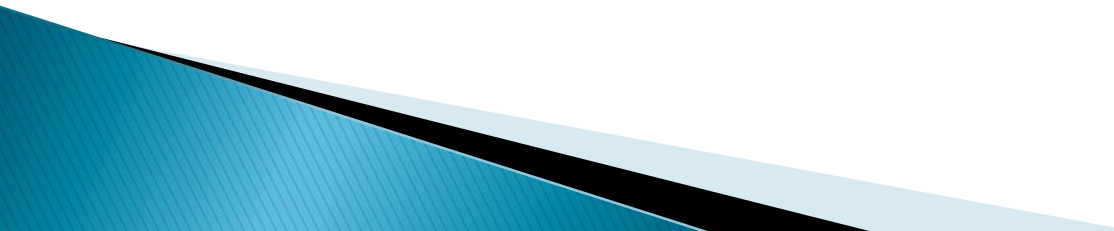


Why and what I need to know?

Winston Tan MD FACP
Associate Professor of Medicine
Vice Chair of Hematology/Oncology Education
Chair Genitourinary Medical Oncology
Mayo Clinic Florida
Vice President
Florida Society of Clinical Oncology

Aims

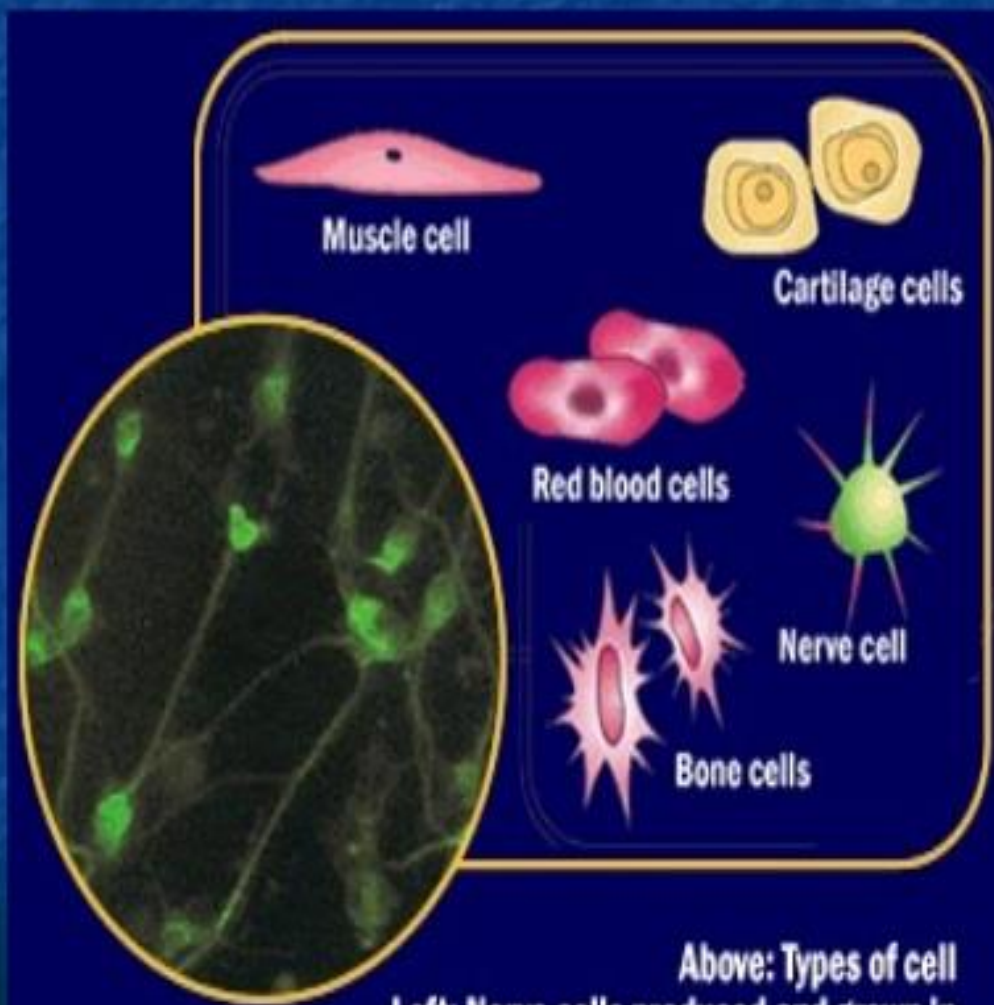
- ▶ Learner be able to understand and review the basic approach to the diagnosis and treatment of cancer
 - ▶ Discuss and comprehend the staging and how this affects the approach to treatment
 - ▶ Evaluate the different approaches to cancer treatment and how decisions are made
- 

Cancer Statistics

- 553,400 Americans died of cancer 2001
- 1.3 million new cases diagnosed
- 1 in 4 deaths from cancer
- Early detection/improvements in technology have improved prognosis for many
- ***What do you think are the contributing factors to the incidence of cancer in the U.S. today?***

Different Types of Cells

- Blood cells
- Muscle cells (smooth, striated, cardiac)
- Nerve cells
- Bone cells
- Cartilage cells
- Liver (hepa) cells

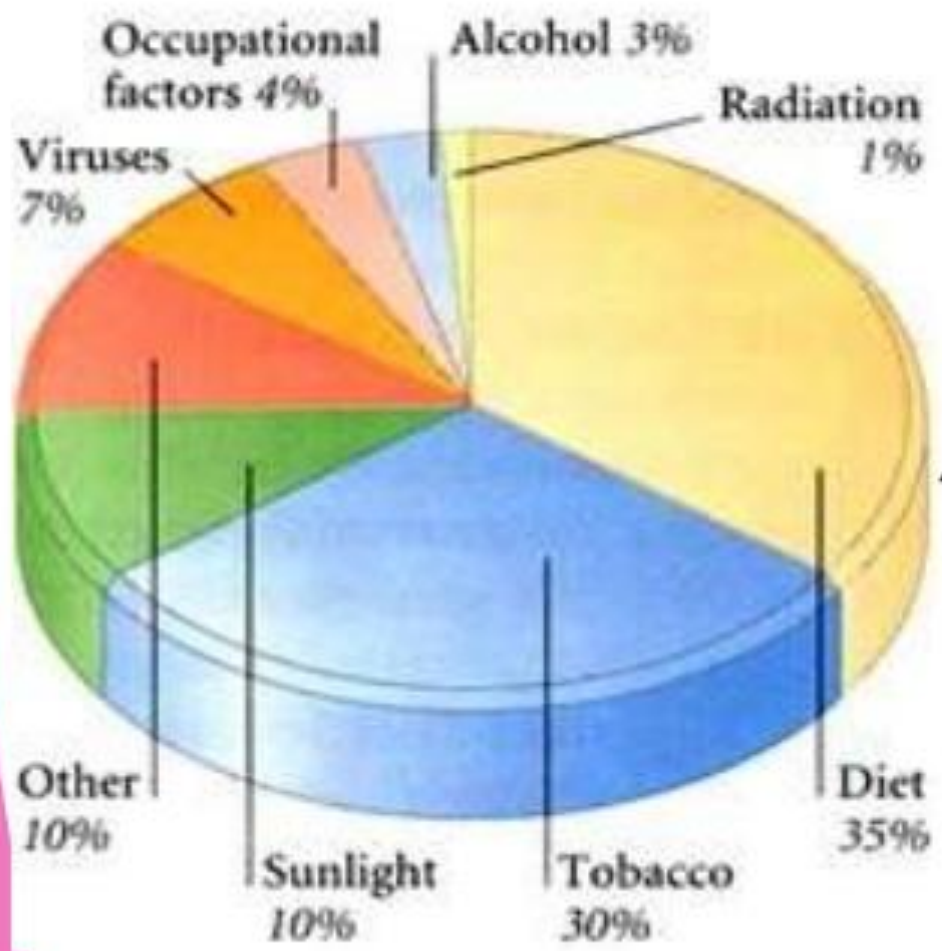


Above: Types of cell
Left: Nerve cells produced and grown in the laboratory from embryonic stem cells

