

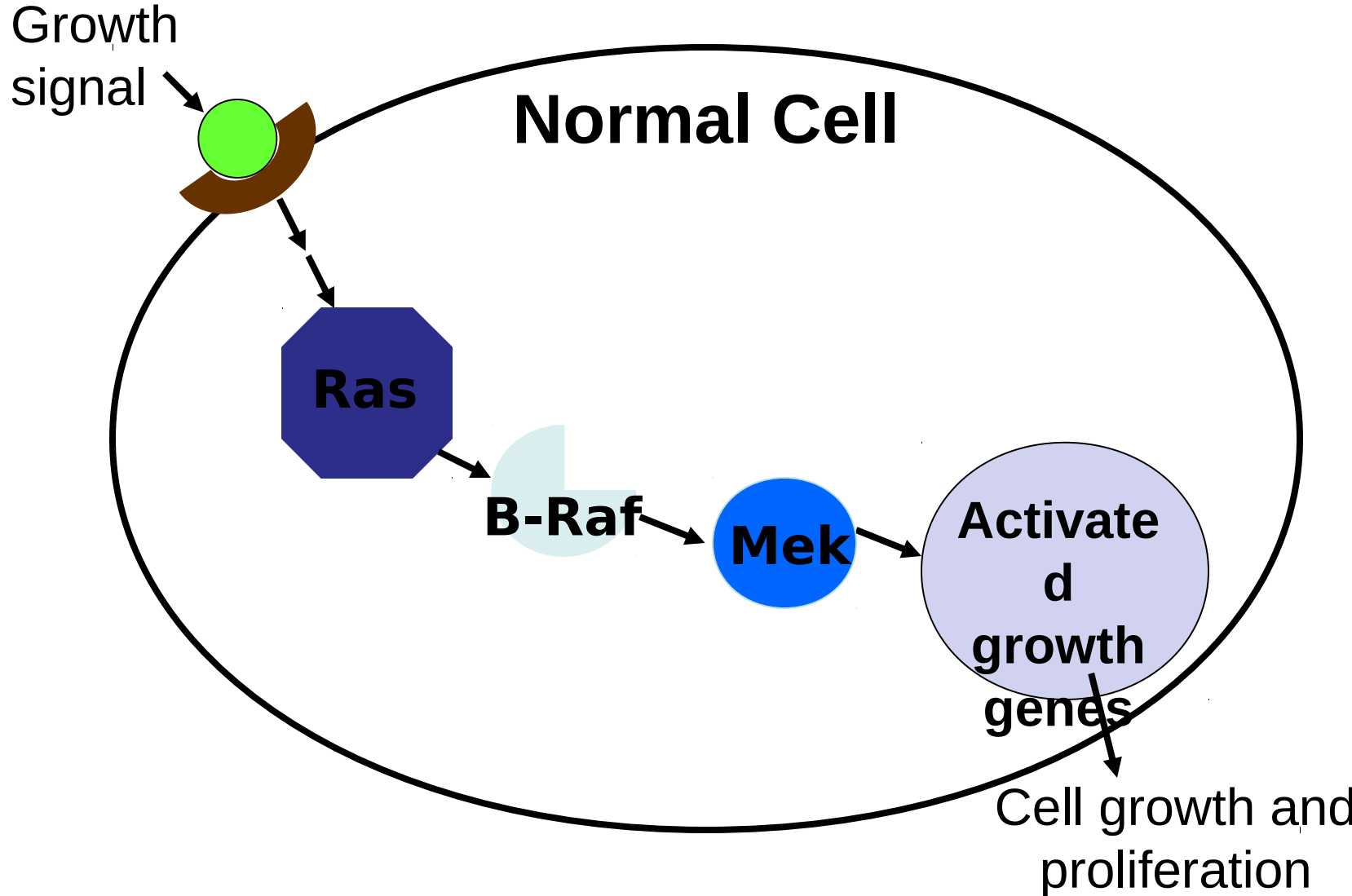
# How do mutations cause cancer?

