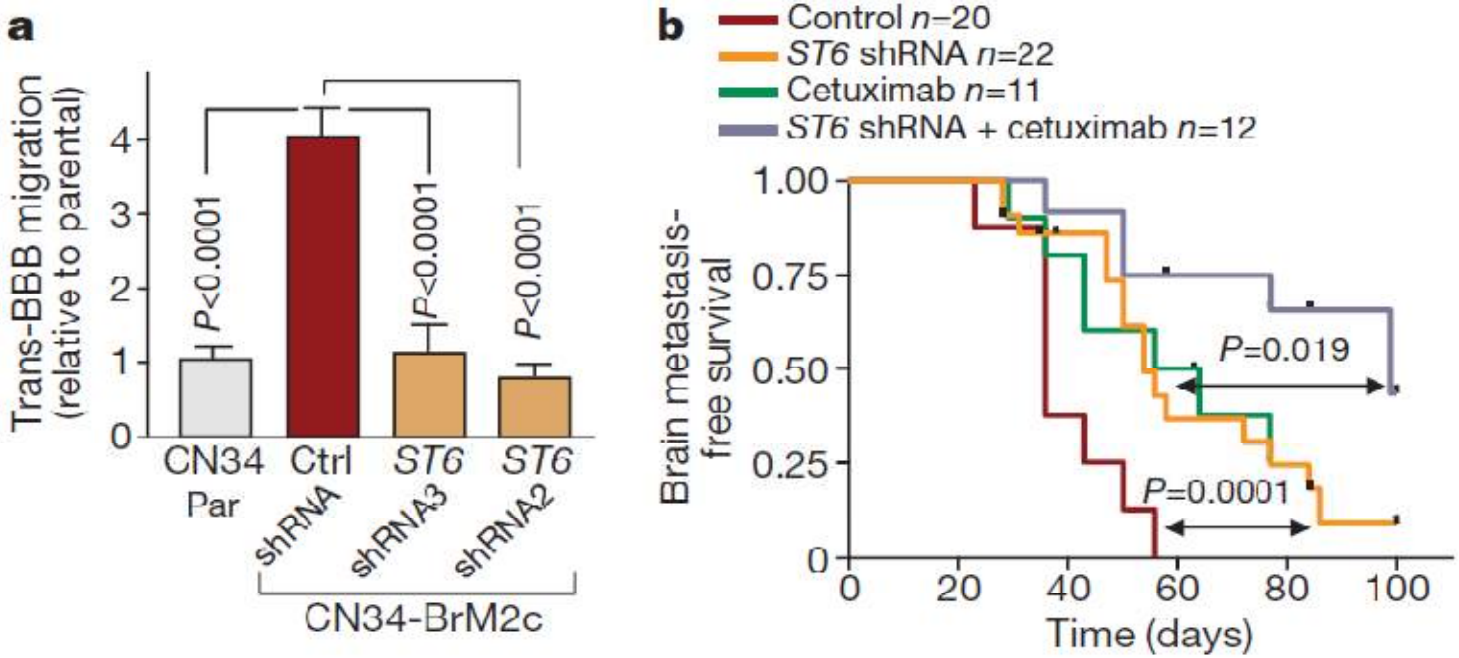

a
CN34 parental
BrM1
BrM2a
BrM2b
BrM2c
CN34 parental
CN34-BrM2a
CN34-BrM2c
Brain metastasis-free survival
1.00
0.75
0.50
0.25
0
P=0.0032
P=0.0004
0 25 50 75 100 125 150
Days
b
MDA-MB-231 parental
BrM1a
BrM1b
BrM2a
BrM2b
BrM3b
MDA-MB-231 parental
MDA231-BrM2a
MDA231-LM2-4175
MDA231-BoM-1833
Brain metastasis-free survival
1.00
0.75
0.50
0.25
0
P=0.43
P=0.85
P=0.0026
0 10 20 30 40 50 60
Days


a
Trans-BBB migration (relative to parental)
0
1
2
3
4
P<0.0001
P<0.0001
P<0.0001
CN34 Par
Ctrl shRNA
ST6 shRNA3
ST6 shRNA2
CN34-BrM2c
b
Control n=20
ST6 shRNA n=22
Cetuximab n=11
ST6 shRNA + cetuximab n=12
Brain metastasis-free survival
1.00
0.75
0.50
0.25
0
P=0.019
P=0.0001
0
20
40
60
80
100
Time (days)

Cell

TGFβ Primes Breast Tumors for Lung Metastasis Seeding through Angiopoietin-like 4

