

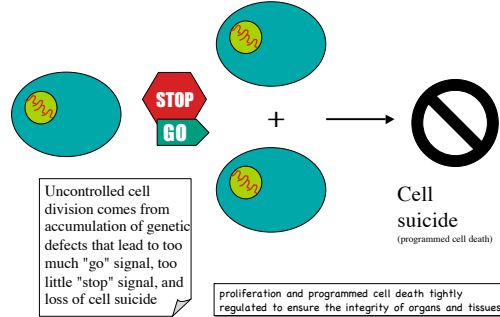
# BREAST CANCER 2

## tumor-suppressor genes

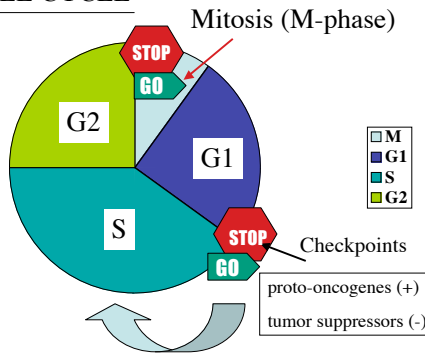
## proto-oncogenes

READING: pp. 202-220

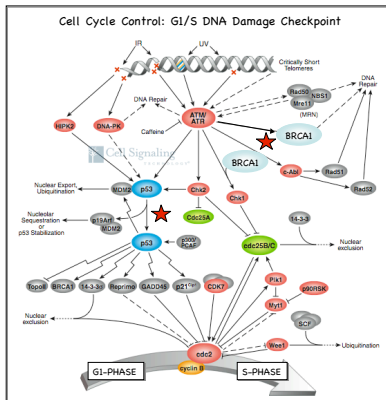
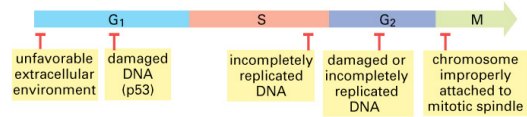
### CELL PROLIFERATION



### THE CELL CYCLE



### Checkpoints ensure the cell cycle proceeds without errors



### INHERITED BREAST CANCERS BRCA1, BRCA2

"Each year in the United States nearly 200,000 women are diagnosed with breast cancer. For as many as 20,000 of these women, the diagnosis comes not as a shock but as the grim conclusion to a dreadful wait.

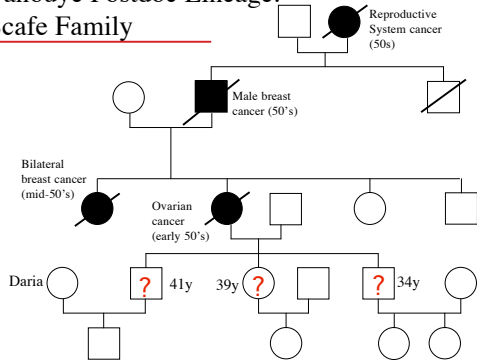
They are women with a strong family history of breast cancer, perhaps with grandmothers and mothers and sisters who fell victim to the disease while still in their thirties and forties.

These are women who harbor a gene that almost guarantees them a place on an appalling statistical list..."

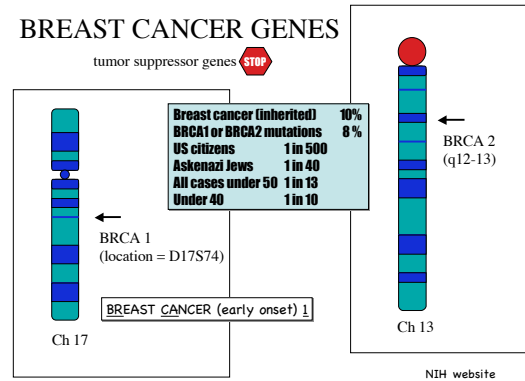
A gene for breast cancer - special issue 1994 - The Year in Science-Discovery, Jan. 1995 - by Josie Glausiusz