# Cell Signaling Pathways

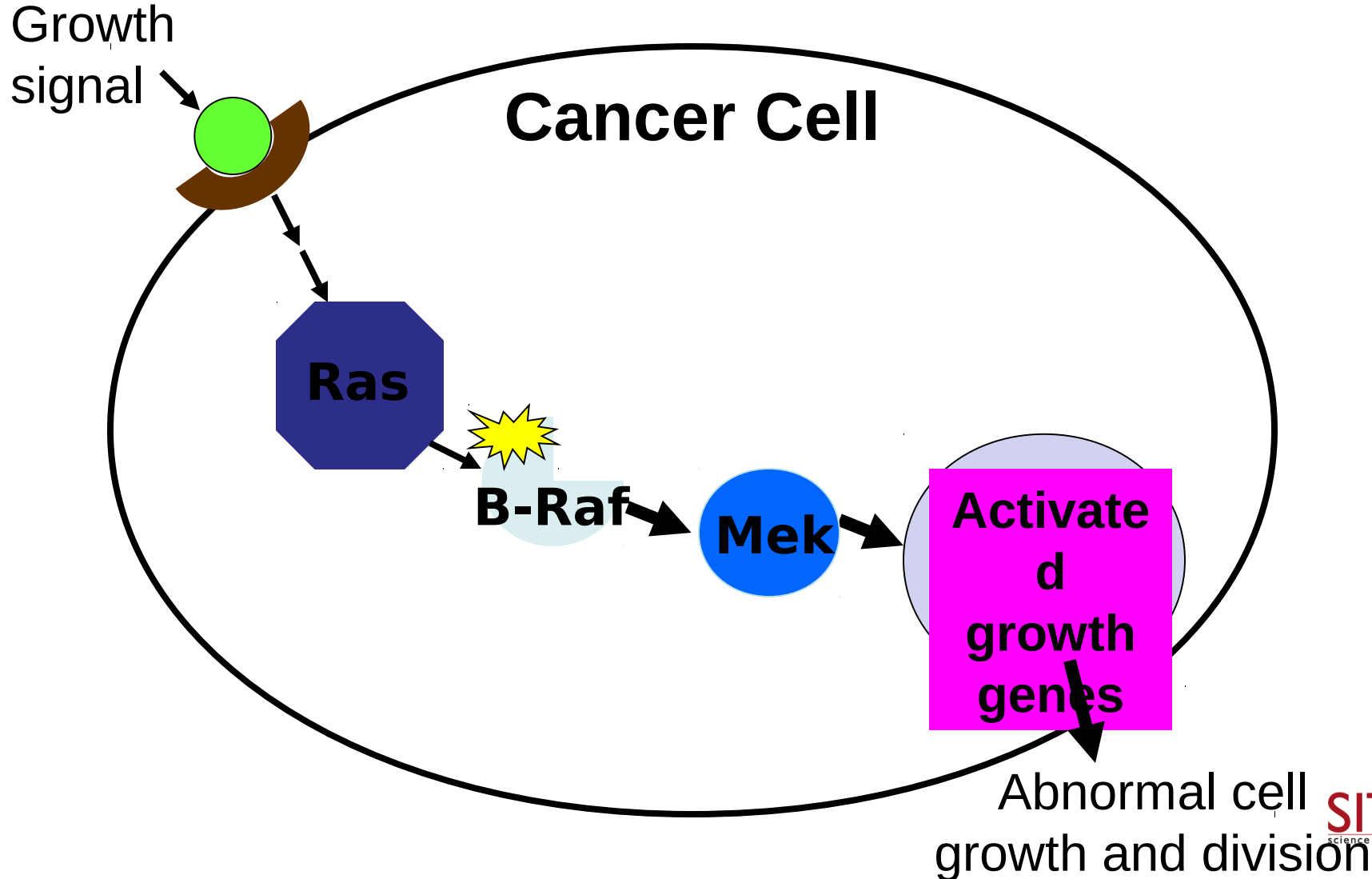
- Take information from outside of the cell and transmit the signal to create an output
- Examples: Cell division, cell death, response



# Ras pathway - cell growth

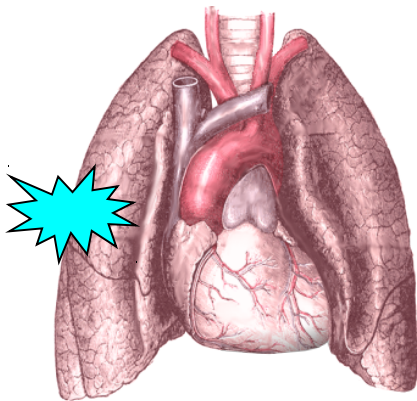


# Ras pathway - cell growth

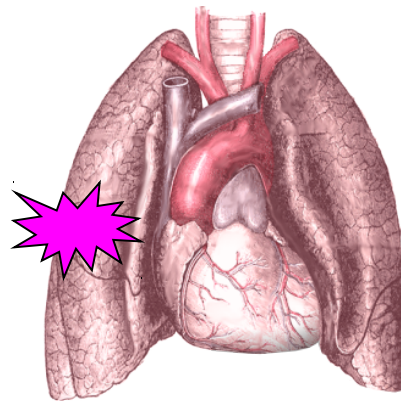


# There are many diverse types of cancer

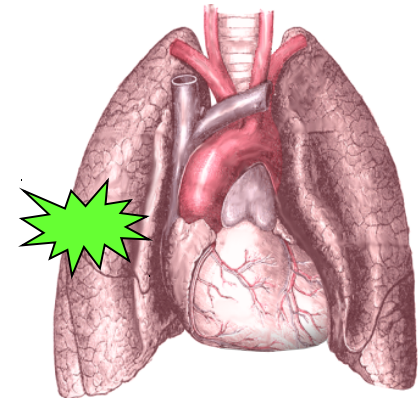
- Depending on mutation, different signaling pathways are affected



Signaling  
Pathway A



Signaling  
Pathway B



Signaling  
Pathway C

# Summary

- Properties of cancer cells
  - Abnormal growth and migration through the body
- Mutations in DNA and signaling pathways can cause cancer
  - Example: mutation in the Ras pathway that controls cell growth
- Cancer is not one disease!