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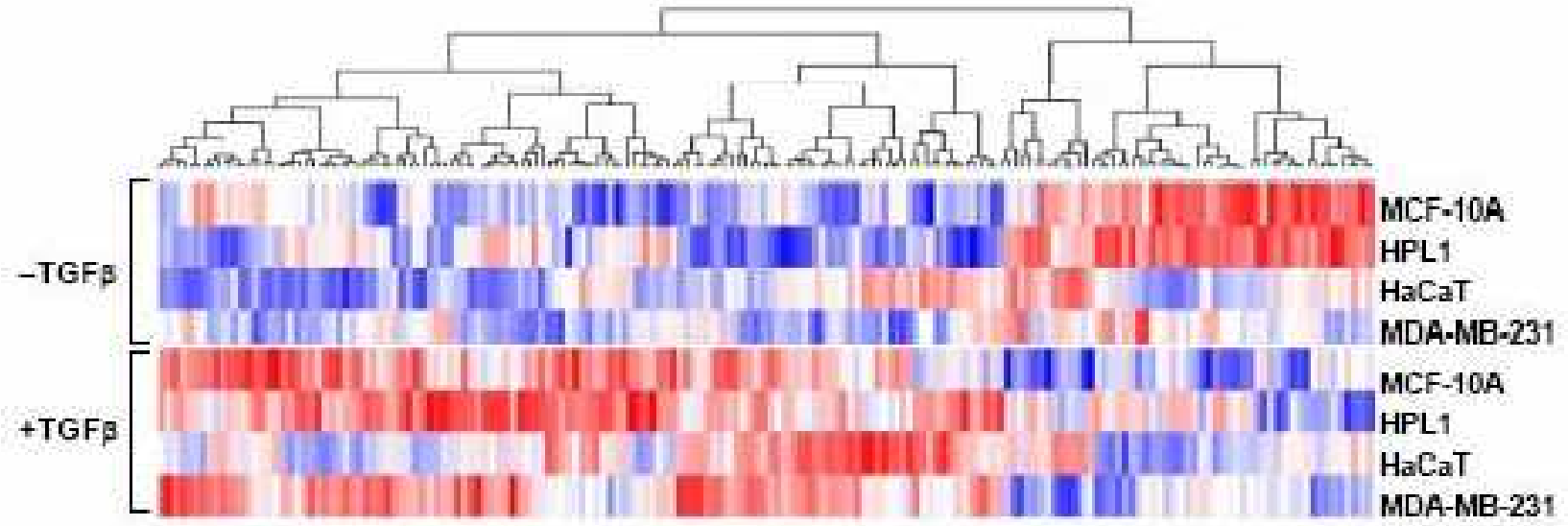
