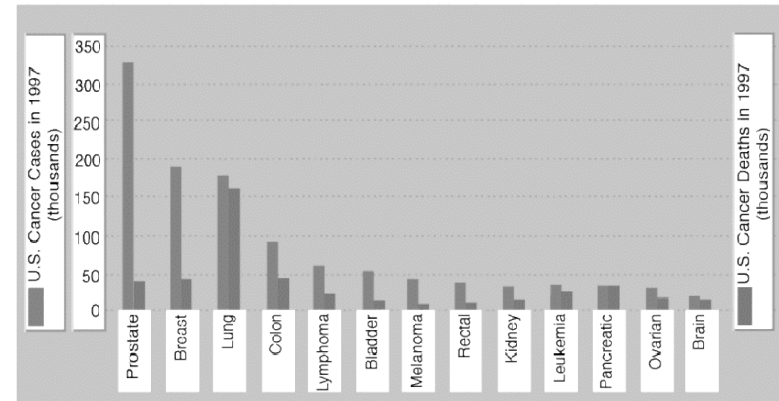


# Genetics of Cancer

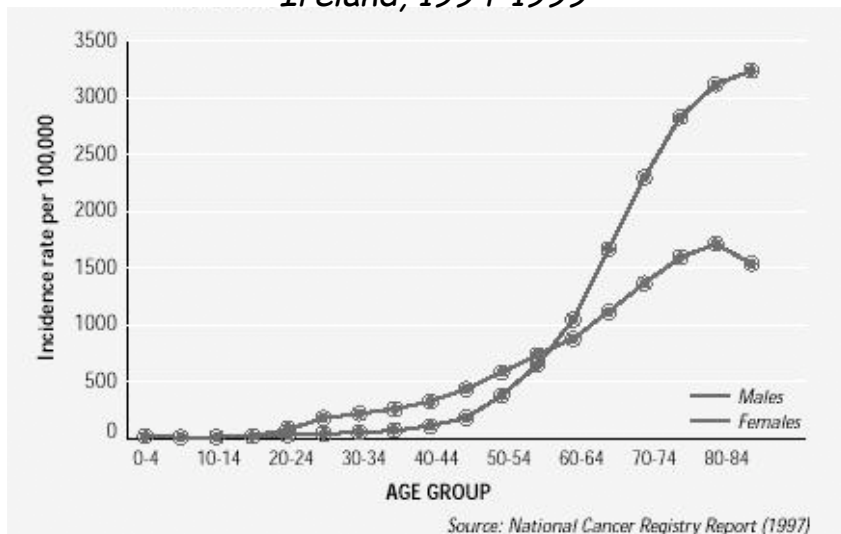
## Lecture 34

### The Estimated Numbers of New Cancer Cases and Deaths



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Age Specific Cancer Rates: Males and Females, Ireland, 1994-1999

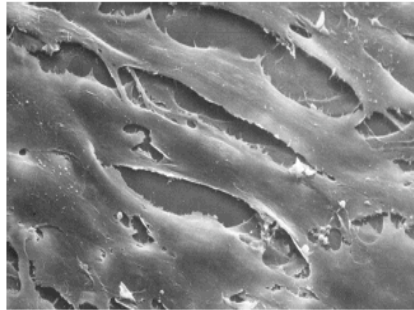


### Properties of Cancer Cells

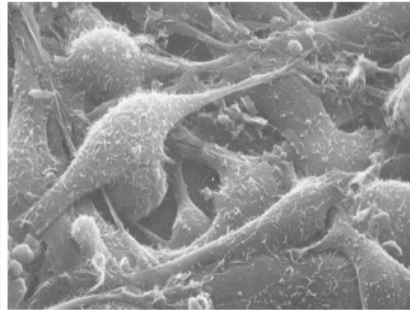
- Loss of Contact inhibition
- Anchorage independent growth
- Can grow indefinitely
- Can grow with low levels of serum growth factors

# What do cancer cells look like?

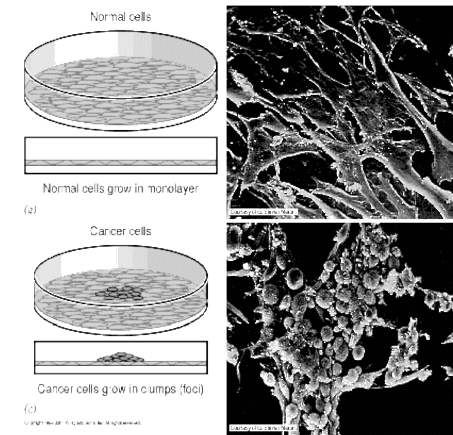
3T3 cells in culture



Transformed 3T3 cells



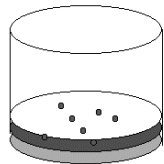
# Loss of Contact Inhibition in Cancer Cells



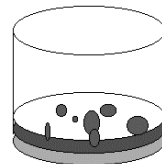
<http://140.116.60.1/mdlai/Handout/cancer-medicine-2000/img009.GIF>