# Part 2: Cancer Therapies, Present and Future

Adrianna San Roman

**Leah Liu**

Clare Malone

# Objectives

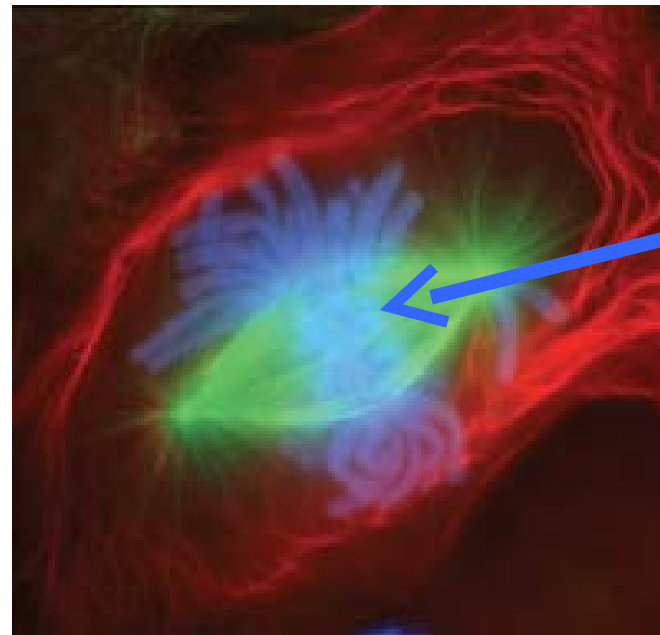
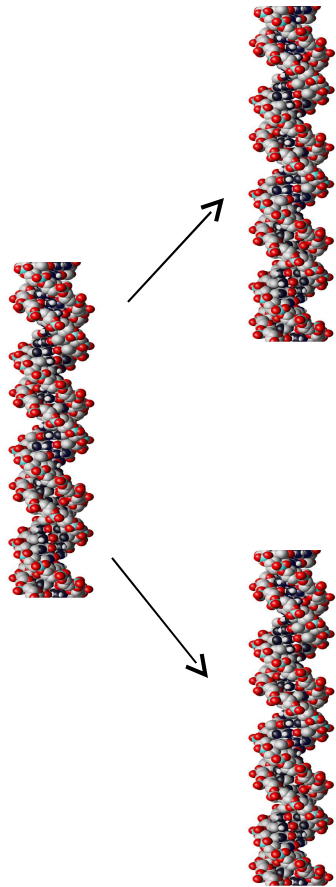
- Learn about cancer therapies that attack general features common to all cancers
- Learn about cancer therapies that attack specific features or mutations found in individual cancers
- The therapeutic window is the medicine dosage range that is both effective AND safe



# Properties of Normal Cells vs. Cancer Cells

<b>Normal Cells</b>	<b>Cancer Cells</b>
<b>Controlled growth</b>	<b>Uncontrolled growth</b>
Stay within their home tissue	Can move to other tissues in the body
Maintain normal tissue structure	Disrupt tissue structure and cause blood vessel growth

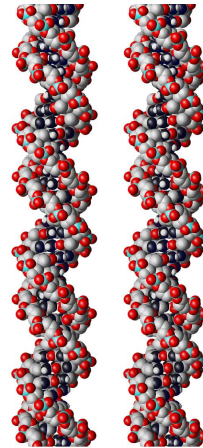
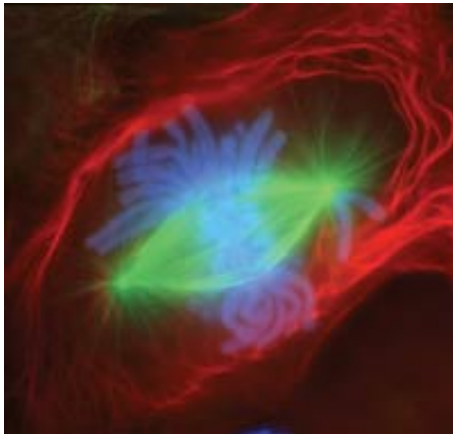
# DNA replication during cell division