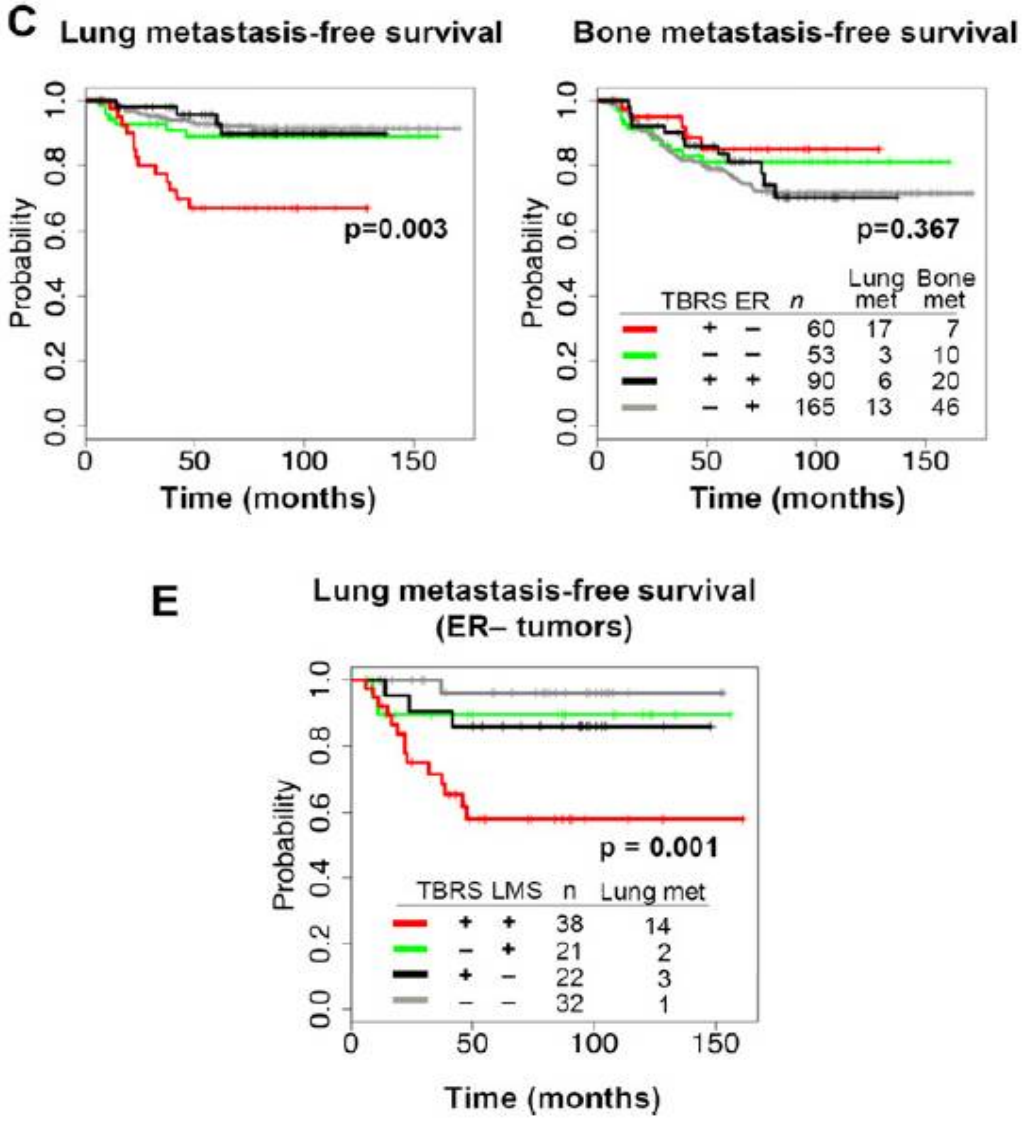
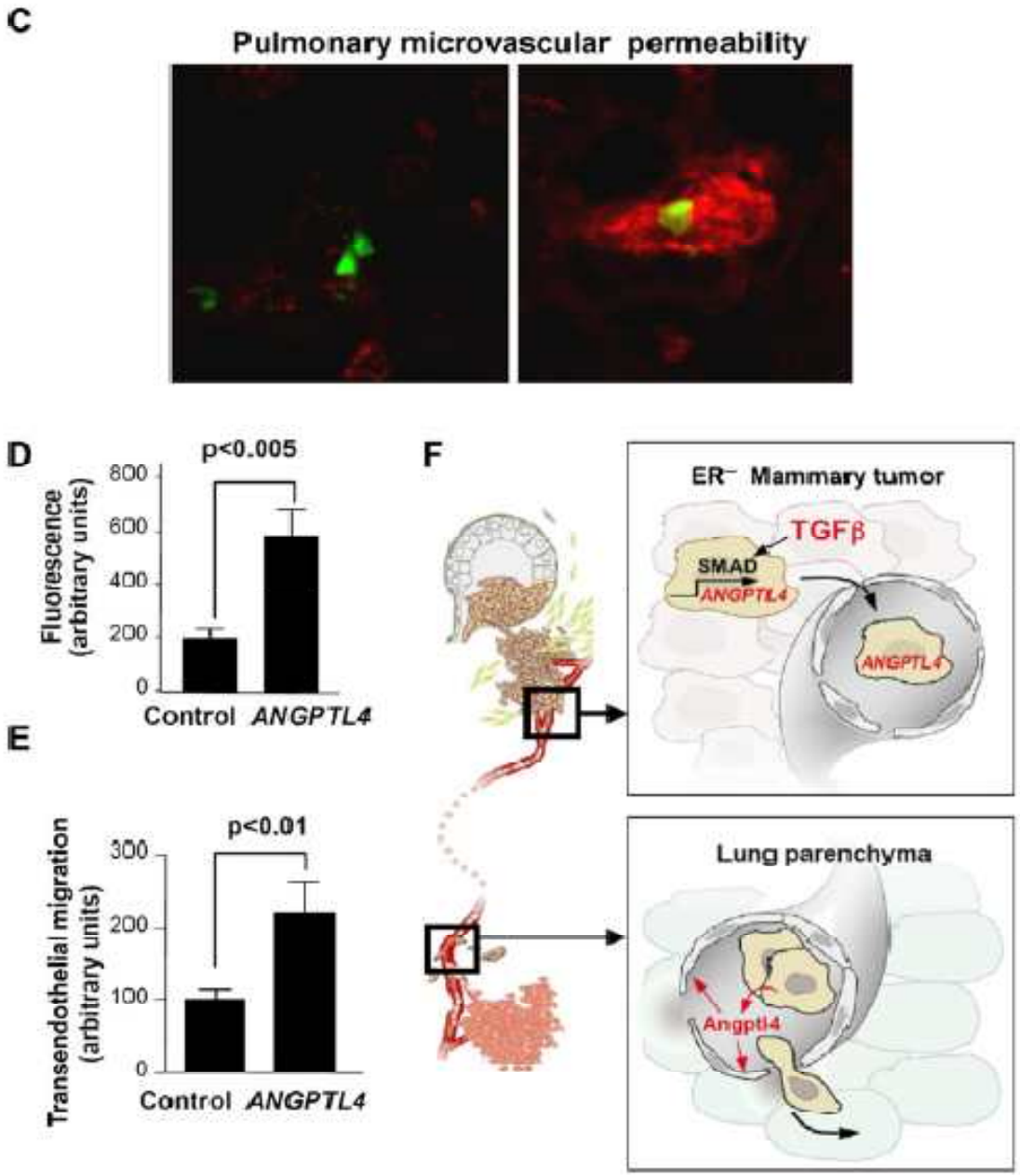