Main Features of Benign and Malignant Tumors

	<i>Malignant Tumor</i>	<i>Benign Tumor</i>
<i>Rate of growth</i>	<i>Rapid</i>	<i>Slow</i>
<i>Nature of growth</i>	<i>Invades surrounding tissue</i>	<i>Expands in the same tissue</i>
<i>Spread</i>	<i>Metastasizes via the bloodstream and the lymphatic system</i>	<i>Does not spread</i>
<i>Cell differentiation</i>	<i>Usually poor</i>	<i>Nearly normal</i>

CAUSES OF CANCER



5-10%
Genes

Environment
90-95%



APPROACHES TO CONTROL CANCER



NO CANCER



► There are four principal approaches to **cancer** control:

1. Prevention
2. Early Detection
3. Diagnosis and Treatment
4. Palliative Care





AVOID



An Overview of Cancer

■ **Variations in Rates**

- Rates have large variations among populations
- 444.6 per 100,000 African Americans
- 402.1 per 100,000 Whites
- 272.4 per 100,000 Hispanics
- 279.3 per 100,000 Asian Pacific Islanders
- 152.8 per 100,000 Native Americans

Factors Believed to Contribute to Global Causes of Cancer

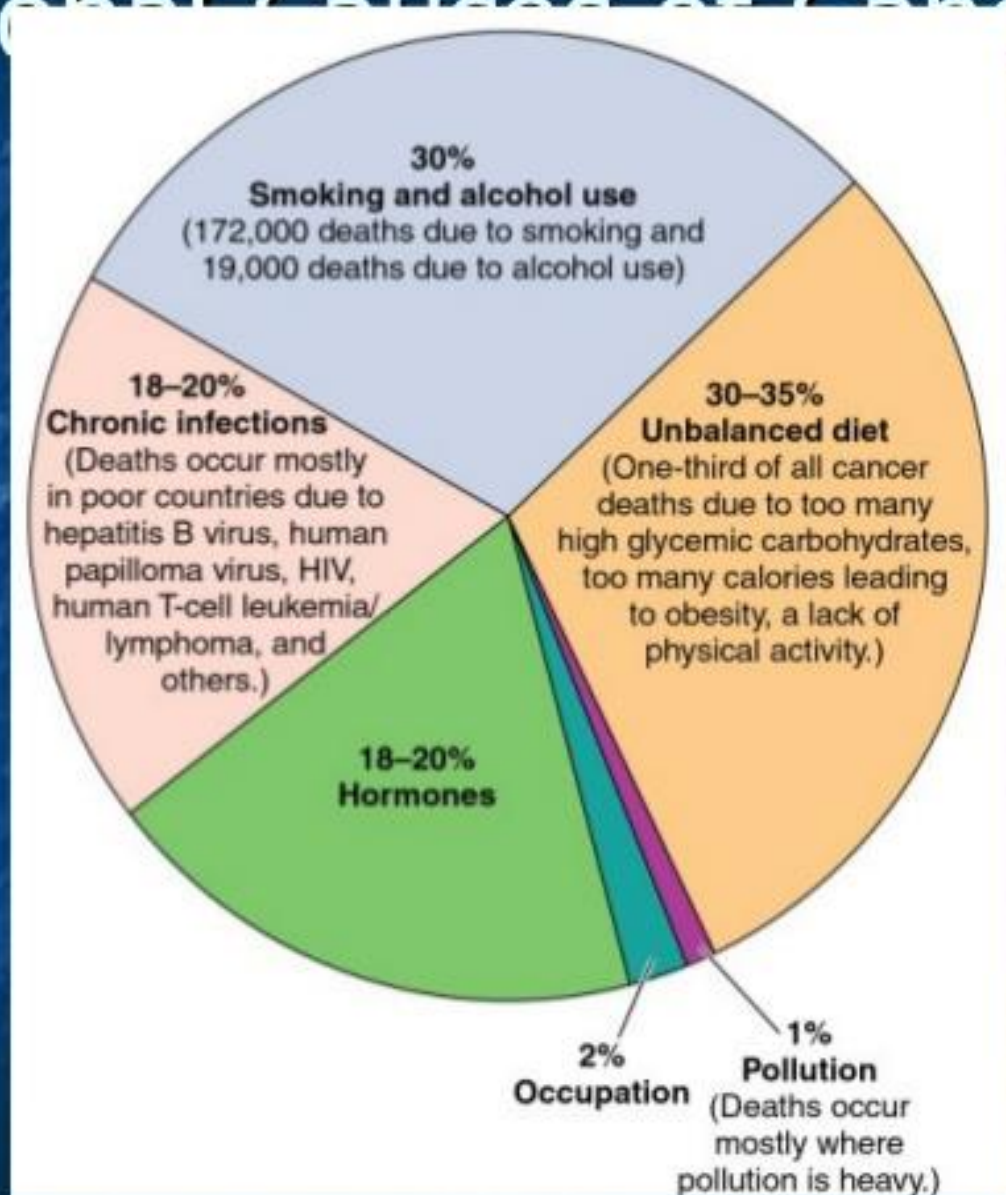


Figure 13.1

Table 13.1
Preventing Cancer through Diet and Lifestyle

Type	Decreases Risk	Increases Risk	Preventable by Diet
Lung	Vegetables, fruits	Smoking; some occupations	33–50%
Stomach	Vegetables, fruits; food refrigeration	Salt; salted foods	66–75%
Breast	Vegetables, fruits	Obesity; alcohol	33–50%
Colon/rectum	Vegetables; physical activity	Meat; alcohol; smoking	66–75%
Mouth/throat	Vegetables, fruits; physical activity	Salted fish; alcohol; smoking	33–50%
Liver	Vegetables	Alcohol; contaminated food	33–66%
Cervix	Vegetables, fruits	Smoking	10–20%
Esophagus	Vegetables, fruits	Deficient diet; smoking; alcohol	50–75%
Prostate	Vegetables	Meat or meat fat; dairy fat	10–20%
Bladder	Vegetables, fruits	Smoking; coffee	10–20%

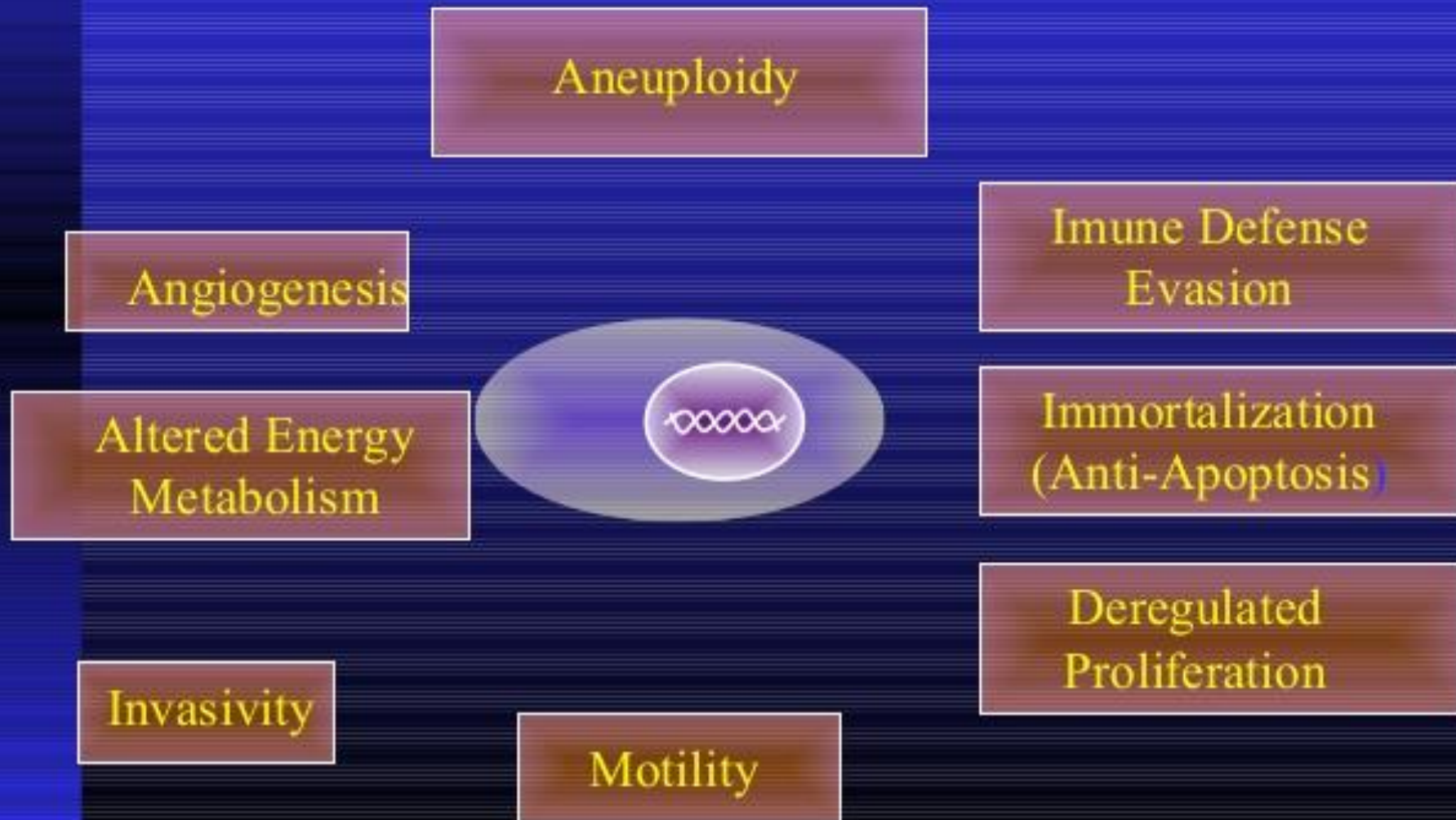
Here are some tips issued by a panel of cancer researchers:

- Avoid being underweight or overweight, and limit weight gain during adulthood to less than 11 pounds.
- If you don't get much exercise at work, take a 1-hour brisk walk or similar exercise daily, and exercise vigorously for at least 1 hour a week.
- Eat 8 or more servings a day of cereals and grains (such as rice, corn, breads, and pasta), legumes (such as peas), roots (such as beets, radishes, and carrots), tubers (such as potatoes), and plantains (including bananas).
- Eat 5 or more servings a day of a variety of other vegetables and fruits.
- Limit consumption of refined sugar.
- Limit alcoholic drinks to less than 2 a day for men and 1 for women.
- Limit intake of red meat to less than 3 ounces a day, if eaten at all.
- Limit consumption of salted foods and use of cooking and table salt. Use herbs and spices to season foods.

Sources: World Cancer Research Fund, American Institute for Cancer Research.

Hallmarks of Cancer

Target Areas for Therapeutic Interventions



Diagnosis

- ▶ Biopsy
- ▶ Surgery
- ▶ Complex cases

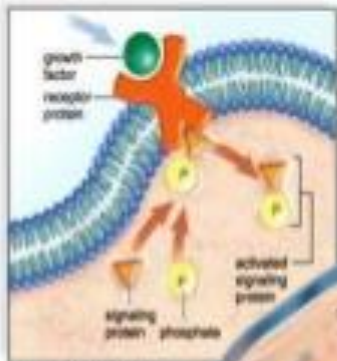
monitoring

Table 13.3

Cancer's Seven Warning Signals

1. Changes in bowel or bladder habits
2. A sore that does not heal
3. Unusual bleeding or discharge
4. Thickening or lump in breast or elsewhere
5. Indigestion or difficulty in swallowing
6. Obvious change in a wart or mole
7. Nagging cough or hoarseness

If you have a warning signal, see your doctor.

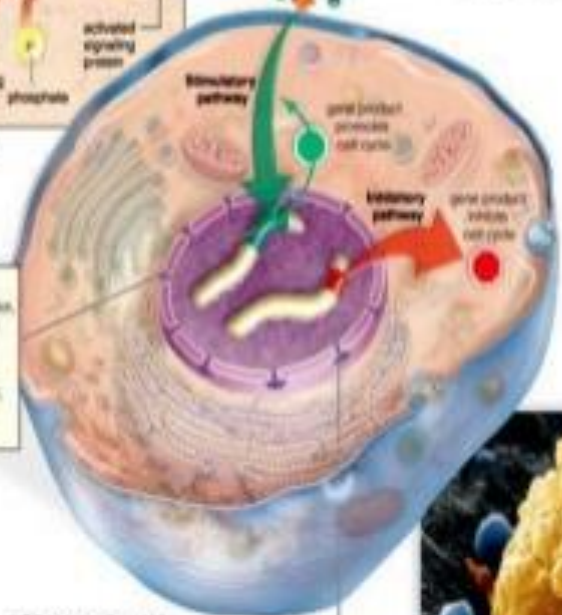


1. Effect of growth factor

growth factor
Activates signaling proteins in a stimulatory pathway that extends to the nucleus.

 Heredity	 Radiation sources
 Prescribed and herbicides	 Viruses and oncogenes

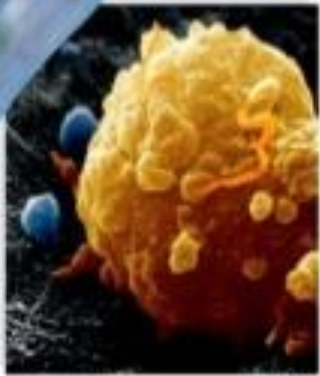
is influences that cause mutated proto-oncogenes (called oncogenes) and mutated tumor suppressor genes



proto-oncogene
Codes for a growth factor, a receptor protein, or a signaling protein in a stimulatory pathway. If a proto-oncogene becomes an oncogene, the end result can be active cell division.

2. Stimulatory pathway and inhibitory pathway

tumor suppressor gene
Codes for a signaling protein in an inhibitory pathway. If a tumor suppressor gene mutates, the end result can be active cell division.



3. Carcinoma skin cell

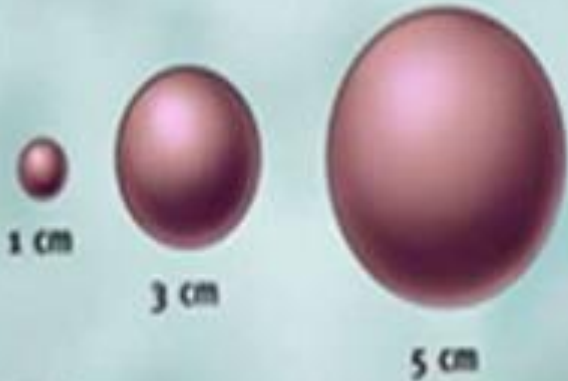


Figure 1



AA Battery

How to Examine Your Breasts

Do you know that 95% of breast cancers are discovered first by women themselves? And that the earlier the breast cancer is detected, the better the chance for a complete cure? Of course, most lumps or changes are not cancer. But you can safeguard your health by making a habit of examining your breasts once a month—a day or two after your period, or, if you're no longer menstruating, on any given day. And, if you notice anything changed or unusual—a lump, thickening, or discharge—contact your doctor right away.

How to Look for Changes



Step 1

Sit or stand in front of a mirror with your arms at your side. Turning slowly from side to side, check your breasts for

- changes in size or shape
- puckering or dimpling of the skin
- changes in size or position of one nipple compared to the other



Step 2

Raise your arms above your head and repeat the examination in Step 1.

Step 3

Gently press each nipple with your fingertips to see if there is any discharge.

How to Feel for Changes



Step 1

Lie down and put a pillow or folded bath towel under your left shoulder. Then place your left hand under your head. (From now on you will be feeling for a lump or thickening in your breasts.)

Step 2

Imagine that your breast is divided into quarters.

Step 3

With the fingers of your right hand held together, press firmly but gently, using small circular motions to feel the inner, upper quarter of your left breast. Start at your breastbone and work toward the nipple. Also examine the area around the nipple. Now do the same for the lower, inner portion of your breast.