**DNA**

Dividing  
cell

# General and Specific Features of Cancer Cells



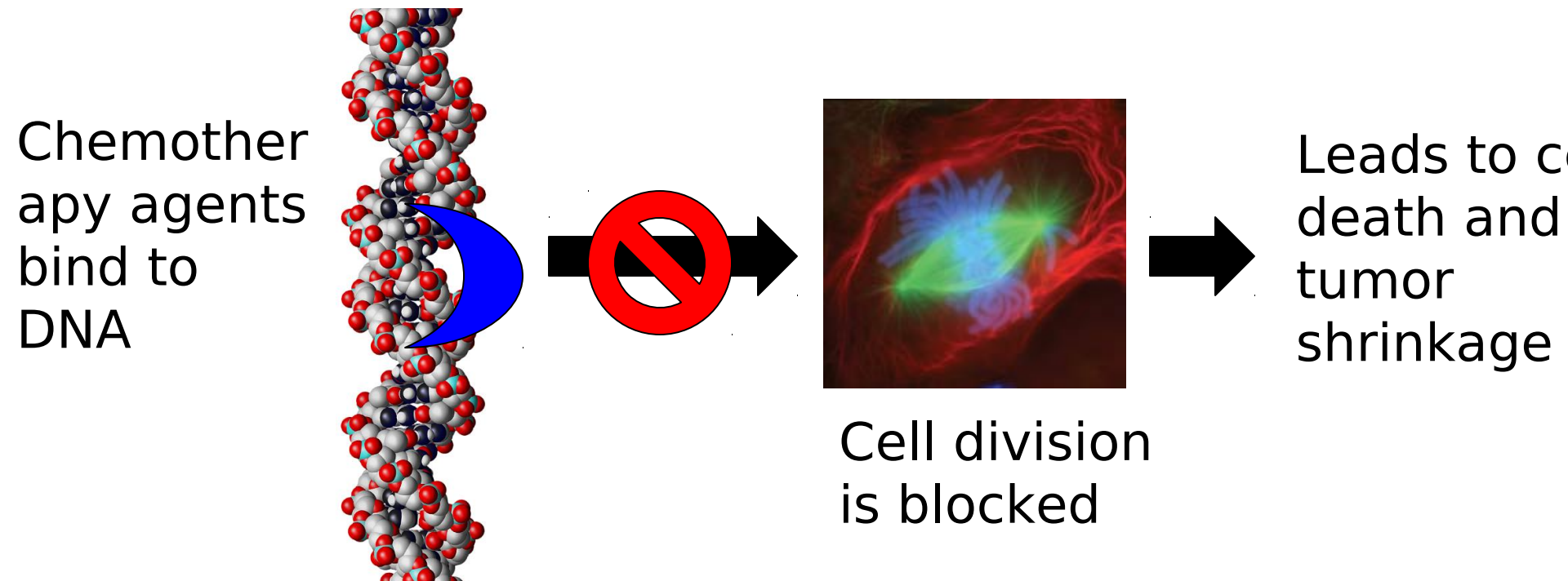
AGCGTATG**G**TGTCAC

AGCGTAT**C**TGTCAC

Uncontrolled cell division  
and DNA replication

DNA mutation

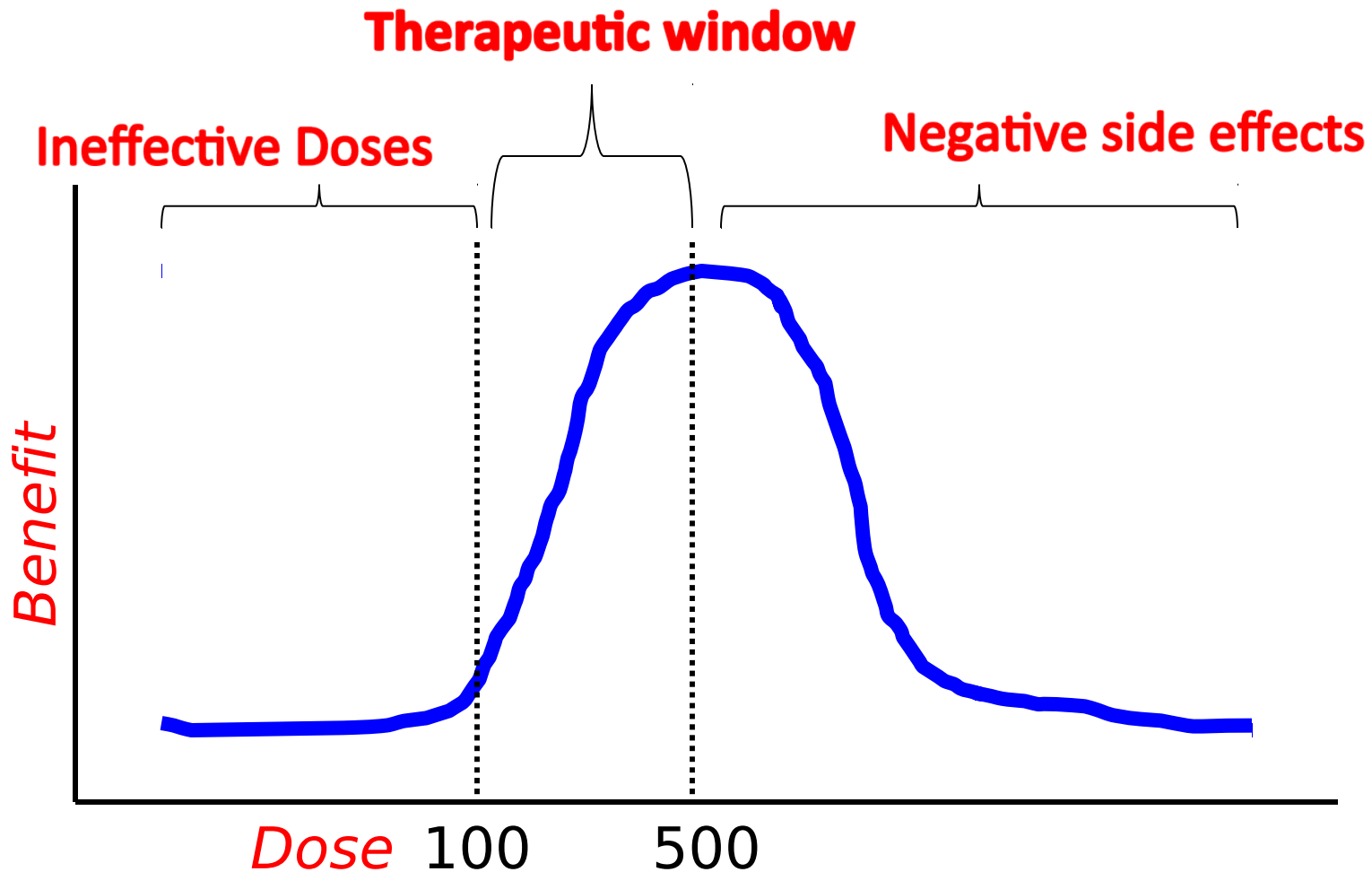
# Chemotherapy consists of chemicals that kill cells that divide rapidly