−TGFβ
+TGFβ
MCF-10A
HPL1
HaCaT
MDA-MB-231
MCF-10A
HPL1
HaCaT
MDA-MB-231


C
Lung metastasis-free survival
Bone metastasis-free survival
Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
Time (months)
p=0.003
p=0.367
TBRS ER n Lung met Bone met
+ – 60 17 7
– – 53 3 10
+ + 90 6 20
– + 165 13 46
E
Lung metastasis-free survival
(ER– tumors)
p = 0.001
TBRS LMS n Lung met
+ + 38 14
– + 21 2
+ – 22 3
– – 32 1


C
Pulmonary microvascular permeability
D
p<0.005
Fluorescence (arbitrary units)
800
600
400
200
0
Control
ANGPTL4
E
p<0.01
Transendothelial migration (arbitrary units)
300
200
100
0
Control
ANGPTL4
F
ER⁻ Mammary tumor
TGFβ
SMAD
ANGPTL4
ANGPTL4
Lung parenchyma
Angptl4

Cancer Cell
Article

Latent Bone Metastasis in Breast Cancer Tied to Src-Dependent Survival Signals

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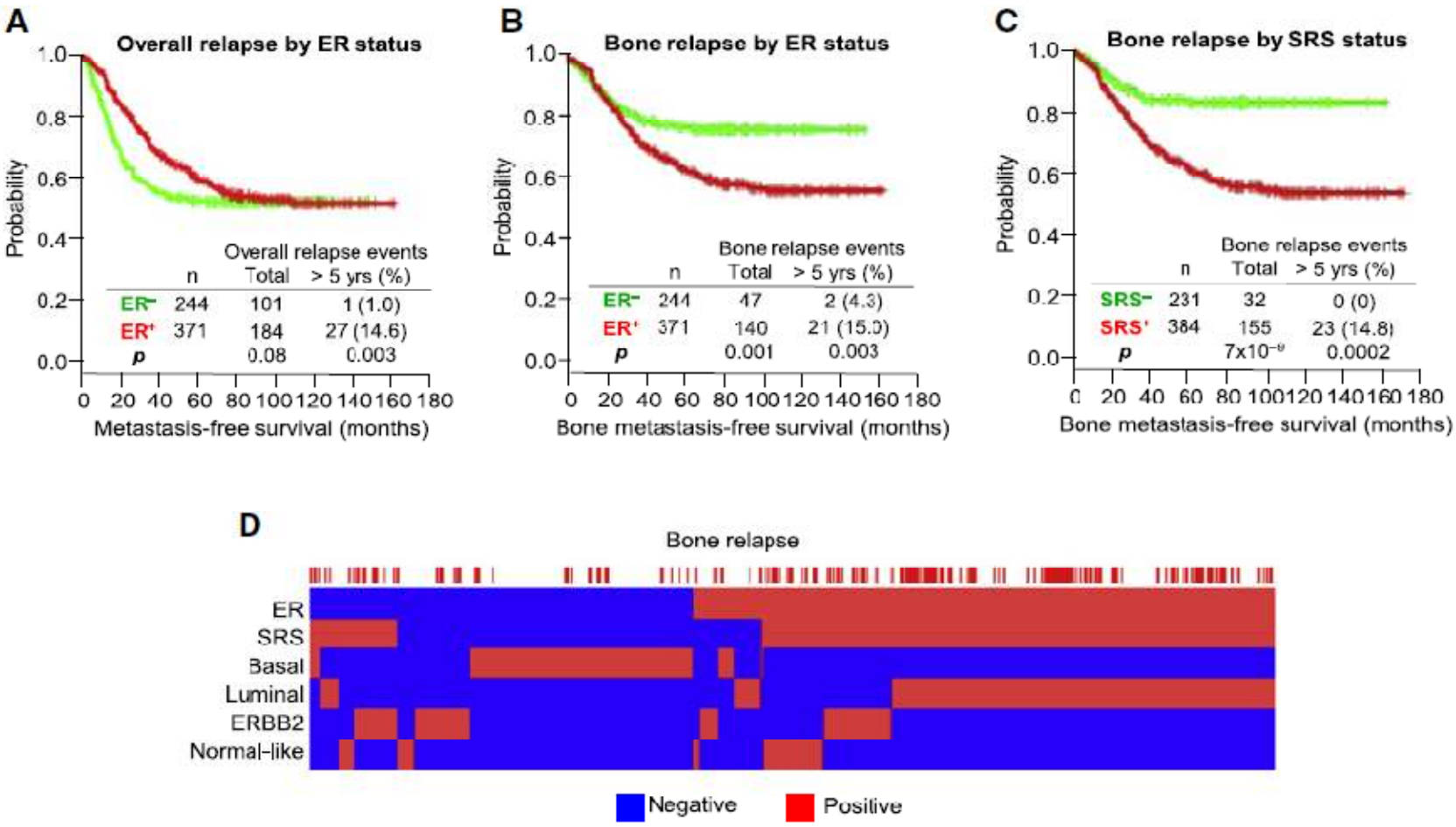
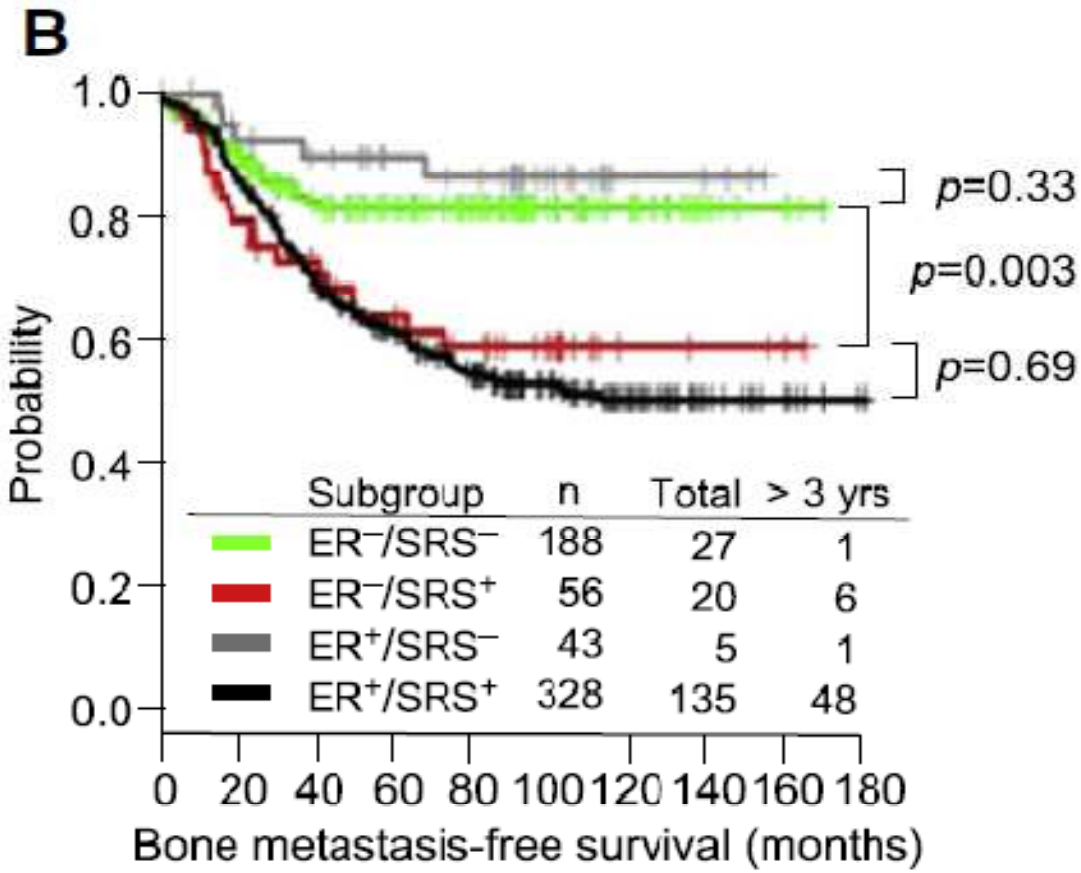
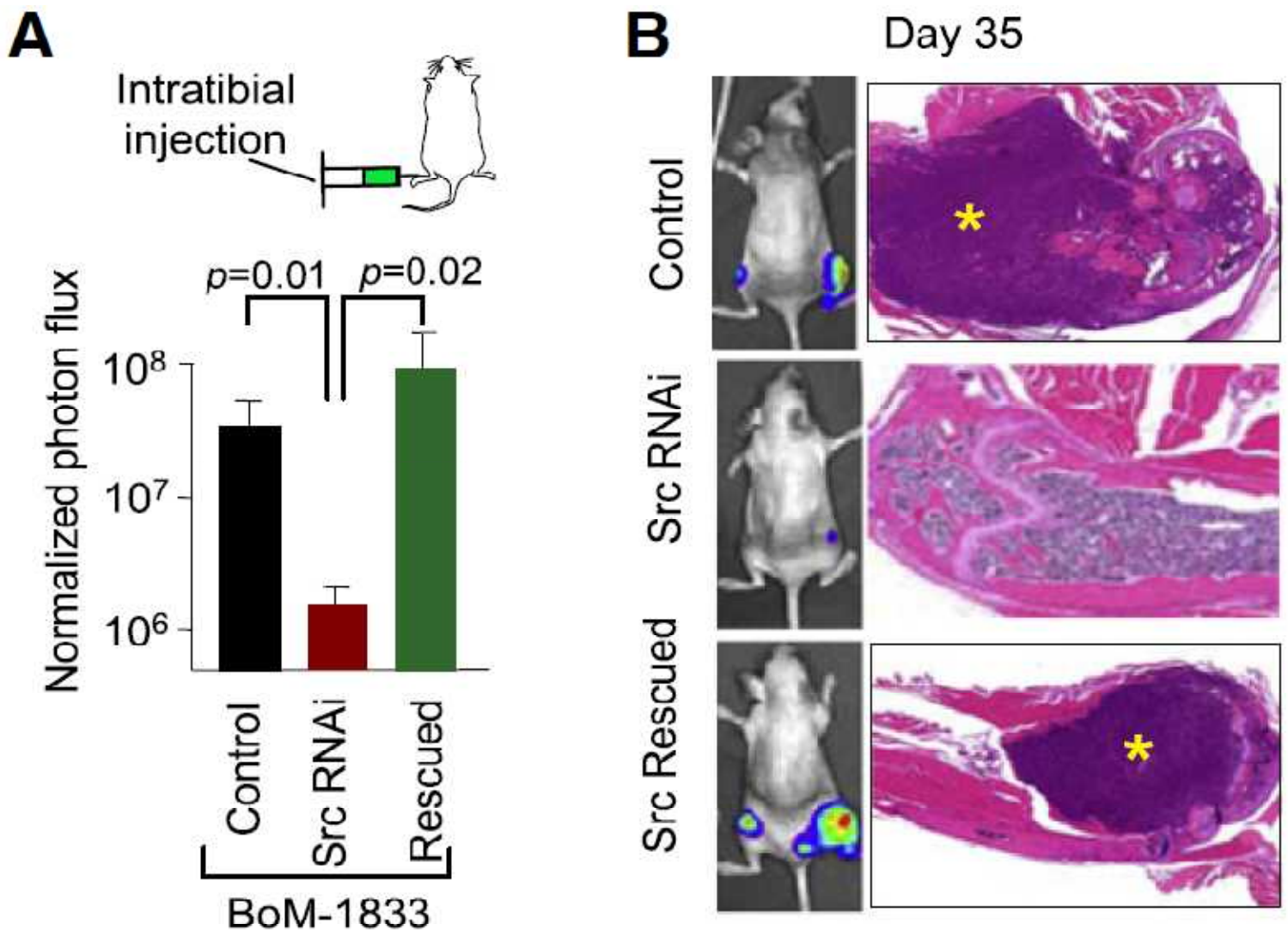
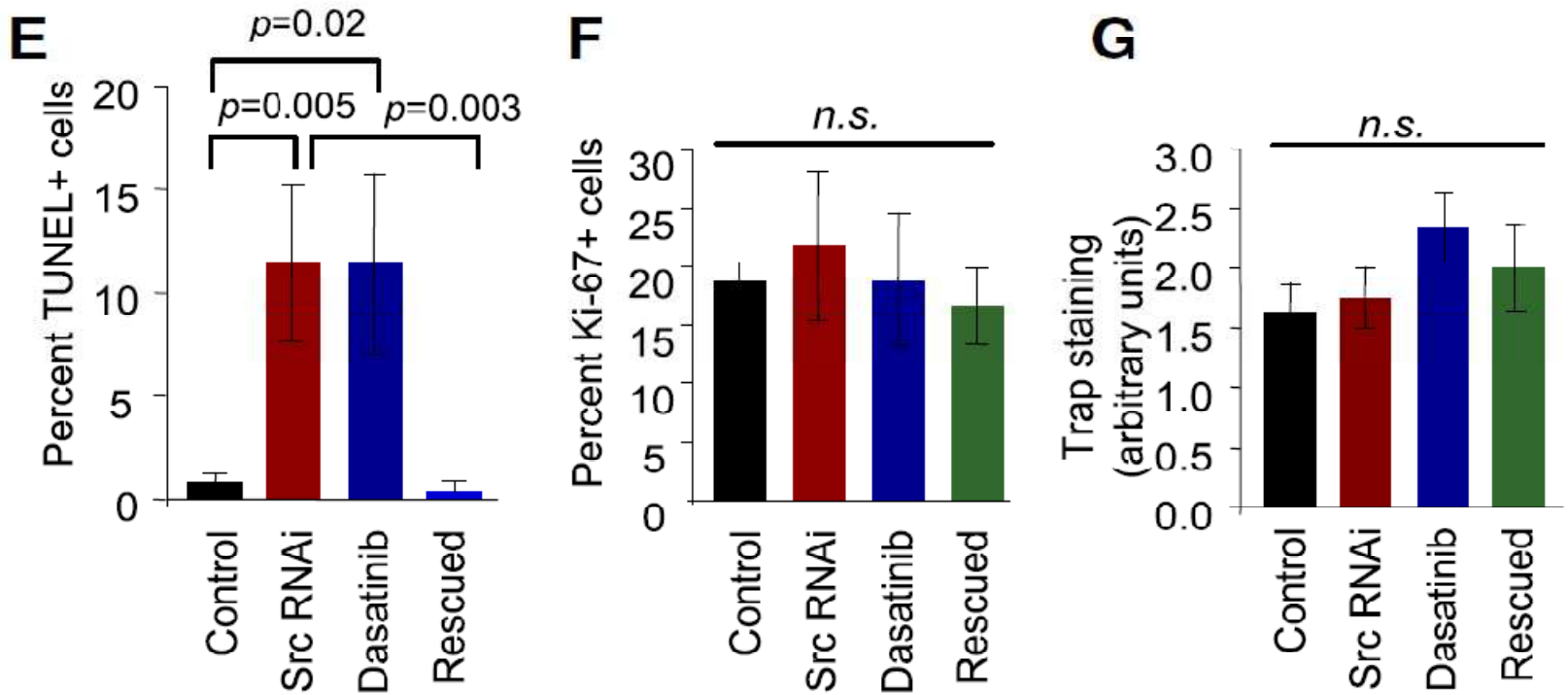
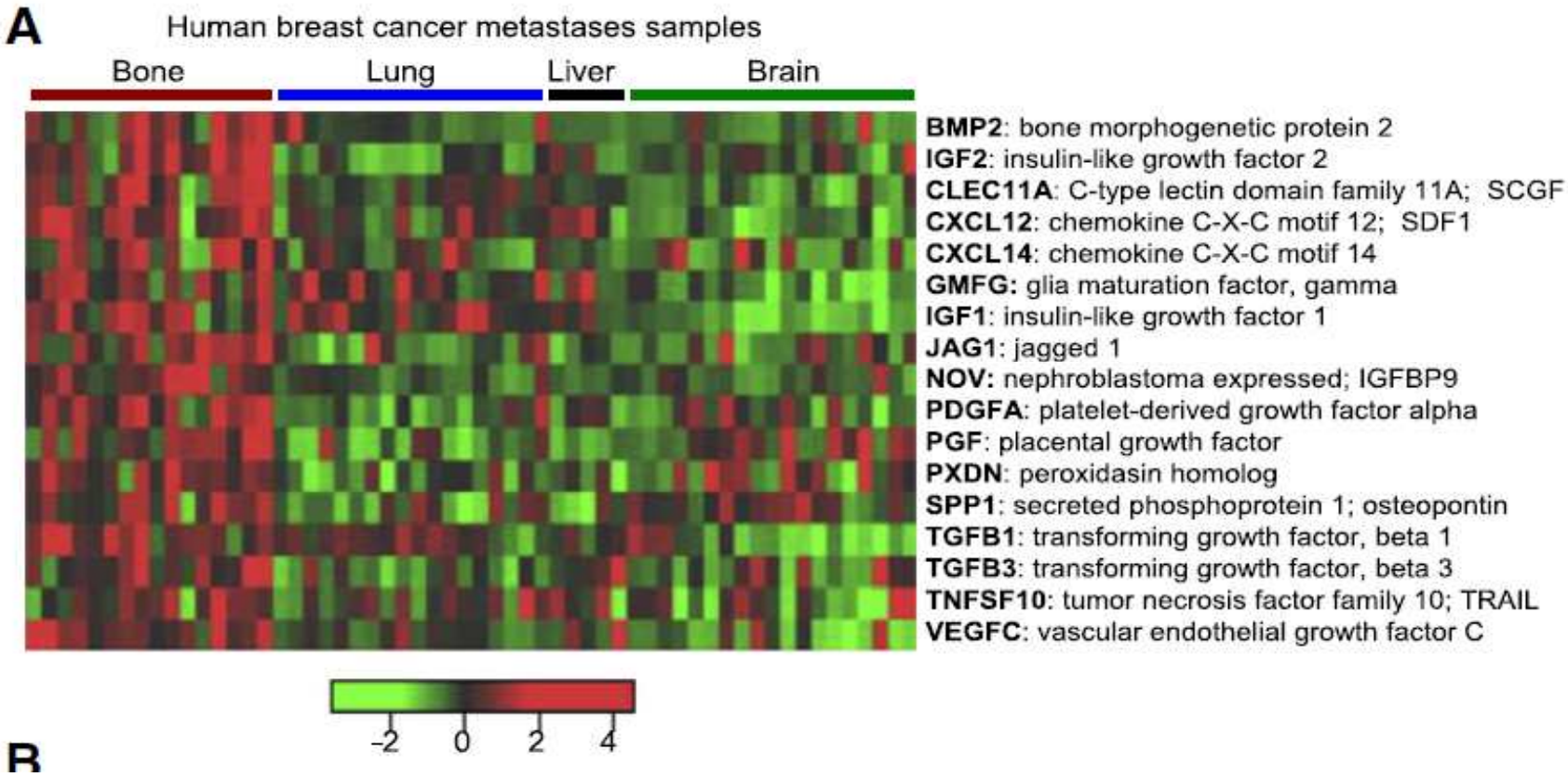
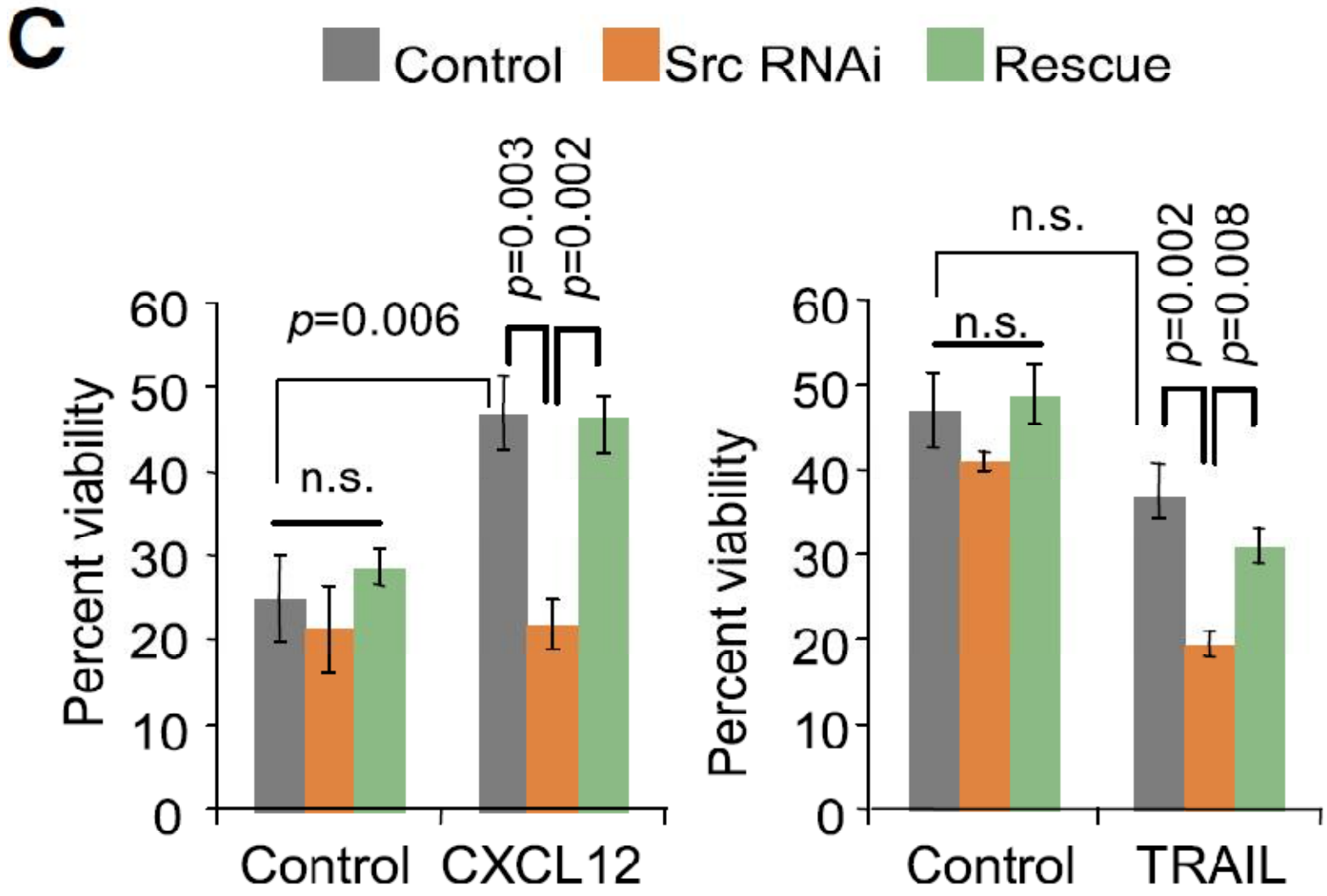