# Anchorage Independence

Normal cells cannot grow in soft agar, exist in single cell



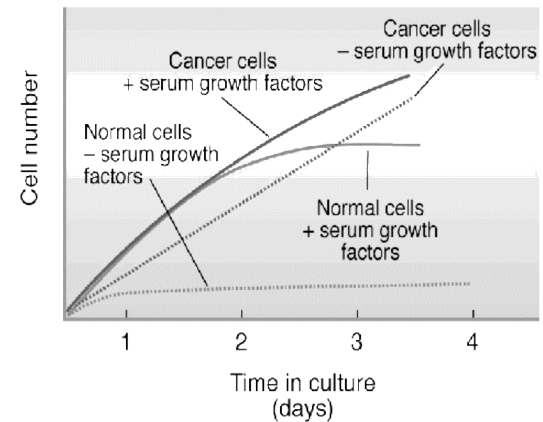
Transformed cells can proliferate and form colonies in soft agar



0.6% agar  
0.3% agar

<http://140.116.60.1/mdlai/Handout/cancer-medicine-2000/img009.GIF>

# Cancer Cells Can Proliferate With Serum Deprivation

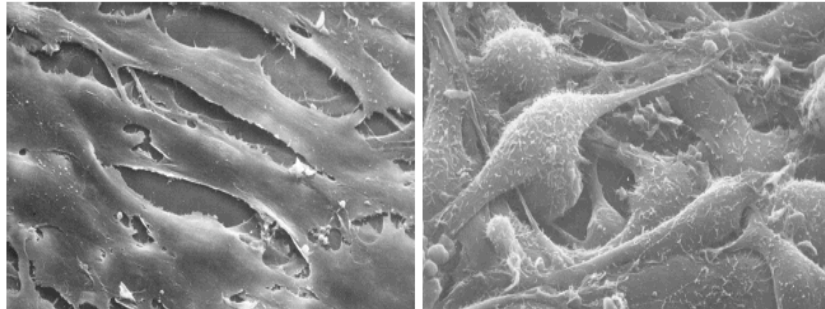


<http://140.116.60.1/mdlai/Handout/cancer-medicine-2000/img009.GIF>

# What do cancer cells look like?

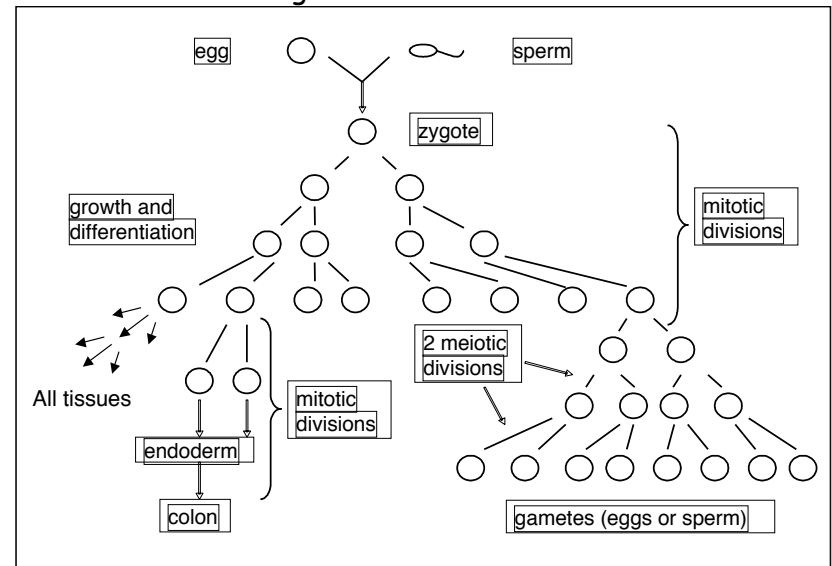
3T3 cells in culture

Transformed 3T3 cells

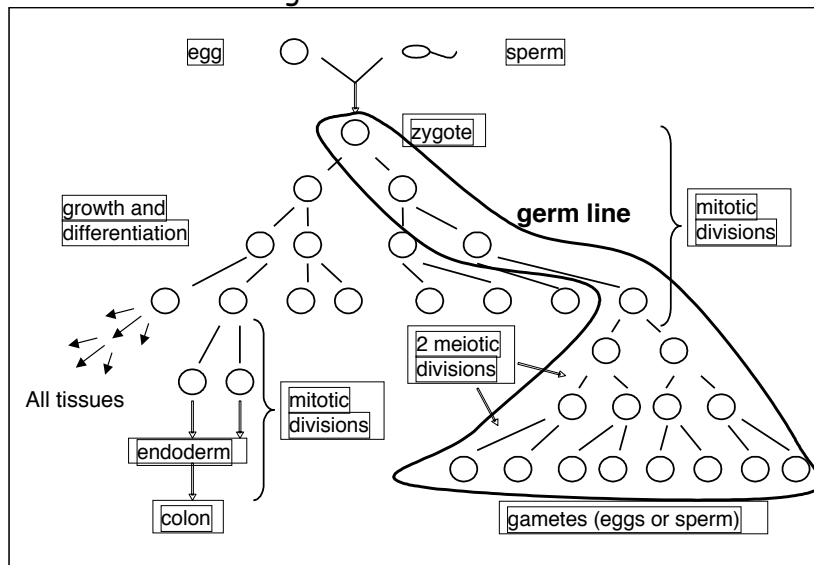


## Where do they come from?

Most of the mutations that contribute to cancer occur in somatic cells - but germ line mutations can also contribute