BRCA 1 mapped genetically Mary Claire King (1991, UC Berkeley)  
BRCA 1 cloned by positional cloning Sasha Kamb, Mark Skolnick et al (1994)  
BRCA 2 cloned Kamb, Skolnick et al (1996) (genetic mapping + positional cloning)

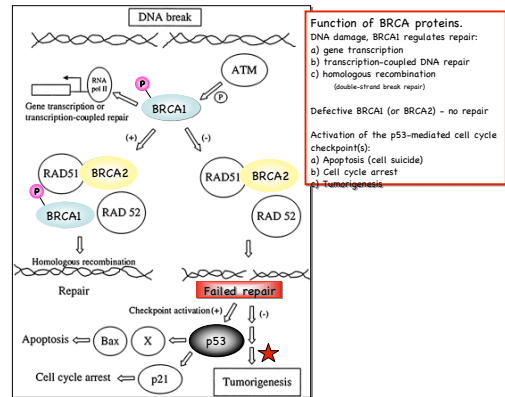
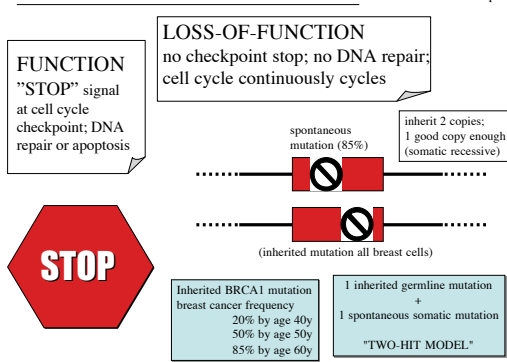
**Tanouye Postdoc Lineage:  
Scafe Family**



**BREAST CANCER GENES**



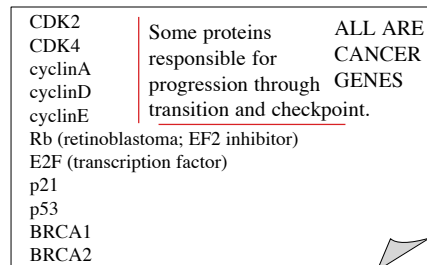
**TUMOR SUPPRESSOR GENES**



**CANCER GENES**

- Accumulation of multiple mutations  
Potential cancer genes - about 100 genes
- 1) Inappropriate signals about need for cell division (hormonal signaling pathways: growth factors)
  - 2) Malfunctions in CDK-cyclin complexes controlling cell cycle transitions
  - 3) Checkpoint breakdowns leading to DNA instability
  - 4) Loss of programmed cell death (cell suicide)

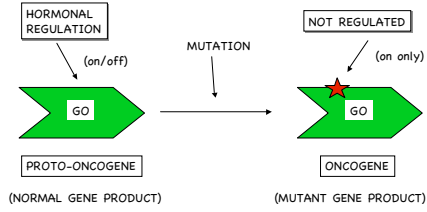
**G<sub>1</sub>-to-S TRANSITION**



**CDK enzymes** are cyclin-dependent protein kinases; control the activity of other proteins by phosphorylating them

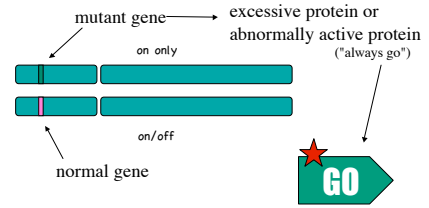
**Cyclins** are proteins necessary for CDK activity