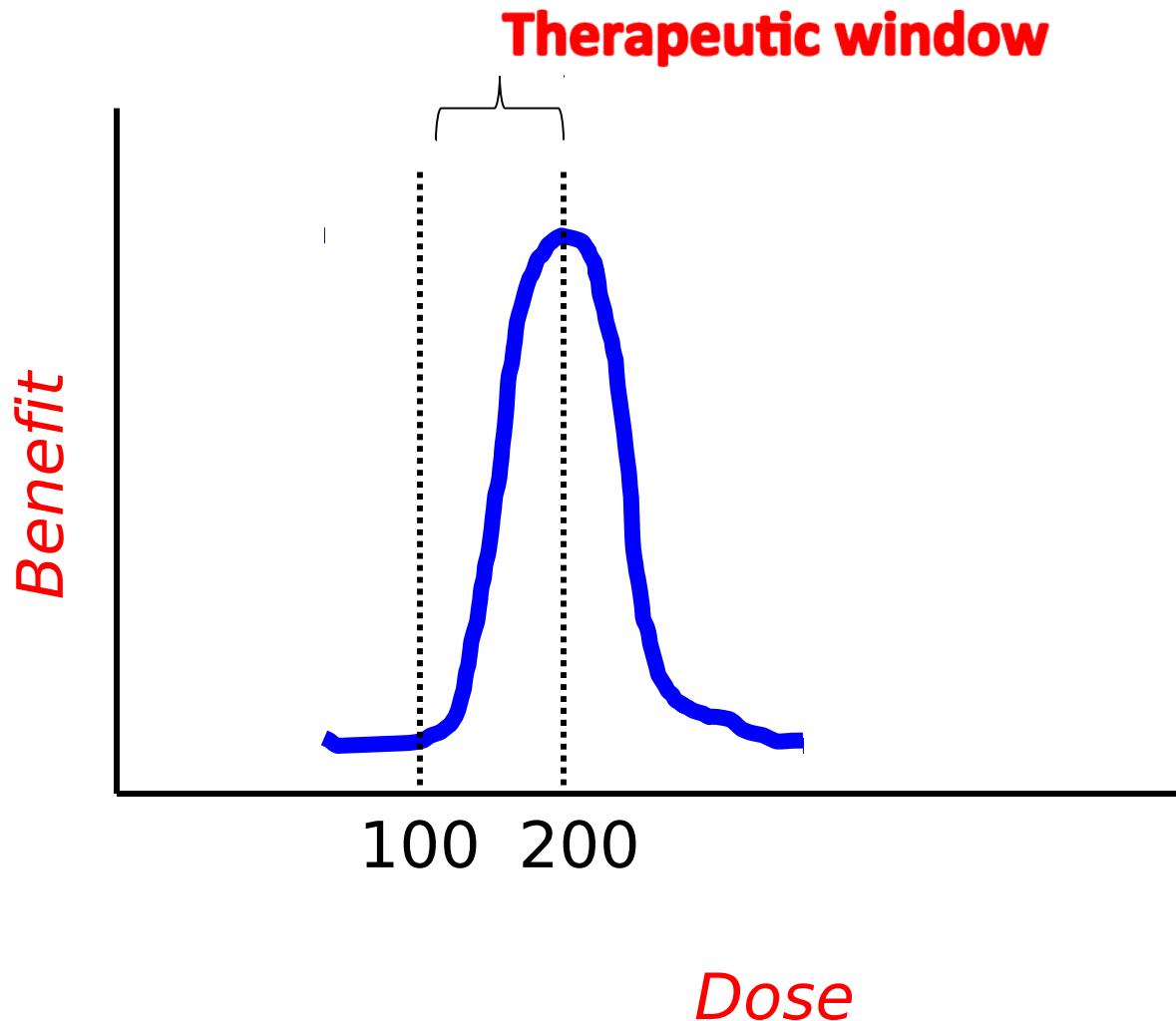
Most cells in the body do not divide frequently