Step 4

Next, bring your arm to your side and feel under your left armpit for swelling.

Step 5

With your arm still down, feel the upper, outer part of your breast, starting with your nipple and working outward. Examine the lower, outer quarter in the same way.

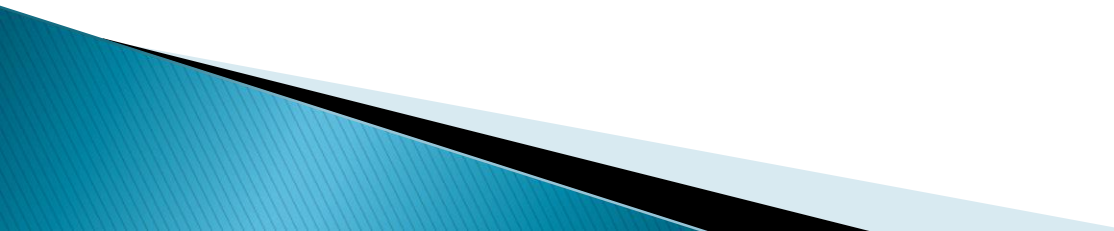
Step 6

Now place the pillow under your right shoulder and repeat all the steps, using your left hand to examine your right breast.





Staging

- ▶ Stage I local
 - ▶ Stage II local
 - ▶ Stage III locally advanced
 - ▶ Stage IV metastasis
- 

STAGES OF CANCER (COLON)



Stage 0



Stage I



Stage II



Stage III

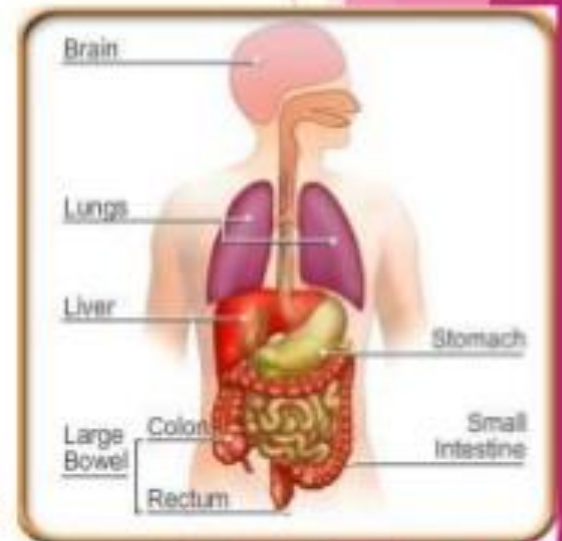
Stage 0: Very early **cancer** on the innermost layer of the intestine

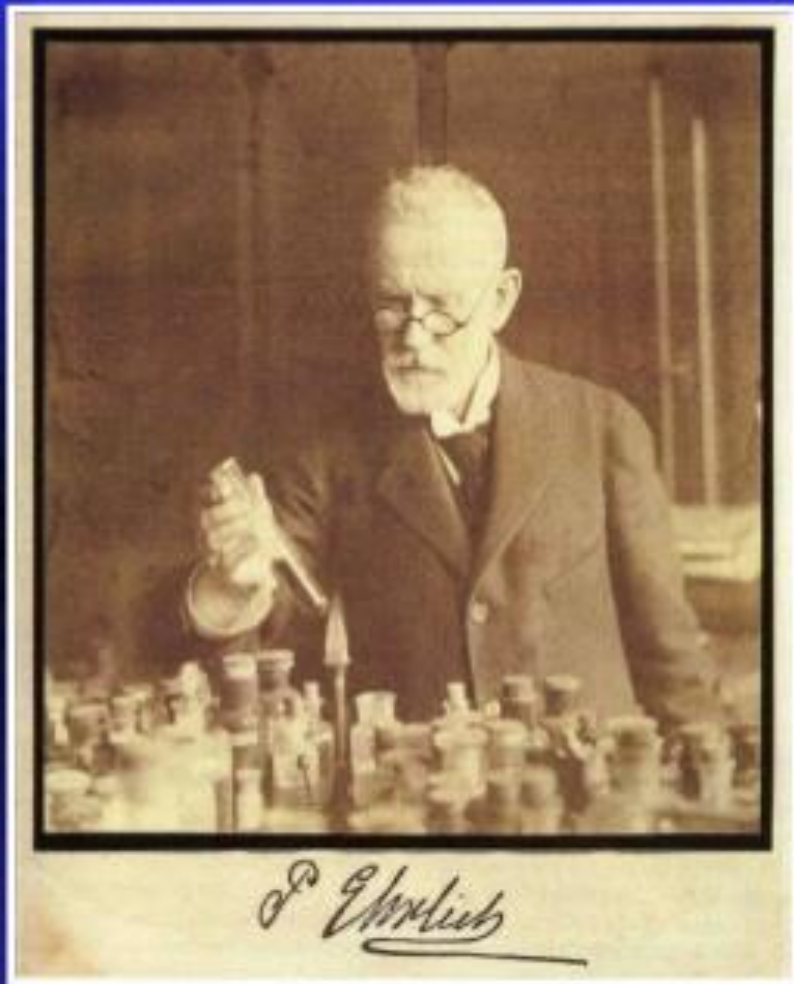
Stage I: **Cancer** is in the inner layers of the colon

Stage II: **Cancer** has spread through the muscle wall of the colon

Stage III: **Cancer** has spread to the lymph nodes

Stage IV: **Cancer** that has spread to other organs





**Paul Ehrlich 1854 -
1915**

- **Father of Chemotherapy**
- **Salvarsan for Treatment of Syphilis**
- **Nobel Prize 1908**
- **"Magic Bullet Concept"**

Multidisciplinary approach

- ▶ Team
 - ▶ Surgeon
 - ▶ Oncologist
 - ▶ Radiation oncologist
 - ▶ Physical Medicine
 - ▶ Cardiologist
 - ▶ Social worker
 - ▶ Psychiatrist
 - ▶ Gastroenterologist
 - ▶ Cancer geneticist
 - ▶ Nurse
 - ▶ Pharmacist
- 

MODALITIES OF TREATMENT

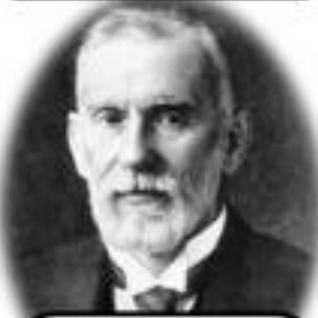
- **1-local therapy:**
 - ◆ **-surgery.**
 - ◆ **-radiation therapy.**
- **2-systemic treatment:**
 - ◆ **chemotherapy.**
 - ◆ **Hormonal therapy.**
 - ◆ **Monoclonal antibodies.**
 - ◆ **Radioactive material.**
- **3-supportive care.**
- **4-non-conventional therapy.**

Timeline history of chemotherapy development



Alexander Fleming 1928-
Penicillin

1908- Discovery
of Arsphenamine



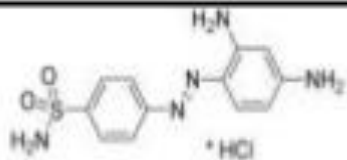
Paul Ehrlich
Father of
Chemotherapy



1900- Paul Ehrlich
Chemotherapy
Animal model
developed



Gerhard Domagk 1939-
Sulfonamidochrysoidine
(Prontosil)



1932- Prontosil-
First sulfonamide-
Bayer's Laboratory

1959- Antitumor
antibiotics

1958- Methotrexate

1957- 5-Fluorouracil

1951- Thiopurines

1948- Anitfolates

1944- Waksman *et al.*, discovered
streptomycin.