Most of the mutations that contribute to cancer occur in somatic cells - but germ line mutations can also contribute



## The Genetic Basis of Cancer and Theodor Boveri 1862 - 1915



*The Boveri.*

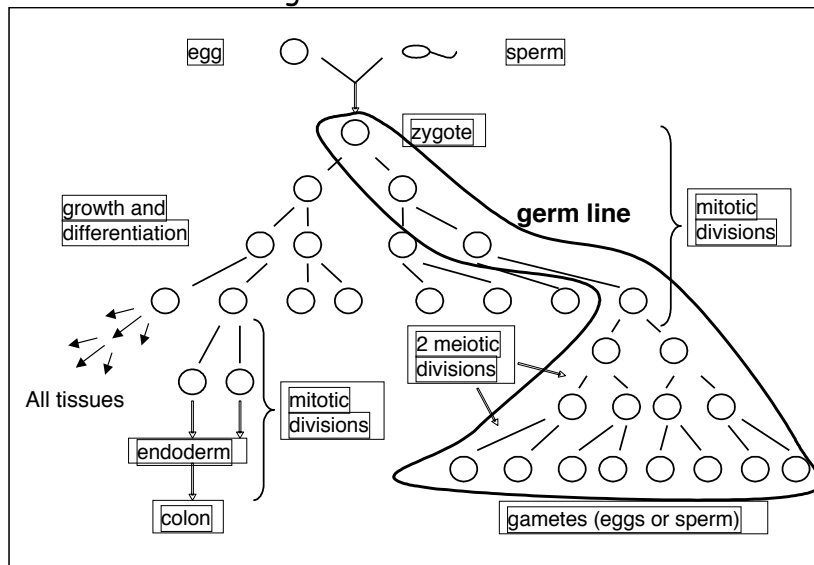
- Established that chromosomes carry the hereditary information by showing that aberrant segregation of chromosomes leads to certain phenotypes in sea urchin eggs.
- Suggested that aberrant segregation of human chromosomes could be responsible for a normal cell becoming a tumor cell
- Suggested that some chromosomes promoted cell growth and others

*Marcella Q'Grady Boveri (1863-1950) also contributed*

## Major complications in understanding the genetic basis of cancer

- Multiple mutations are necessary to produce a tumor cell
- Different types of tumor have different genes mutated
- Early initiating events occur rarely in complex tissues and are therefore extremely difficult to detect
- The key initiating event often leads to an increase in mutation rate thus tumor cells often bear many fortuitous mutations

Most of the mutations that contribute to cancer occur in somatic cells - but germ line mutations can also contribute