# Therapeutic Window:

- Medicine dosages that are both safe and effective

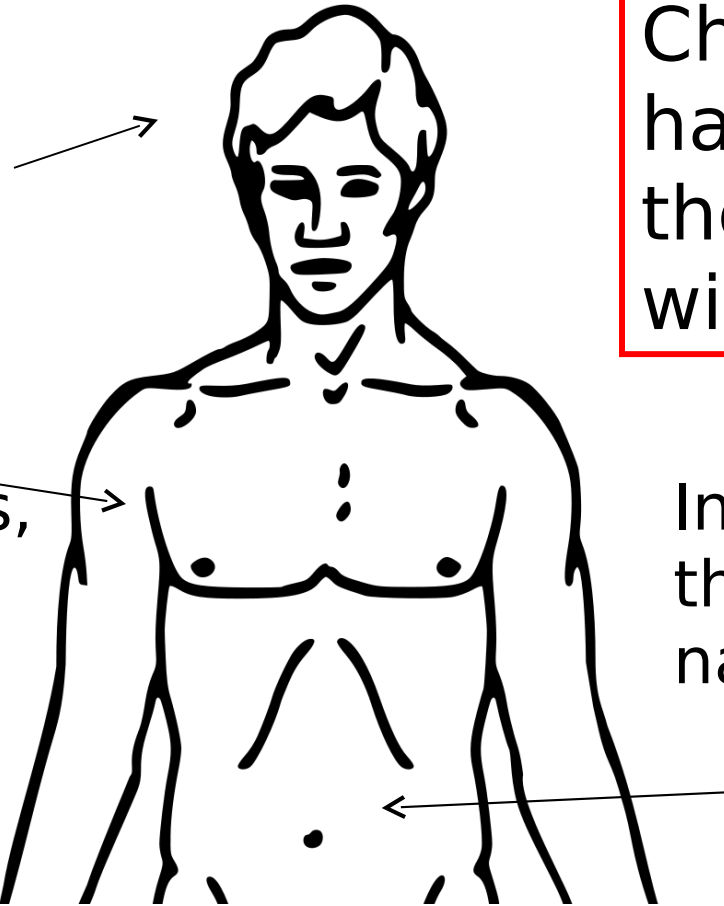


# Therapeutic Window:



# Chemotherapy causes side effects

Hair loss



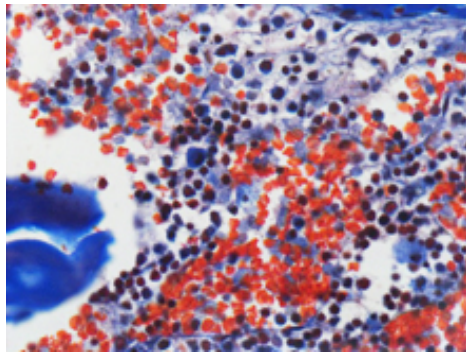
Chemotherapy has a small therapeutic window

Fewer blood cells, suppressed immune system (bone marrow)

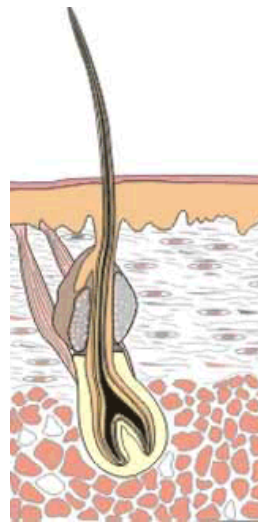
Inflammation of the digestive tract, nausea, diarrhea

# Why are the bone marrow, hair, and digestive tract affected?

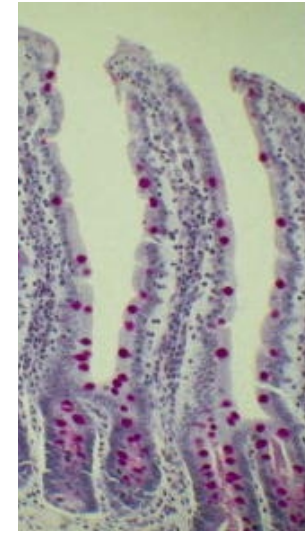
- Chemotherapy attacks ANY fast-dividing cells, including but not limited to cancer cells