1943- Nitrogen
mustard in
lymphomas

1963-
Vinca alkaloids

1962- nalidixic acid

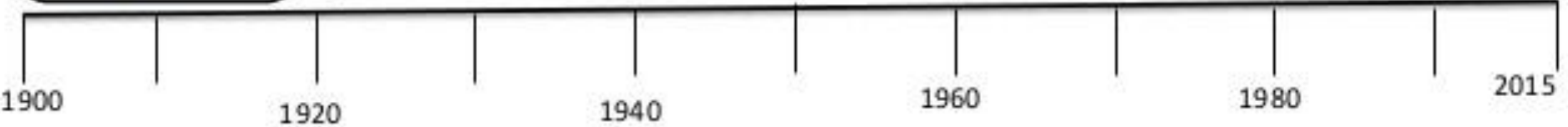
1963 to 1970-
Treatment for
Hodgkin's disease

2007- Target specific
screens

2005- Tyrosine kinase
inhibitors

1997- Monoclonal
antibody approved
for the treatment of
tumor.

1996- Imatinib

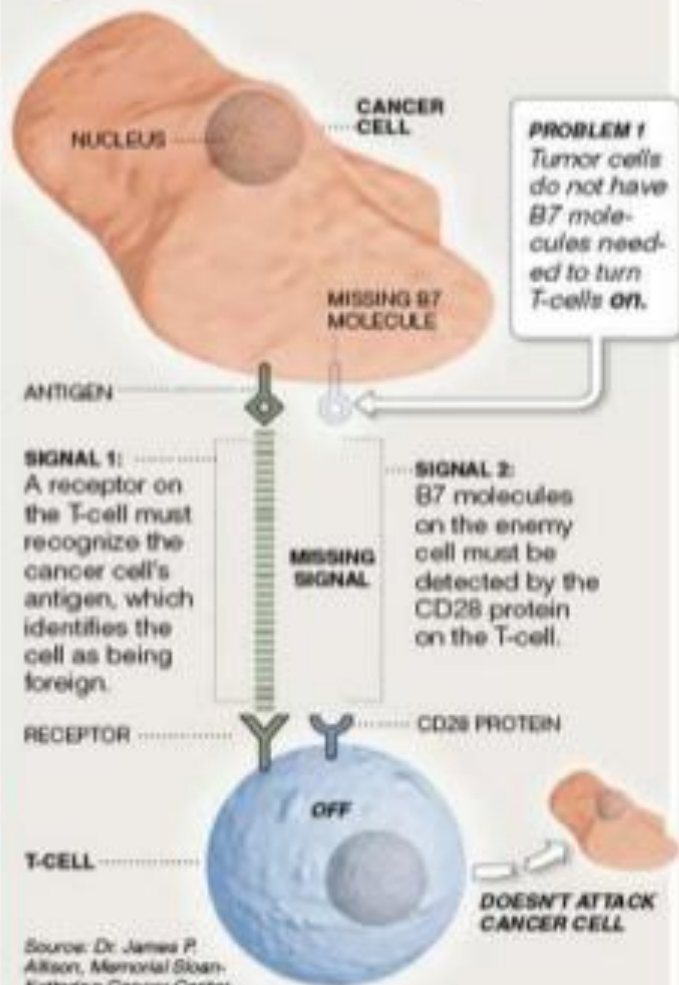


Cancer and the Immune System

For years, scientists have questioned why the immune system does not aggressively fight off cancer cells. New evidence suggests that T-cells, which are crucial to the body's immune response, have a protein (CTLA-4) that actually suppresses their ability to attack cancer cells. Researchers are focusing on that protein in hopes of creating a more aggressive immune system that could kill cancer cells.

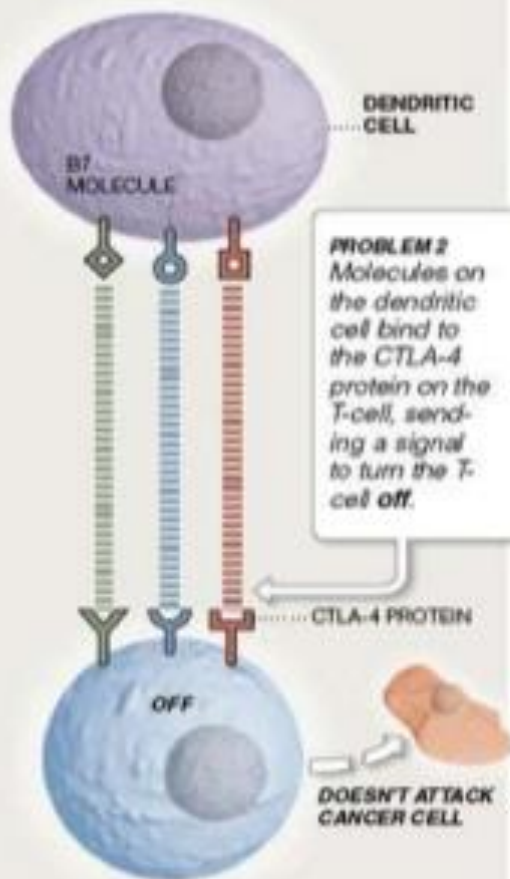
HOW T-CELLS DETECT ENEMY CELLS

For T-cells to be turned on, they must receive **two signals** that tell them to attack a foreign cell.



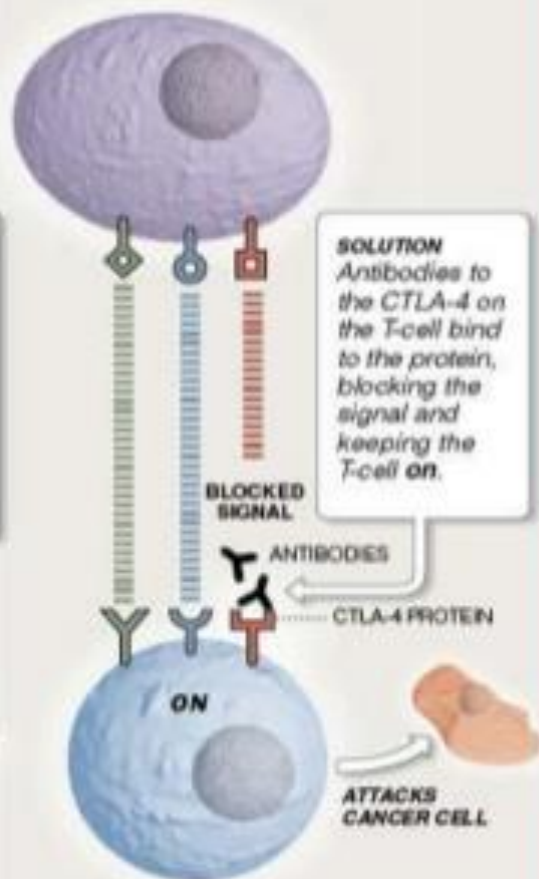
TURNING T-CELLS ON

Dendritic cells, part of the immune system, break up the cancer's antigen and present it to the T-cell to provoke a response. But they also have the ability to turn the T-cell off.