## Alterations in different kinds of Genes cause Cancer

### Oncogenes

dominant gain-of-function mutations  
promote cell transformation

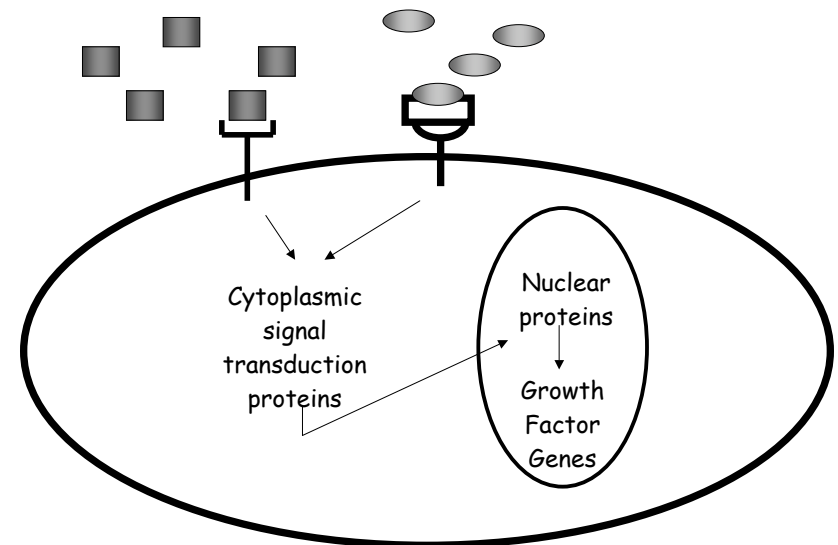
### Tumor suppressor genes

recessive, loss-of-function mutations  
promote cell transformation

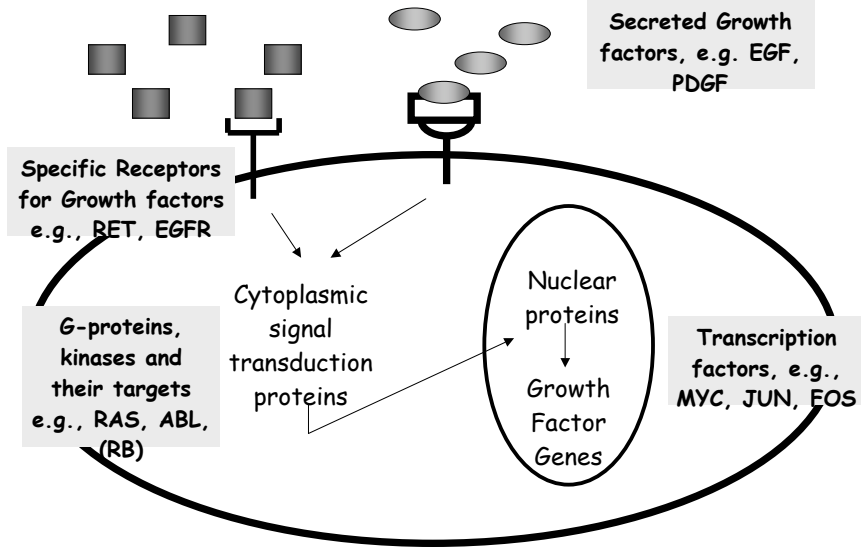
### Mutator genes

Usually recessive, loss-of-function mutations  
that increase spontaneous and environmentally

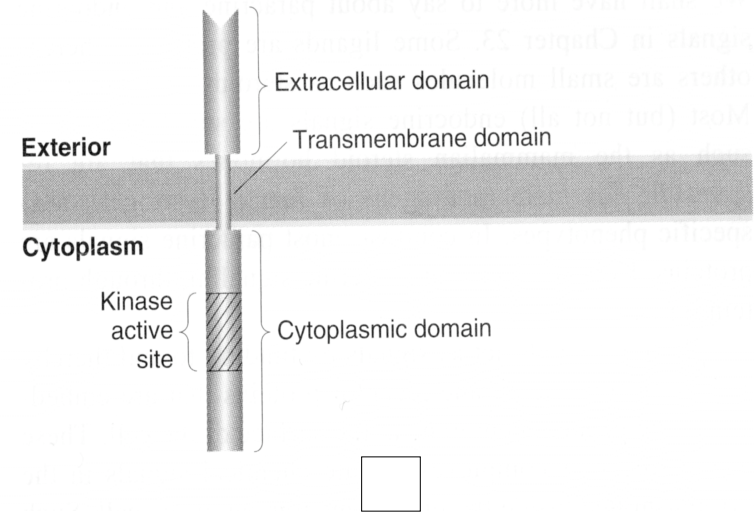
## Signal Transduction and Growth Regulation



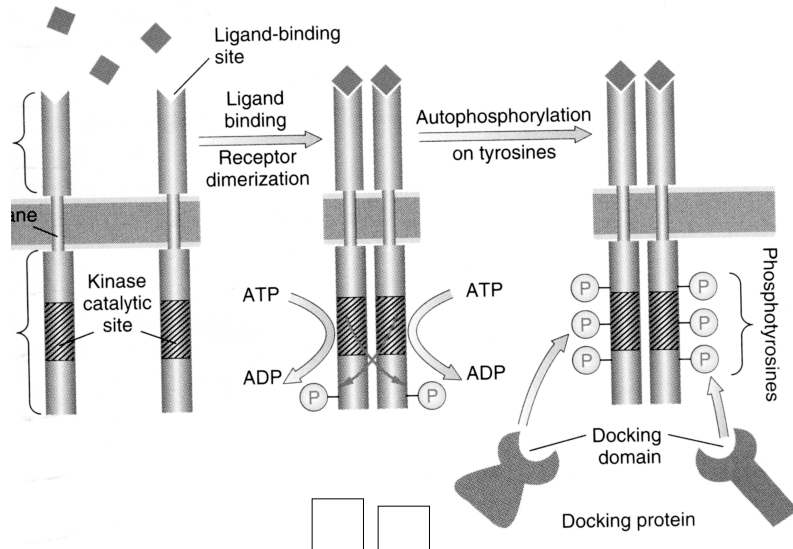
## Great Targets for Dominant Acting Oncogenes