## PROTO-ONCOGENE



sarc - Steve Martin, UC Berkeley

## DOMINANT ONCOGENE ("GAIN-OF-FUNCTION" MUTATION)



ONE MUTANT COPY AND IT IS A GO = DOMINANT

## MUTATIONS ACTIVATING ONCOGENES

### THREE ACTIVATION TYPES

#### PROTEIN CONCENTRATION CHANGED

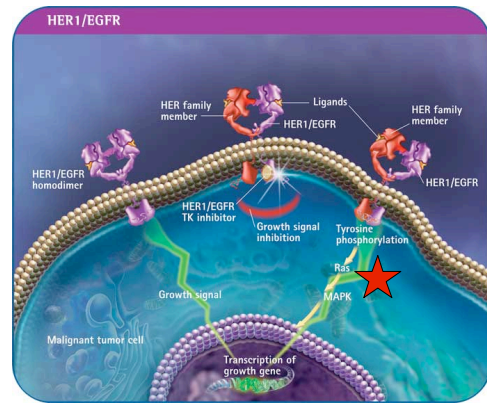
- a) increased expression (through misregulation)
- b) increased protein stability, prolonging its existence
- c) gene duplication

#### PROTEIN STRUCTURE CHANGED

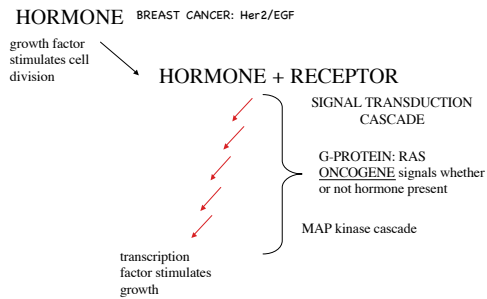
- a) increased enzyme activity
- b) loss of regulation

#### CHROMOSOMAL TRANSLOCATION

- a) expression in wrong cell type or at wrong times
- b) constitutively active hybrid protein (responsible for adult leukemia in hematopoietic stem cell)



## ONCOGENE: RAS



## HUMAN PAPPILOMA VIRUS (HPV)

AGE 14 to 19y (female)	25% HPV prevalence
AGE 20 to 24y (female)	45% HPV prevalence

### GENITAL WARTS CERVICAL CANCER

14,000 U.S. women/year diagnosed cervical cancer  
3,900 U.S. women/year die

National Cervical Cancer Coalition (NCCC)  
and Journal of the American Medical Association

## "HIGH RISK" HPV TYPES

HPV - Family of about 100 DNA-based viruses

**GENITAL WARTS**  
types 6 and 11 (90% of all cases)

**CERVICAL CANCER**  
types 16, 18, 31 and 45

A group of about 30-40 HPVs typically transmitted through sexual contact

HPV-induced cancers often have viral sequences integrated into the cellular DNA.

Some of the HPV "early" genes, such as E6 and E7, known to act as **ONCOGENES** that promote tumor growth and malignant transformation.

E6 inhibits p53  
E7 inhibits p53, p21, and RB.

## TEXAS LAWMAKERS REJECT HPV VACCINE ORDER

## HPV VACCINE

Texas lawmakers rejected Governor Rick Perry's HPV vaccine order last week. The bill essentially would bar state officials from requiring the vaccine for four years. The Governor still has the opportunity to veto the bill.

Republican Rep. Dennis Bonnen, the bill's House sponsor, said he believes it is fair and reasonable. "I think the governor should see this as the Legislature making a very clear and respectful statement, and I hope he'll accept our wishes," Bonnen said.

Governor's spokeswoman, Krista Moody, had this to say on his behalf: "The governor looks forward to a day when cervical cancer is eradicated and Texas women no longer have to cope with the devastating effects of this disease," she said, adding that the Legislature's actions will "delay that day for another four years."

Merck's Gardasil, the vaccine protects against four strains of the sexually transmitted HPV infection. The U.S. Food and Drug Administration recently approved the vaccine for girls and women ages 9 to 26.

Published May 3rd, 2007 in HPV News, also AP news

HPV Vaccine: The vaccine, Gardasil® (Merck) protects against four HPV types, which together cause 70% of cervical cancers and 90% of genital warts