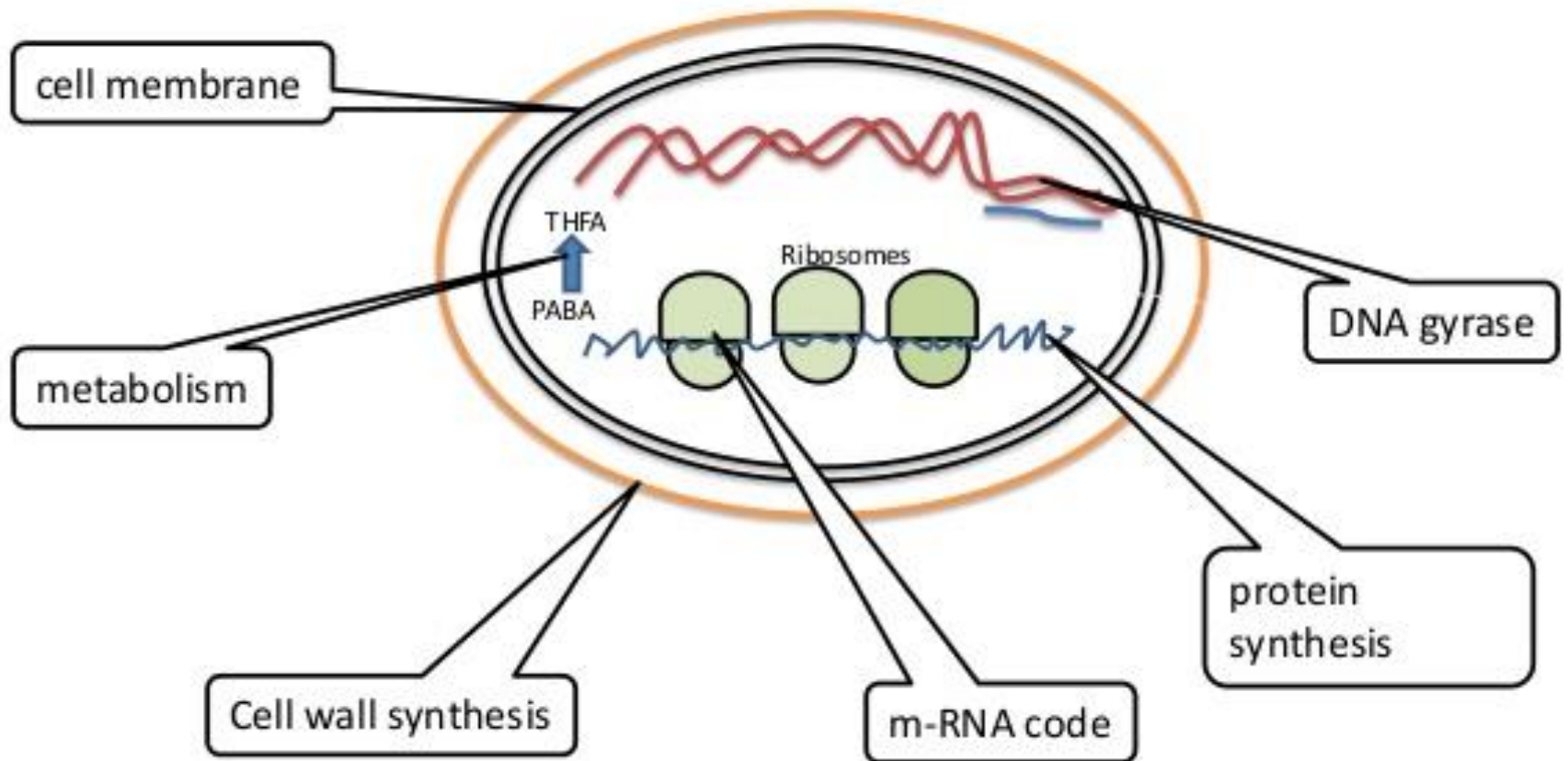


ONE POSSIBLE SOLUTION

Scientists have shown that injecting antibodies to CTLA-4 prevented the protein from binding with molecules on the T-cell and sending the third signal.



B. Mechanism of action



MODES OF CHEMOTHERAPY

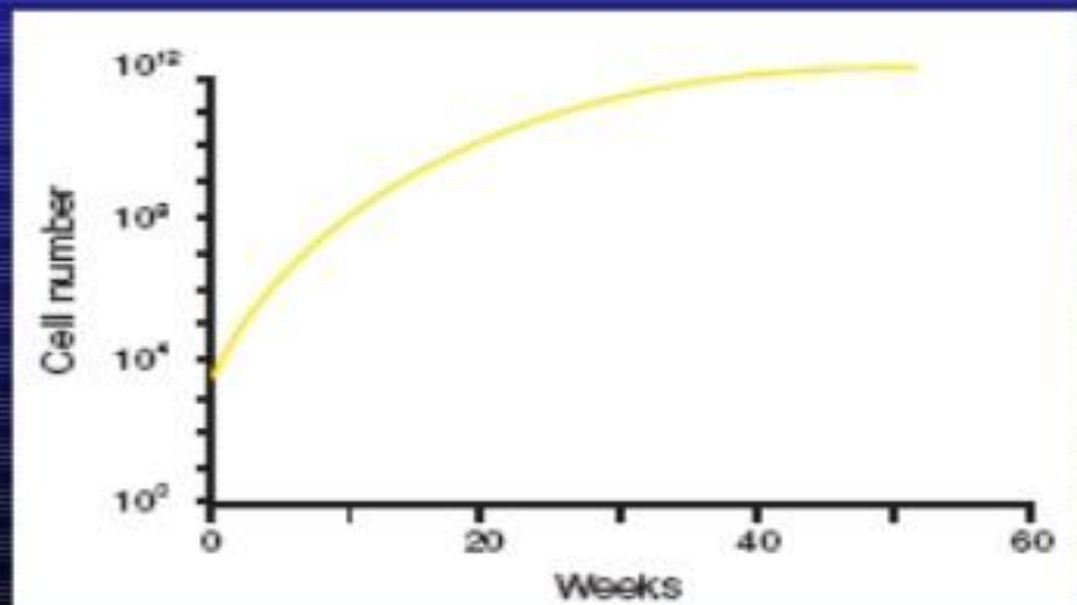
- **PRIMARY CHEMOTHERAPY** - chemotherapy is used as the sole anti-cancer treatment in a highly sensitive tumor types
 - ◆ Example – CHOP for Non-Hodgkins lymphoma
- **ADJUVANT CHEMOTHERAPY** – treatment is given after surgery to “mop up” microscopic residual disease
 - ◆ Example – Adriamycin, cyclophosphamide for breast cancer
- **NEOADJUVANT CHEMOTHERAPY** – treatment is given before surgery to shrink tumor and increase chance of successful resection
 - ◆ Example – Adriamycin, ifosfamide for osteosarcoma

MODES OF CHEMOTHERAPY

- **CONCURRENT CHEMOTHERAPY** – treatment is given simultaneous to radiation to increase sensitivity of cancer cells to radiation
 - ◆ **Example – Cisplatin, 5-fluourouracil, XRT for head and neck tumors**

GOMPERTZIAN GROWTH

- Growth rates are exponential at **early stages** of development and slower at later stages of development



Biological growth follows this characteristic curve.

AIM OF COMBINATION

CHEMOTHERAPY

INCREASED EFFICACY

ACTIVITY

SAFETY

Different mechanisms of action
Different mechanisms of resistance

Compatible side effects



Combination chemotherapy: Metastatic Breast Cancer

Agents	Dose Intensity		PR (%)*	CR (%)*
<u>C</u> yclophosphamide	1	1	35	0
<u>M</u> ethotrexate	1	1	25	0
<u>F</u> luorouracil	1	1	25	0
Doxorubicin (A)	1	1	50	5
CMF	0.5+0.33+0.33	1.17	50	5
CAF	0.5+0.7+0.33	1.53	75	10

* Patients with overt metastases and no prior chemotherapy except in the adjuvant setting

PR = partial response

CR = complete response

G1: Gap 1
(Cell Grows)

S: Replication
of DNA

G2: Gap 2
(Cell Prepares
to Divide)