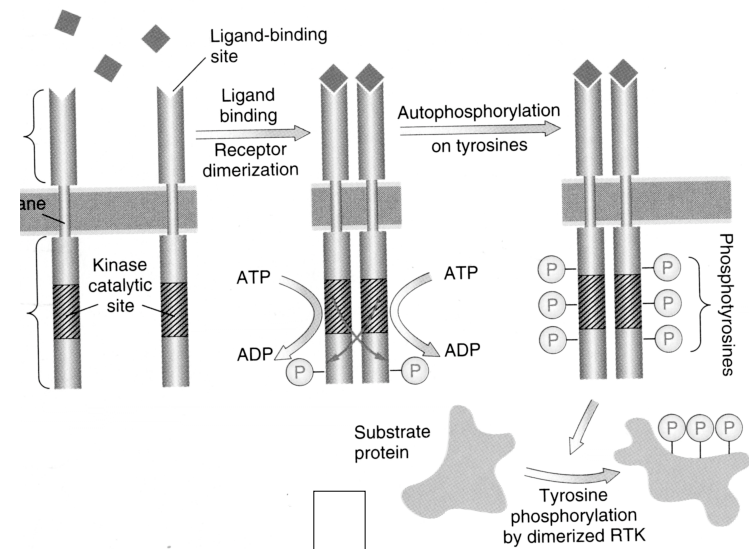
## Receptor Tyrosine Kinases (RTKs)

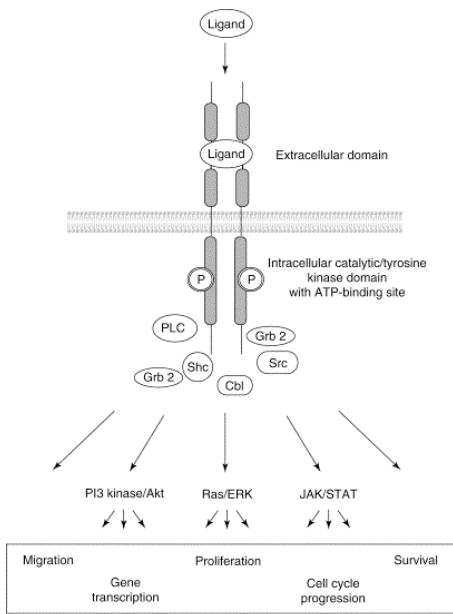


## Receptor Tyrosine Kinases (RTKs)



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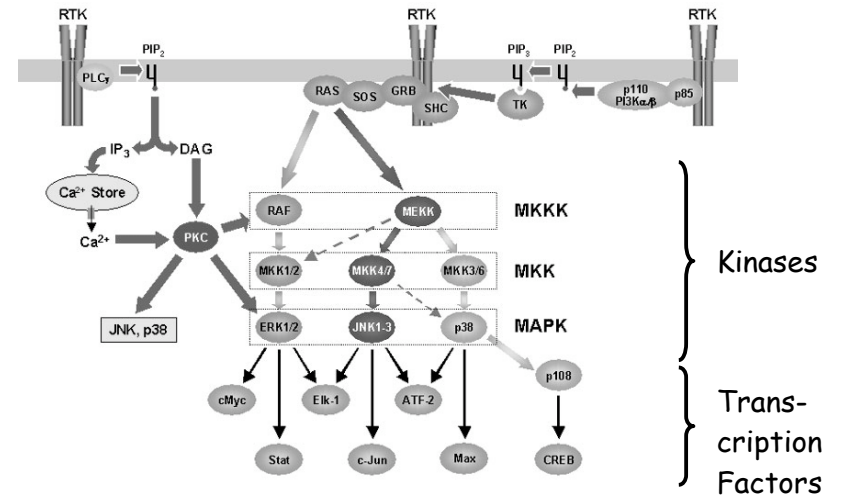




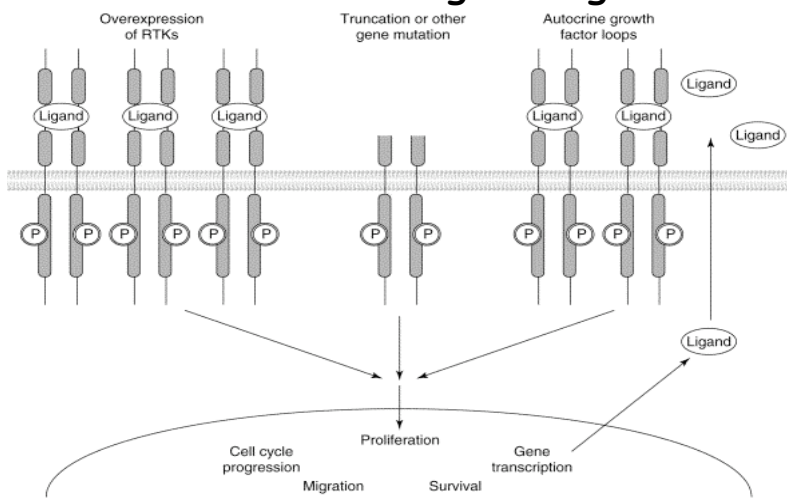
Zwick et al, (2002) TIMM 8:17-23 *TRENDS in Molecular Medicine*

Extracellular Growth factor  
 ↓  
 Engages with and dimerizes specific receptors on cell surface  
 ↓  
 Dimerized Receptor activates cascade of molecular events  
 ↓  
 Machinery for increased cell proliferation is mobilized