A
Overall relapse by ER status
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0 20 40 60 80 100 120 140 160 180
Metastasis-free survival (months)
Overall relapse events
n Total > 5 yrs (%)
ER- 244 101 1 (1.0)
ER+ 371 184 27 (14.6)
p 0.08 0.003
B
Bone relapse by ER status
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0 20 40 60 80 100 120 140 160 180
Bone metastasis-free survival (months)
Bone relapse events
n Total > 5 yrs (%)
ER- 244 47 2 (4.3)
ER+ 371 140 21 (15.0)
p 0.001 0.003
C
Bone relapse by SRS status
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0 20 40 60 80 100 120 140 160 180
Bone metastasis-free survival (months)
Bone relapse events
n Total > 5 yrs (%)
SRS- 231 32 0 (0)
SRS+ 384 155 23 (14.8)
p 7x10-9 0.0002
D
Bone relapse
ER
SRS
Basal
Luminal
ERBB2
Normal-like
Negative
Positive

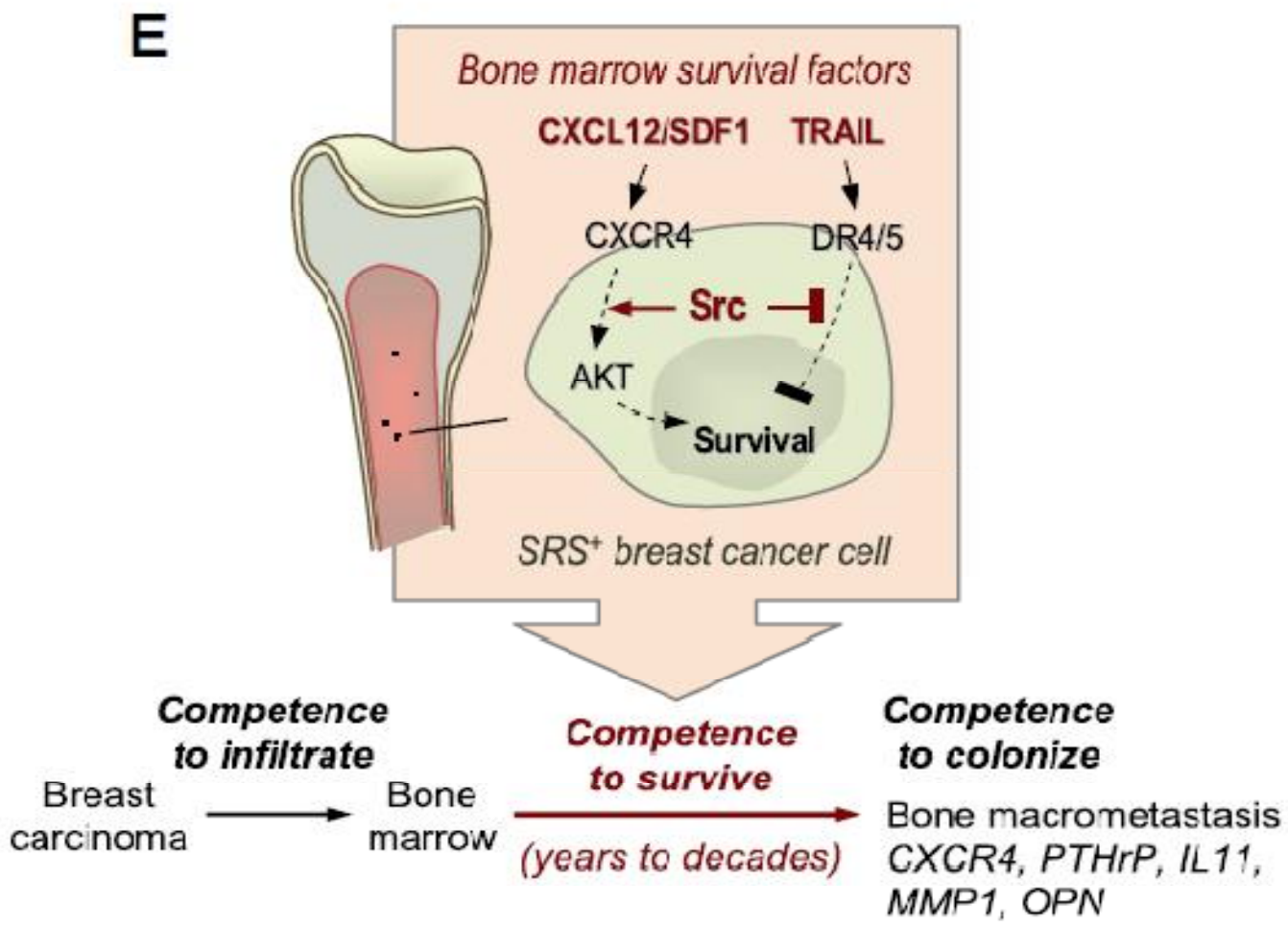

B
1.0
0.8
0.6
0.4
0.2
0.0
Probability
p=0.33
p=0.003
p=0.69
Subgroup n Total > 3 yrs
ER−/SRS− 188 27 1
ER−/SRS+ 56 20 6
ER+/SRS− 43 5 1
ER+/SRS+ 328 135 48
0 20 40 60 80 100 120 140 160 180
Bone metastasis-free survival (months)


A
Intratibial injection
p=0.01
p=0.02
Normalized photon flux
10^8
10^7
10^6
Control
Src RNAi
Rescued
BoM-1833
B
Day 35
Control
Src RNAi
Src Rescued

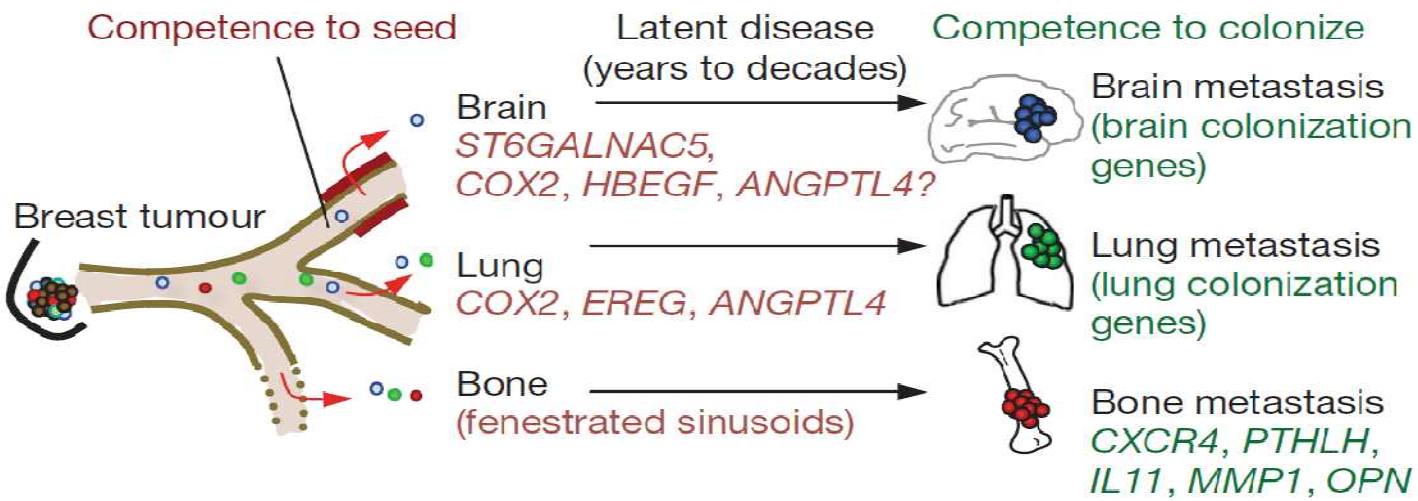

E
p=0.02
p=0.005
p=0.003
Percent TUNEL+ cells
20
15
10
5
0
Control
Src RNAi
Dasatinib
Rescued
F
n.s.
Percent Ki-67+ cells
30
25
20
15
10
5
0
Control
Src RNAi
Dasatinib
Rescued
G
n.s.
Trap staining (arbitrary units)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Control
Src RNAi
Dasatinib
Rescued


A
Human breast cancer metastases samples
Bone
Lung
Liver
Brain
BMP2: bone morphogenetic protein 2
IGF2: insulin-like growth factor 2
CLEC11A: C-type lectin domain family 11A; SCGF
CXCL12: chemokine C-X-C motif 12; SDF1
CXCL14: chemokine C-X-C motif 14
GMFG: glia maturation factor, gamma
IGF1: insulin-like growth factor 1
JAG1: jagged 1
NOV: nephroblastoma expressed; IGFBP9
PDGFA: platelet-derived growth factor alpha
PGF: placental growth factor
PXDN: peroxidasin homolog
SPP1: secreted phosphoprotein 1; osteopontin
TGFB1: transforming growth factor, beta 1
TGFB3: transforming growth factor, beta 3
TNFSF10: tumor necrosis factor family 10; TRAIL
VEGFC: vascular endothelial growth factor C
-2
0
2
4
B


C
Control
Src RNAi
Rescue
Percent viability
60
50
40
30
20
10
0
p=0.006
n.s.
p=0.003
p=0.002
Control
CXCL12
n.s.
n.s.
p=0.002
p=0.008
Control
TRAIL