INTERPHASE

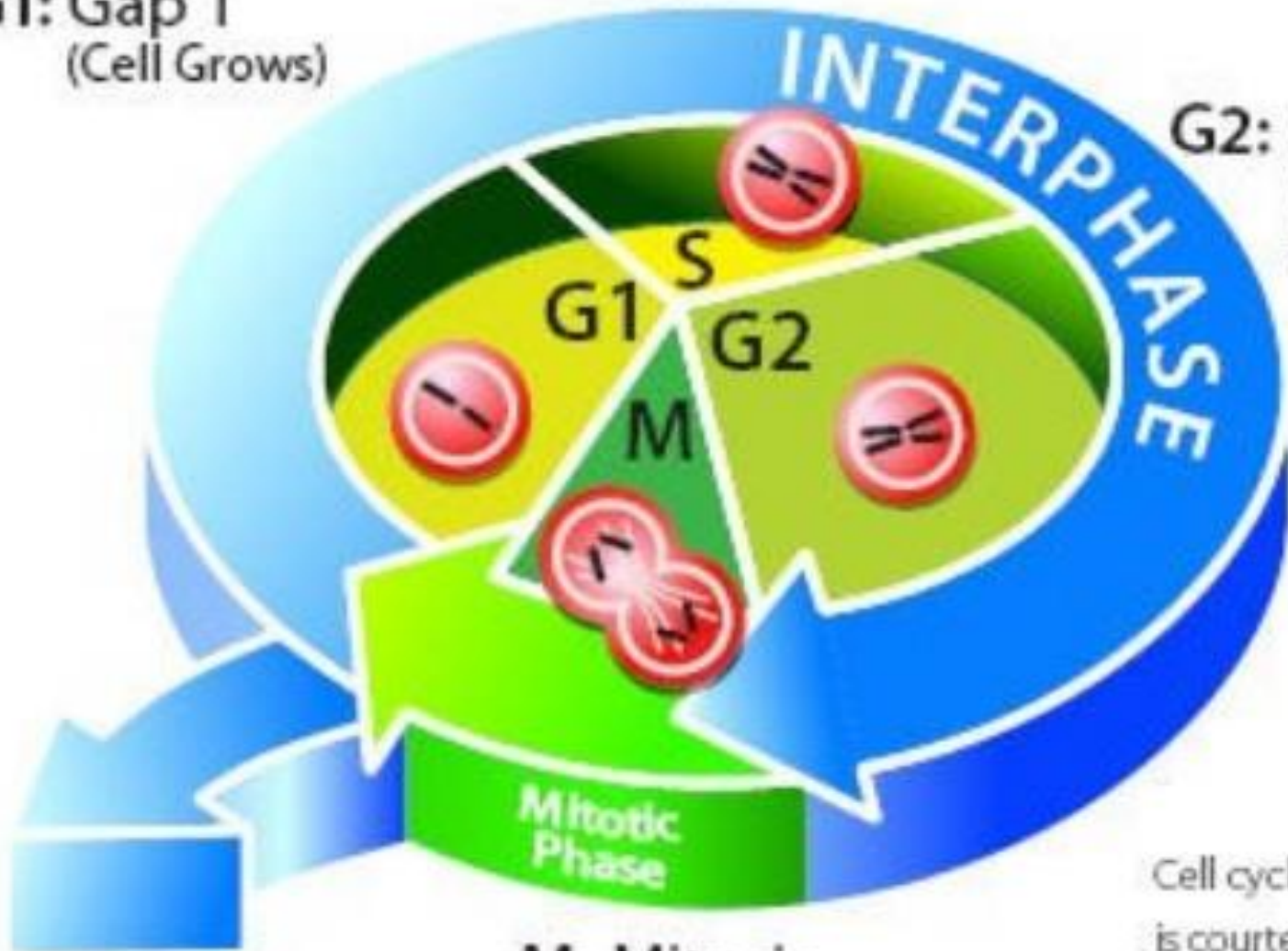
G1
S
G2
M

Mitotic
Phase

M: Mitosis
(Cell Division)

Cells that
Cease Division

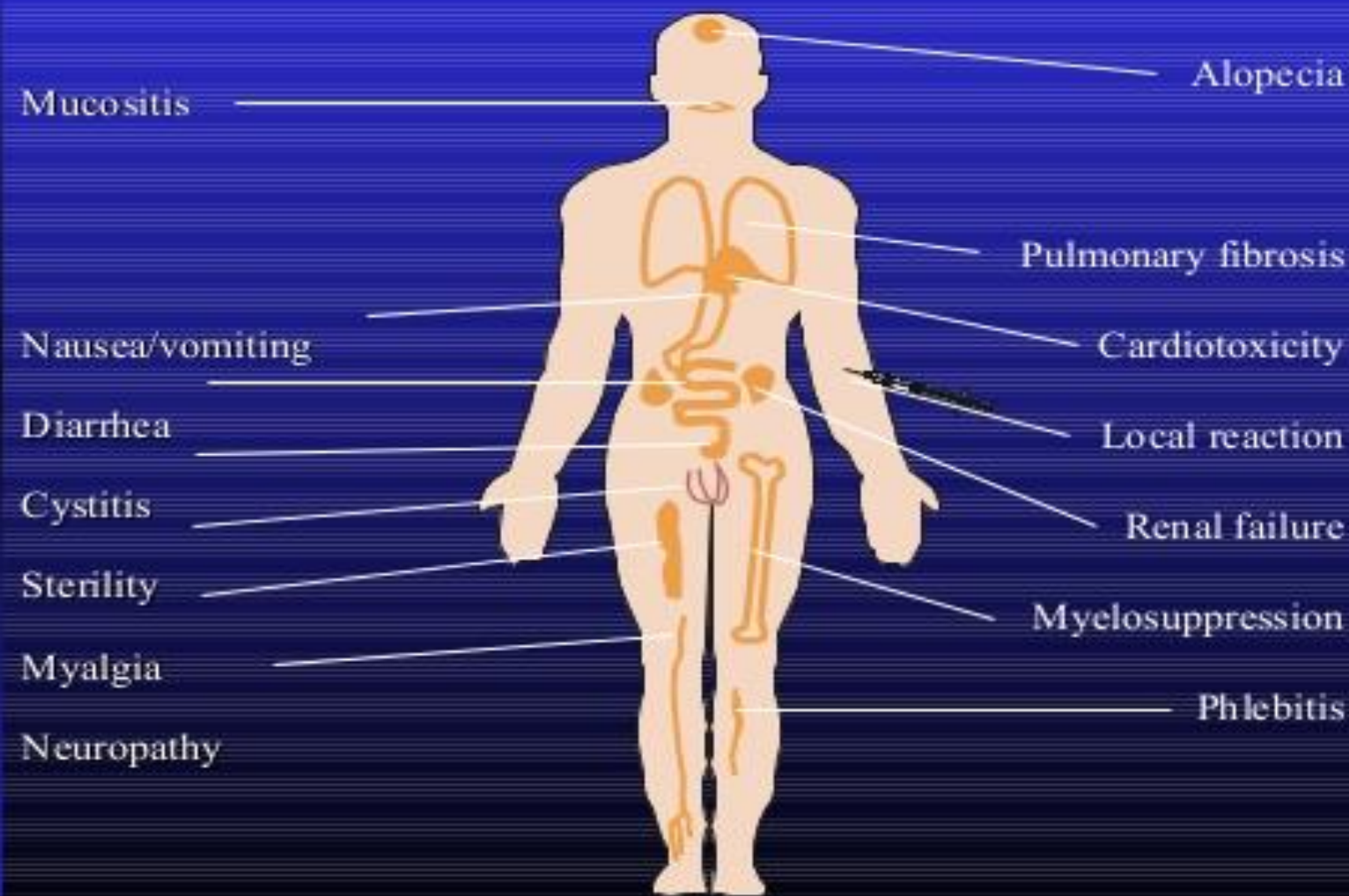
Cell cycle cartoon image
is courtesy of *The Science
Creative Quarterly* (www.scq.ubc.ca), Jane Wang,
Illustrator.



HEMATOLOGICAL CONSIDERATIONS FOR DOSE SCHEDULING

- Lifespan
 - ◆ Platelet - 7-10 days
 - ◆ Red blood cell - 120 days
 - ◆ Neutrophils - 6-12 hours
- Time from Stem Cell to Mature Neutrophil
 - ◆ ~7-10 days