## Receptor Tyrosine Kinases (RTKs)



## Constitutive Activation converts RTKs to Dominant Acting Oncogenes

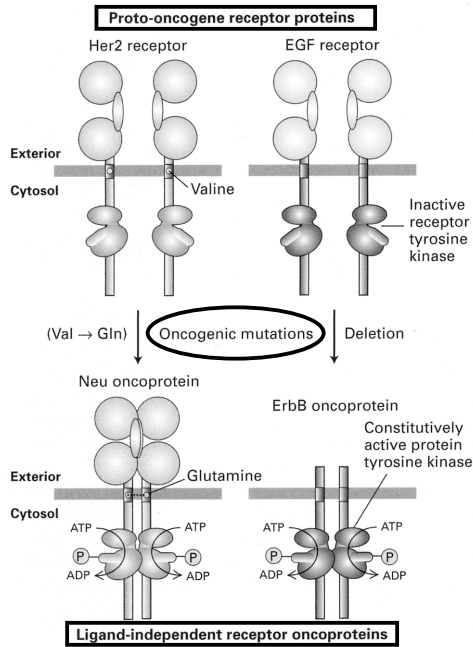


Zwick et al, (2002) TIMM 8:17-23

*TRENDS in Molecular Medicine*

## Genetic alterations leading to Constitutive Activation of RTKs

- Deletion of extracellular domain
- Mutations that stimulate dimerization without ligand binding
- Mutations of the kinase domain
- Overexpression of Ligand
- Overexpression of Receptor



## Two Classic Examples

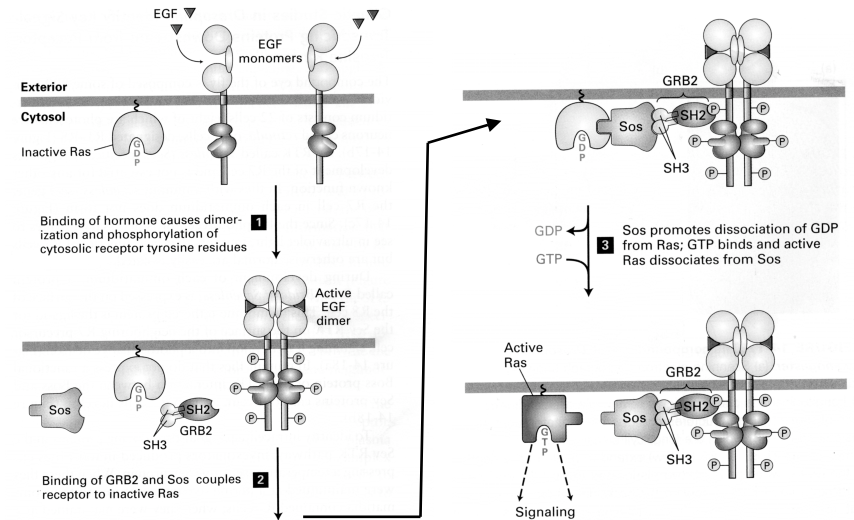
Her2 receptor

EGF receptor

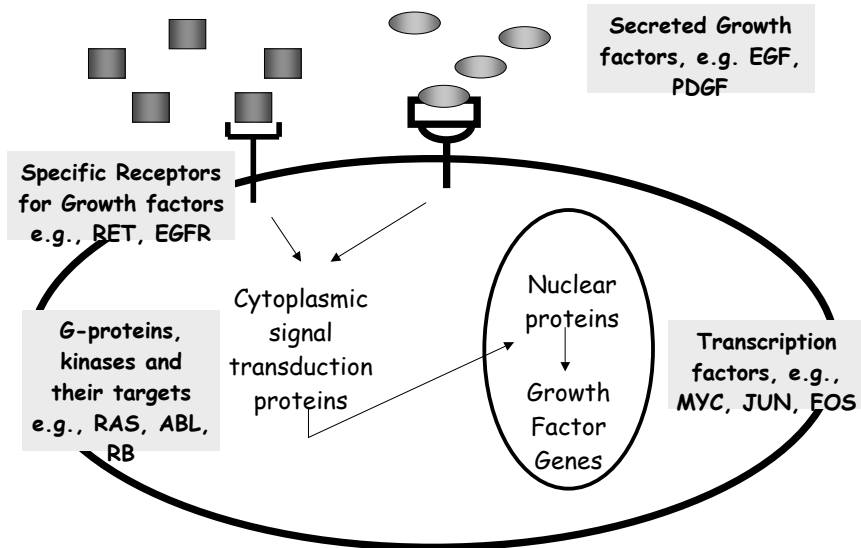
Her2 = Human Epidermal growth factor receptor 2