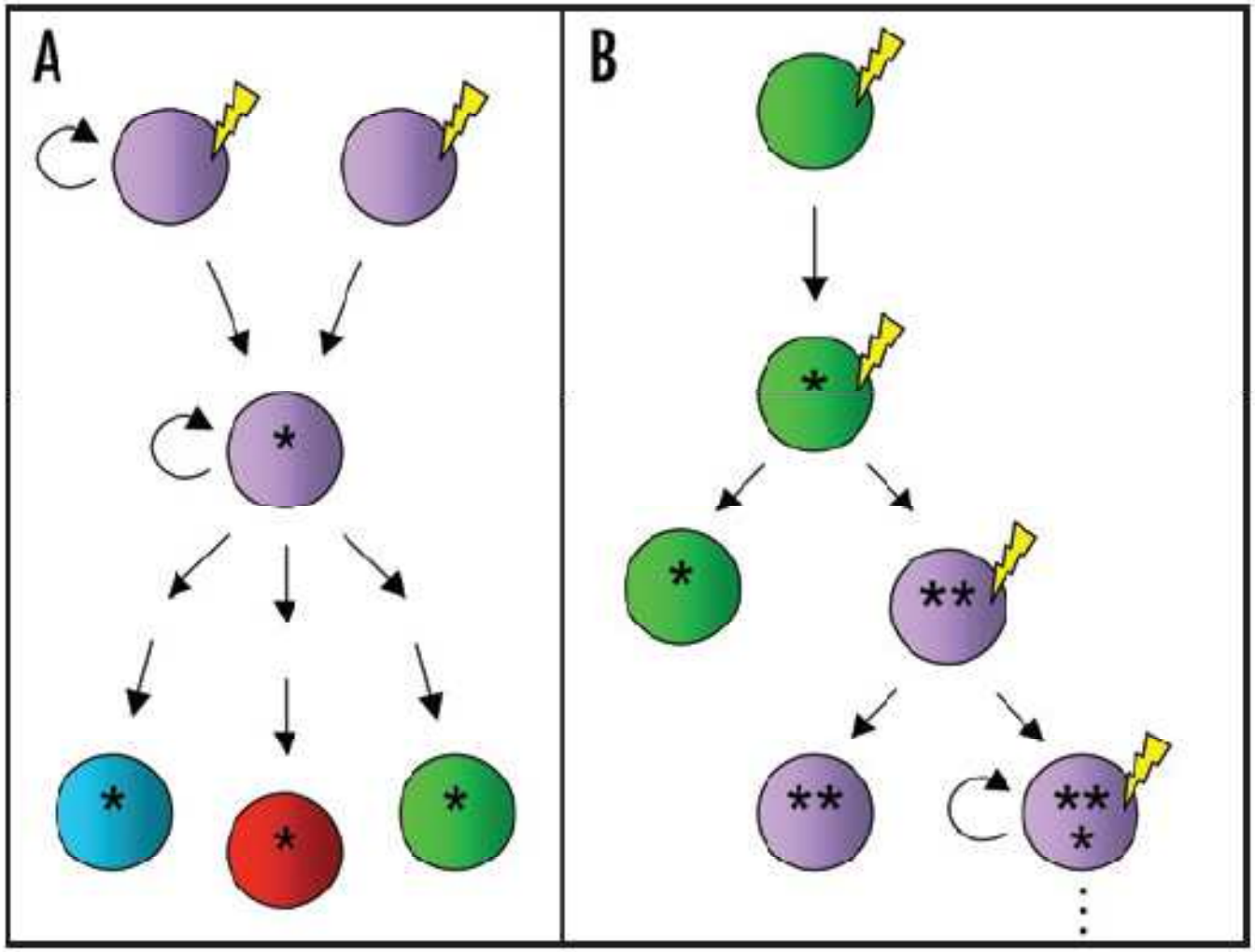

E
Bone marrow survival factors
CXCL12/SDF1
TRAIL
CXCR4
DR4/5
Src
AKT
Survival
SRS+ breast cancer cell
Competence to infiltrate
Breast carcinoma
Bone marrow
Competence to survive
(years to decades)
Competence to colonize
Bone macrometastasis
CXCR4, PTHrP, IL11, MMP1, OPN

Organ specific metastases



original magnification, ×10. **e**, Schematic model of organ-specific metastatic extravasation of breast cancer cells. Extravasation into the bone marrow is a relatively permissive process owing to the fenestrated endothelium lining the sinusoid capillaries. Extravasation into the pulmonary or brain parenchyma requires specific functions for breaching the non-fenestrated capillary walls of these organs. Shared mediators of extravasation include, among others, *COX2* and EGFR ligands such as epiregulin and *HBEGF*. Passage through the BBB requires further mediators including, but not limited to, the brain-specific sialyltransferase *ST6GALNAC5*. Competence to colonize each organ requires additional mediators.

Cancer Stem Cells vs Clonal Evolution



[Cell Cycle 6:19, 2332-2338, 1 October 2007]; ©2007 Landes Bioscience

Perspective

Breast Tumor Heterogeneity

Cancer Stem Cells or Clonal Evolution?

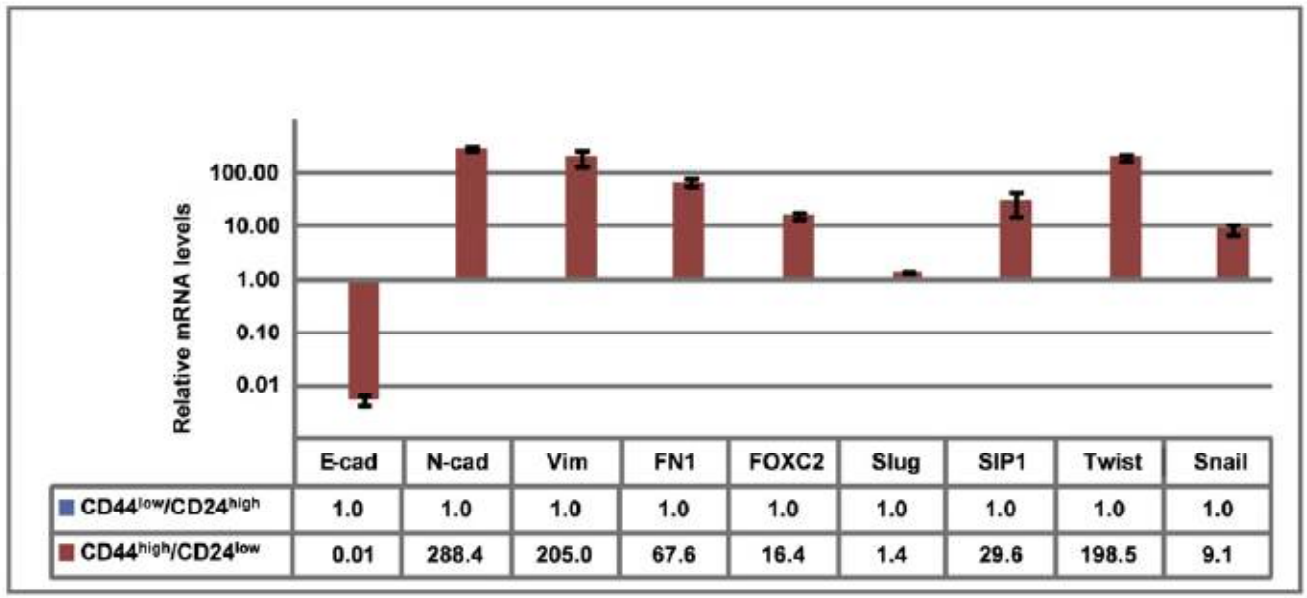
Lauren L. Campbell[1,2]
Kornelia Polyak[1-3,*]

Cell

The Epithelial-Mesenchymal Transition Generates Cells with Properties of Stem Cells

Sendurai A. Mani,[1,3,10,*] Wenjun Guo,[1,10] Mai-Jing Liao,[1,10] Elinor Ng. Eaton,[1] Ayyakkannu Ayyanan,[4] Alicia Y. Zhou,[1,2] Mary Brooks,[1] Ferenc Reinhard,[1] Cheng Cheng Zhang,[1] Michail Shipitsin,[5,6] Lauren L. Campbell,[5,7] Kornelia Polyak,[5,6,7] Cathrin Brisken,[4] Jing Yang,[8] and Robert A. Weinberg[1,2,9,*]

B



	E-cad	N-cad	Vim	FN1	FOXC2	Slug	SIP1	Twist	Snail
$CD44^{low}/CD24^{high}$	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
$CD44^{high}/CD24^{low}$	0.01	288.4	205.0	67.6	16.4	1.4	29.6	198.5	9.1

Figure 3. Stem-like $CD44^{high}/CD24^{low}$ Cells Isolated from HMLE Cells Exhibit Attributes of Cells that Have Undergone an EMT

Induction of EMT results in acquisition of stem cell properties