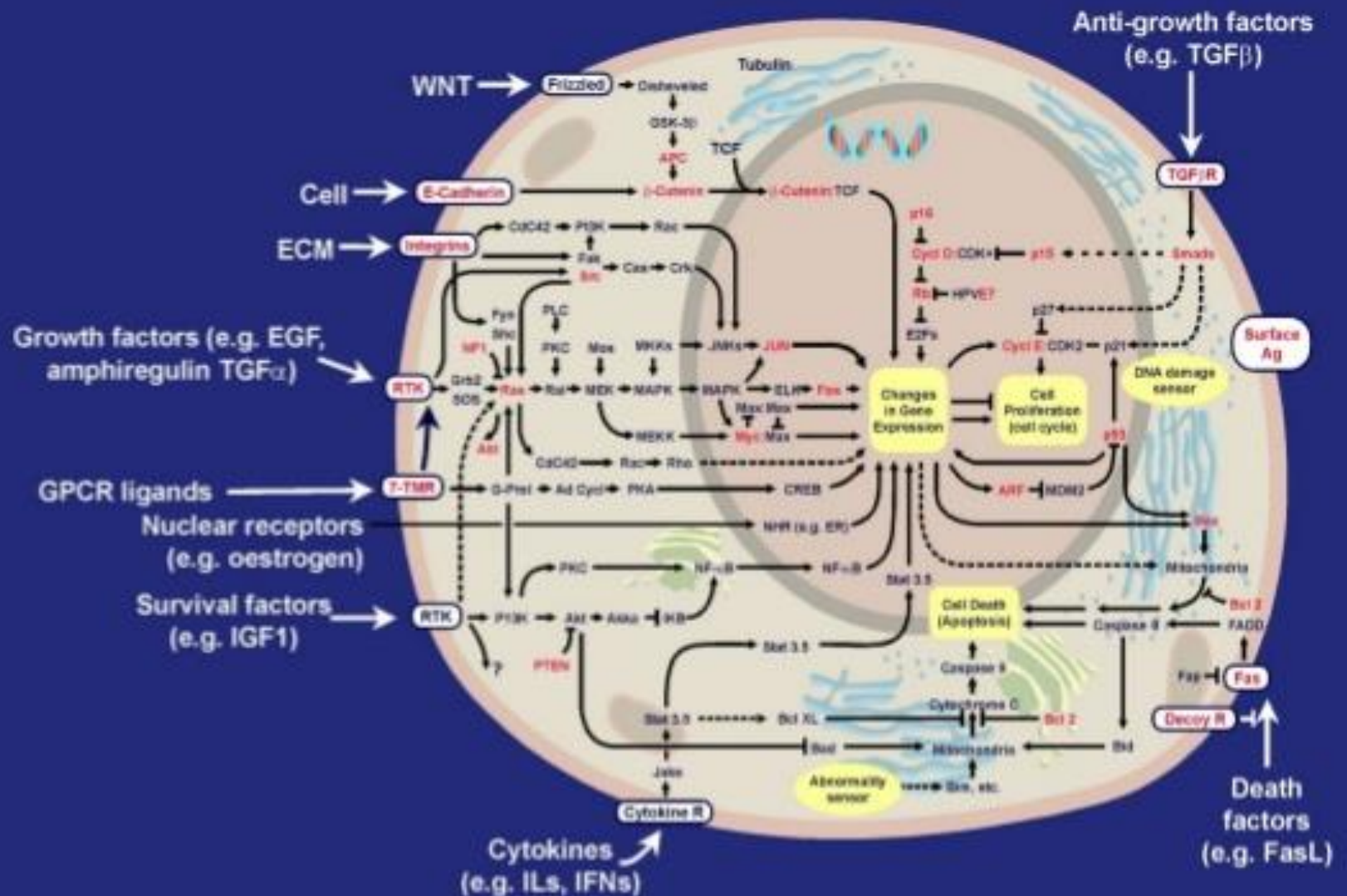
SIDE EFFECTS OF CHEMOTHERAPY



CRITERIA USED TO DESCRIBE RESPONSE ARE:

- **Complete response** (complete remission) is the disappearance of all detectable malignant disease.
- **Partial response** : is decrease by more than 50% in the sum of the products of the perpendicular diameters of all measurable lesions.
- **Stable disease** : no increase in size of any lesion nor the appearance of any new lesions.
- **Progressive disease** : means an increase by at least 25% in the sum of the products of the perpendicular diameters of measurable lesion or the appearance of new lesions.

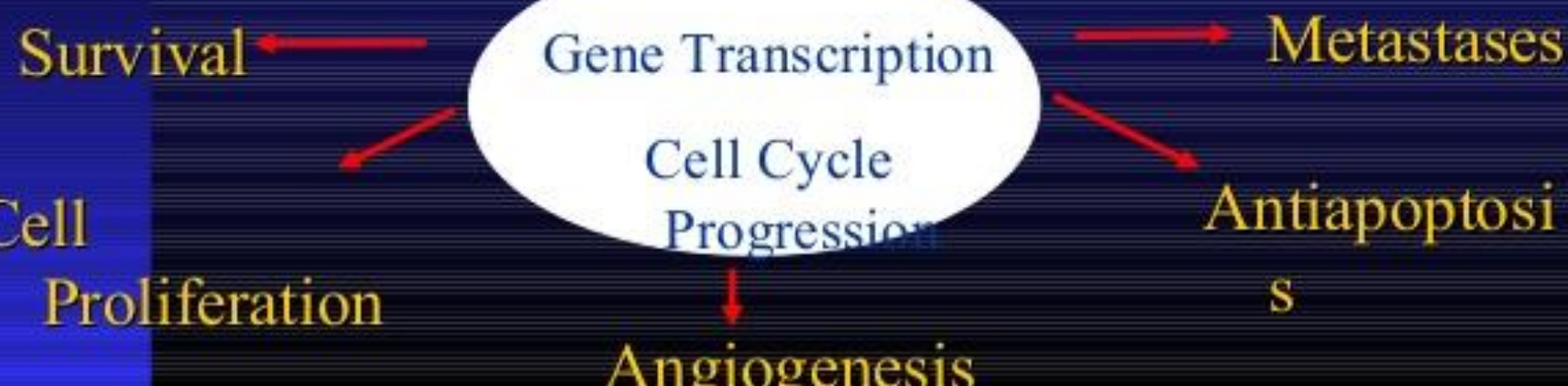
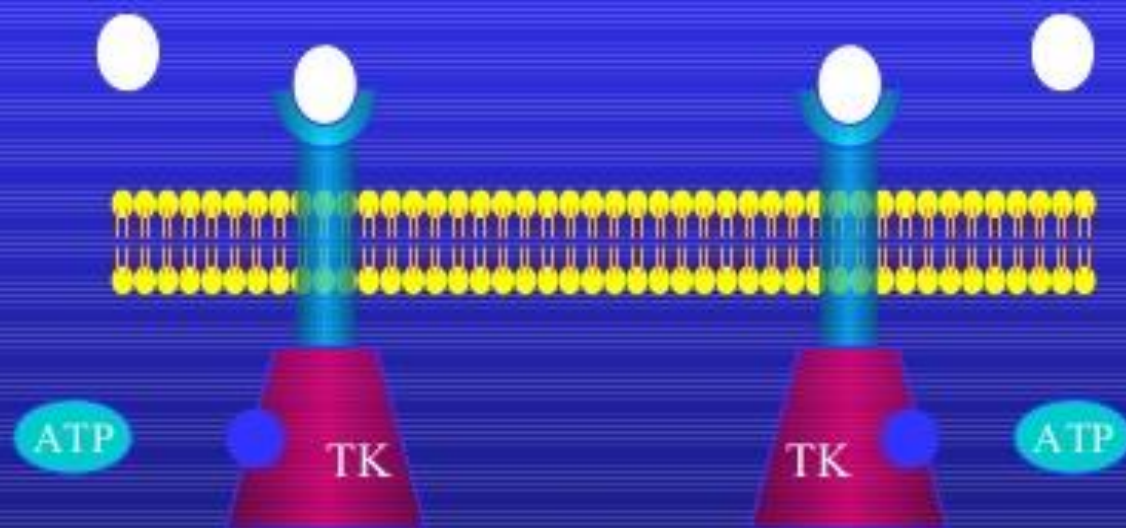
SIGNALLING PATHWAYS



TARGETED THERAPIES

- **Monoclonal antibodies:** proteins that trigger the body's pathways involved in cancer growth to fight cancer more effectively.
- **EGFR:** family of receptors found on surface of normal and cancer cells that bind with an epidermal growth factor (EGF) causing cells to divide.
- **Tyrosine Kinase Inhibitors:** Part of the cell that signals it to divide and multiply; enhances cell growth. Still investigational

Tumor Cell Stimulation



PREVENTION IS BETTER THAN CURE!!



BAD HABITS

Good Habits





✓  DO  ✓



Thank you

tan.winston@mayo.edu



THANK YOU!
THE END!