EGFR = Epidermal growth factor receptor

## EGF Receptors signal through the RAS G-protein



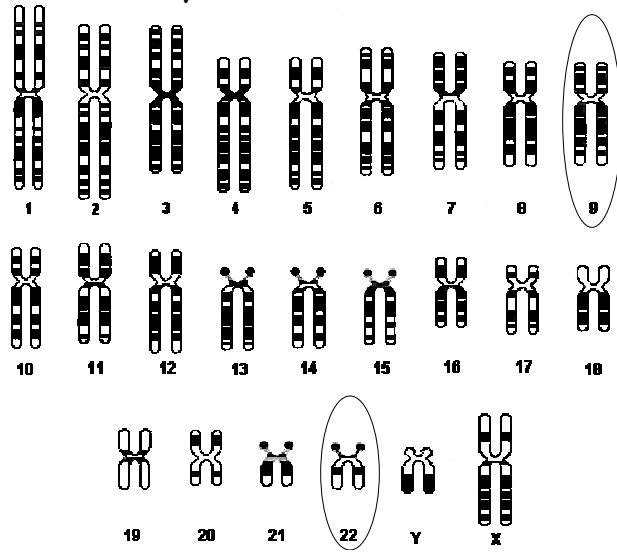
## Signal Transduction and Growth Regulation



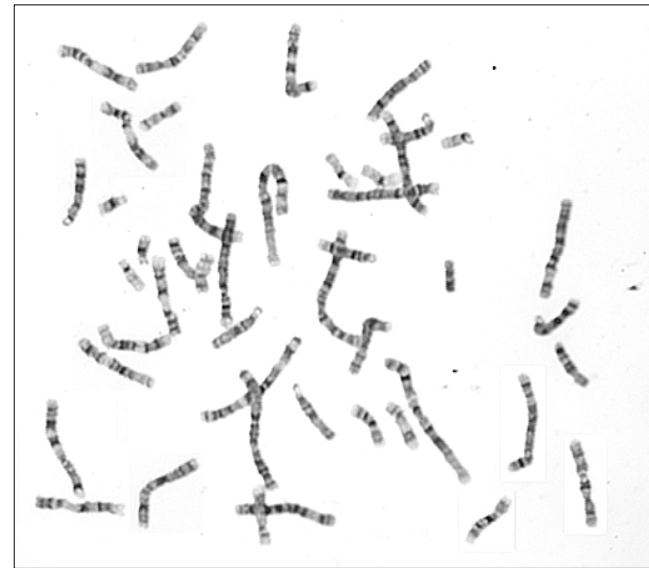
cABL - A non-receptor, cytoplasmic tyrosine kinase that can be converted into an oncoprotein

- cABL proto-oncogene product signals to many of the same molecules as the RTKs
- Signals cell cycle progression and cell proliferation

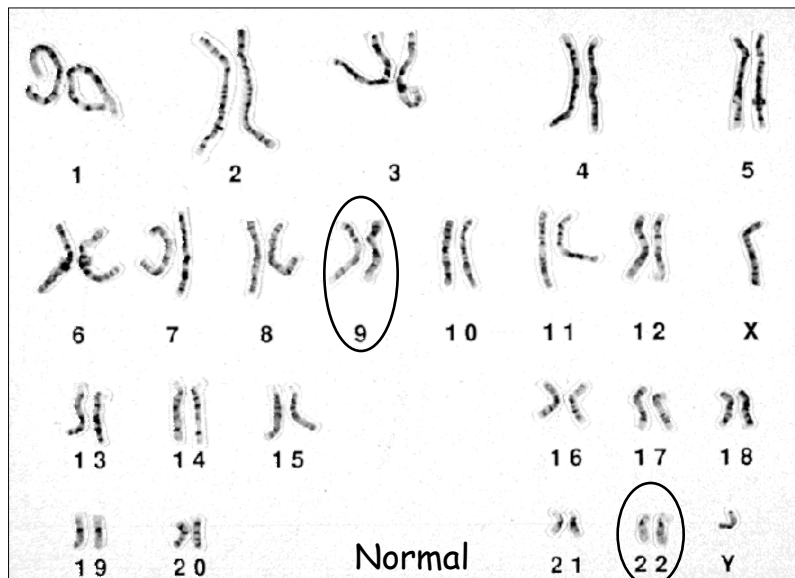
# The Philadelphia Chromosome and Chronic Myeloid Leukemia



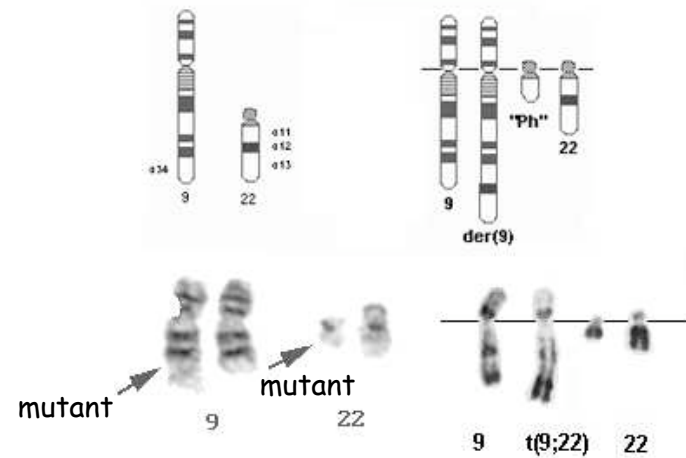
# Human Chromosome Spread - G-banding Karyotype



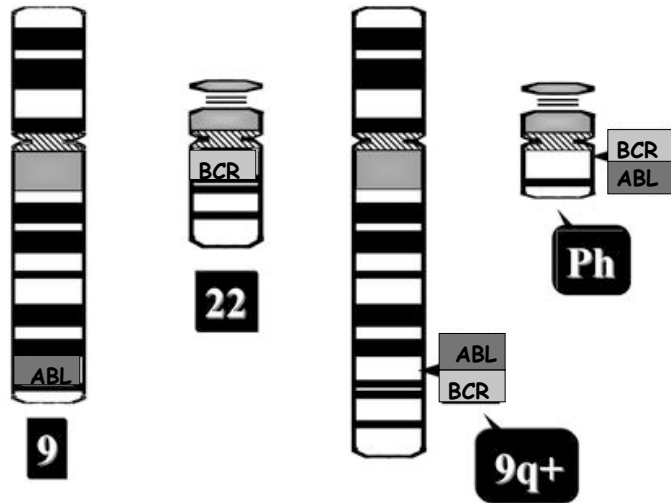
# Human Chromosome Spread - G-banding Karyotype



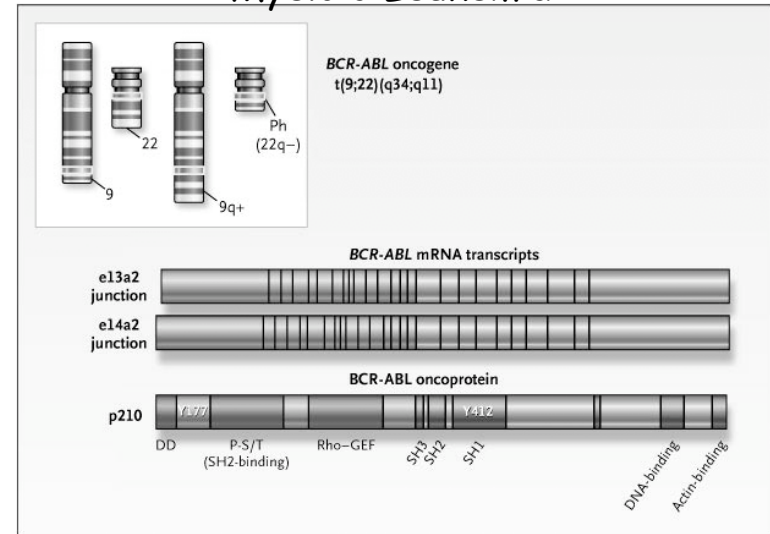
# The Philadelphia Chromosome created by a Translocation between Chrs 9 and 22 → Chronic Myeloid Leukemia



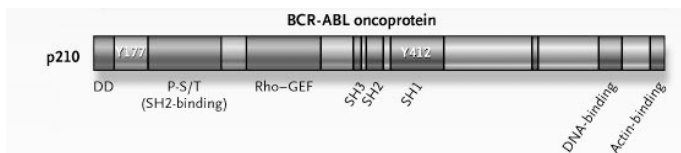
# The Philadelphia Chromosome and Chronic Myeloid Leukemia



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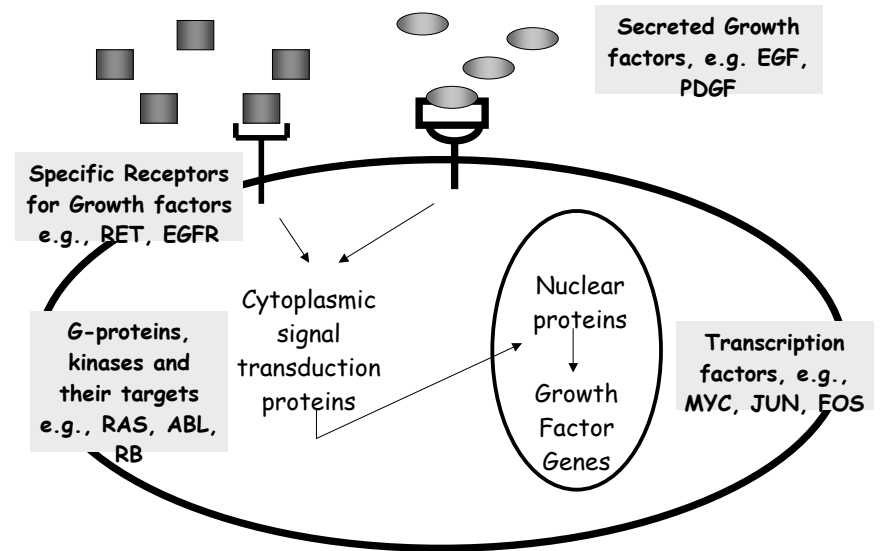


## Fusion Protein



Uncontrolled ABL Kinase Activity  
and Signal Transduction  
Chronic Myeloid Leukemia

## Signal Transduction and Growth Regulation



# Alterations in different kinds of Genes cause Cancer

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