Blood cells in bone marrow



Hair follicle



Intestinal cells

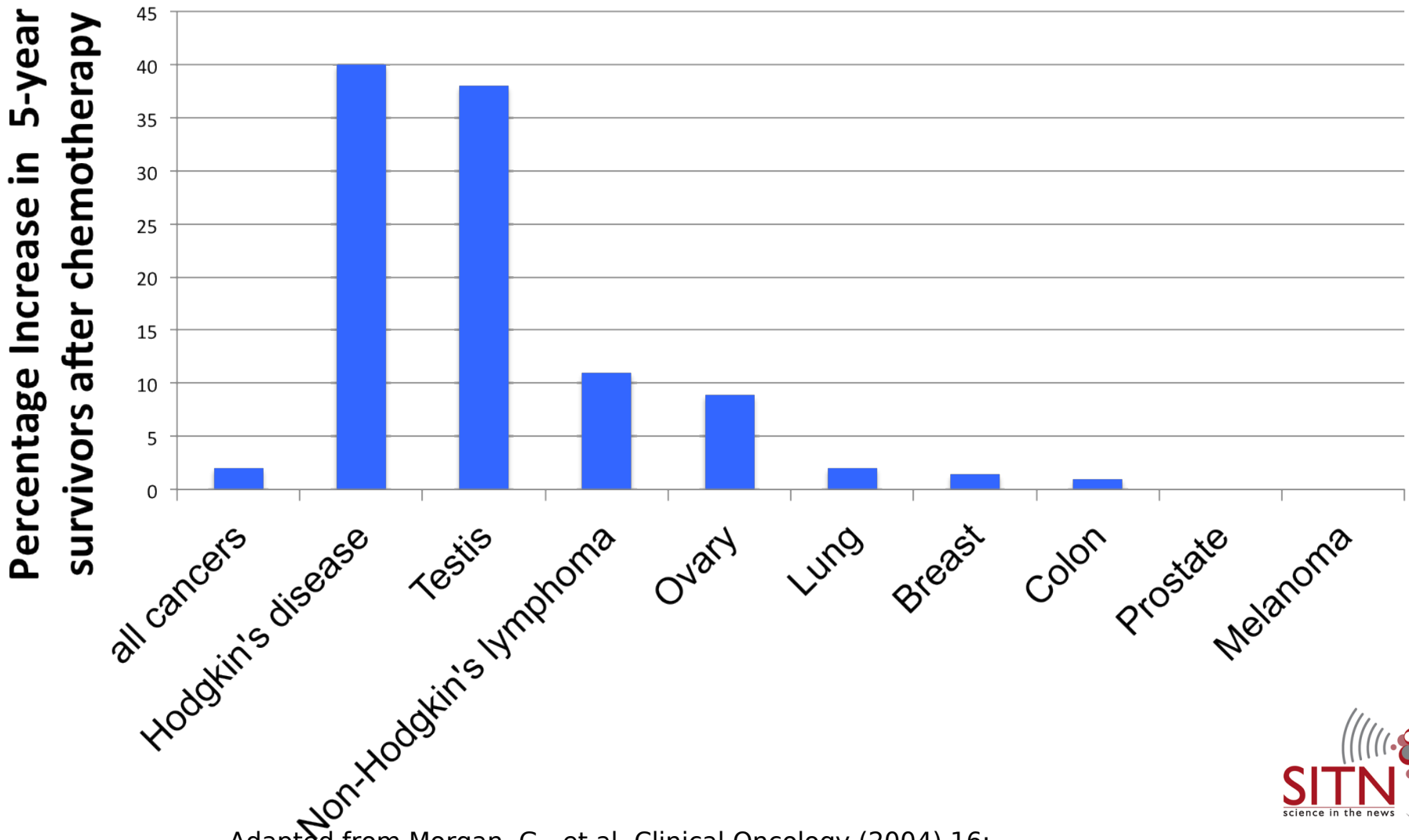


# How effective is chemotherapy?

- The 5 year survival rate for all cancers is 63%
- What would be the 5 year survival rate **without** chemotherapy?
  - A. 2%
  - B. 33%
  - C. 61%

63% - 61% = **2%** of survival rate can be attributed to chemotherapy

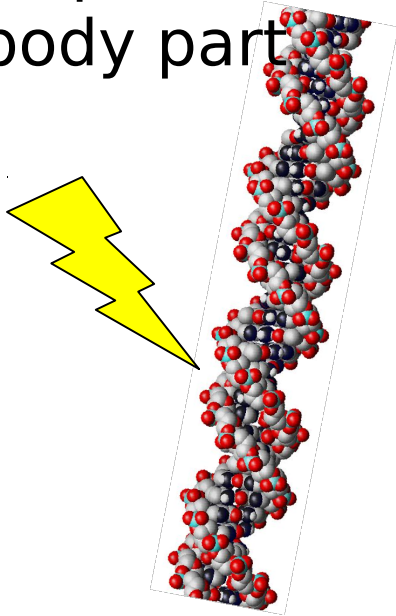
# Each type of cancer responds very differently to chemotherapy



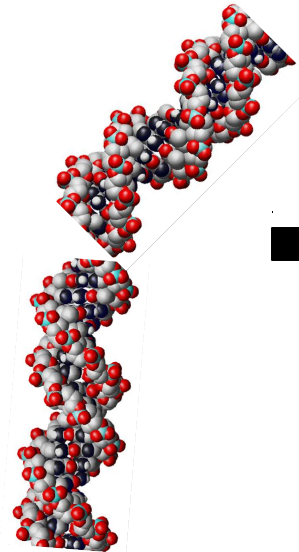
Adapted from Morgan, G., et al. Clinical Oncology (2004) 16:

# Radiation therapy damages DNA

Radiation is targeted to a specific body part



DNA Damage



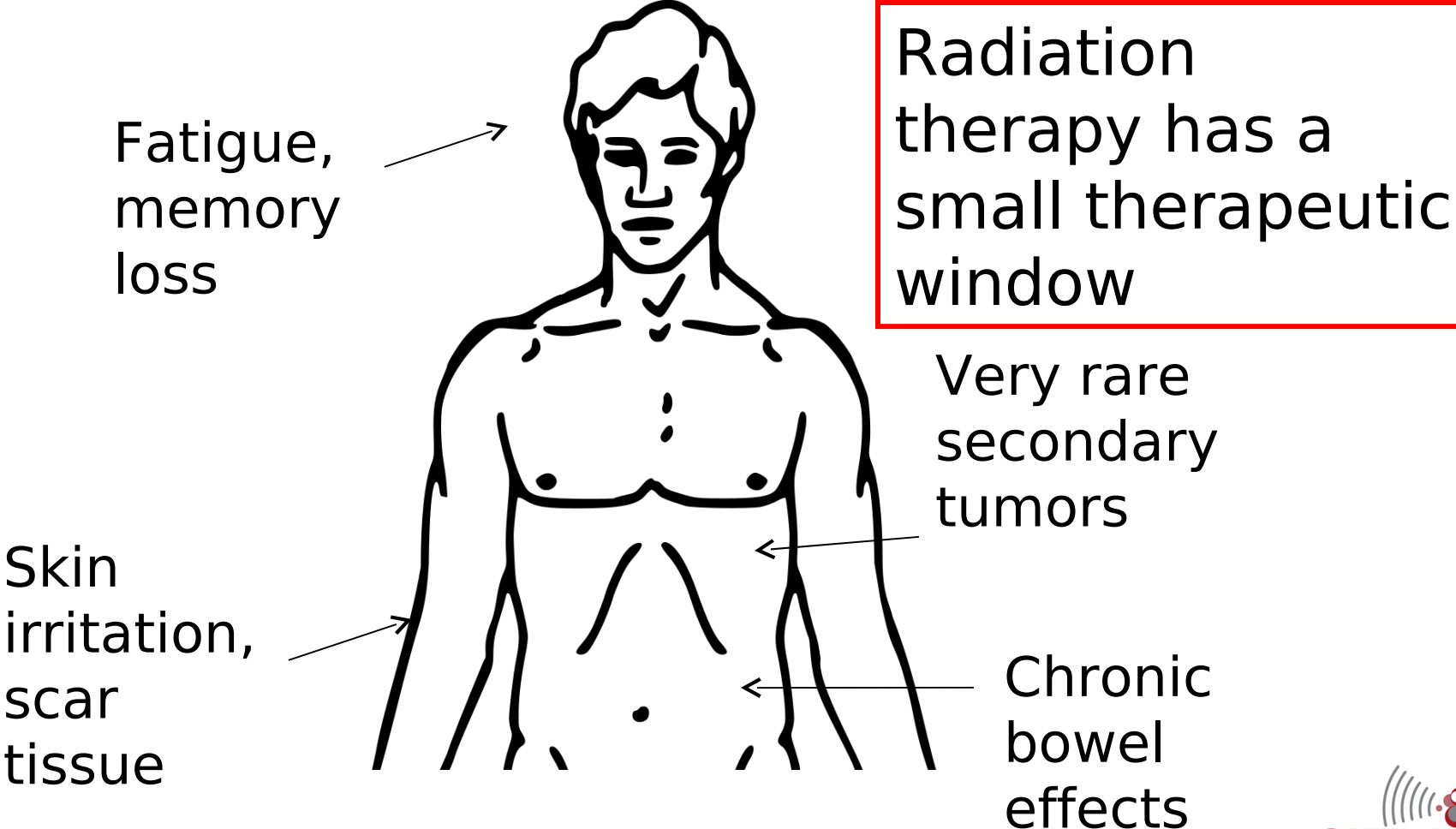
Cancer cells are bad at repairing DNA



Cell death,  
tumor  
shrinkage

Normal cells can also be affected

# Radiation Therapy causes side effects



# Different cancers respond very differently to radiation therapy

## Responsive Cancers

Lymphoma

Medulloblastoma

Neuroblastoma

## Resistant Cancers

Melanoma

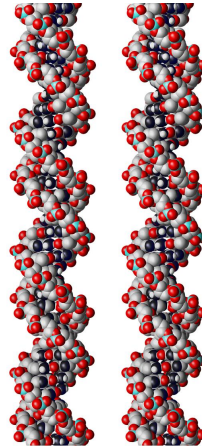
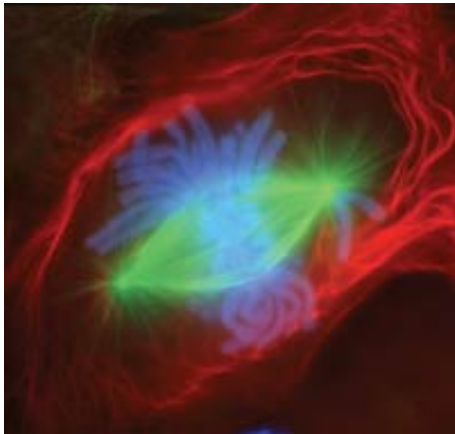
Glioma

Large bowel cancer

# Summary: Current Cancer Therapies

- Chemotherapy attacks cells that divide rapidly such as cancer cells but other tissues too
- Radiation therapy damages DNA in cancer cells such that it cannot be repaired
- Both chemotherapy and radiation therapy have small therapeutic windows

# General and Specific Features of Cancer Cells



AGCGTATG**G**TGTCAC

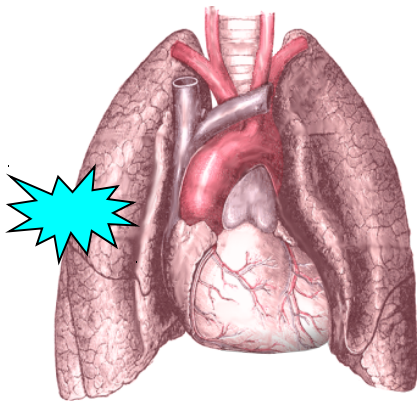
AGCGTAT**C**TGTCAC

DNA mutation

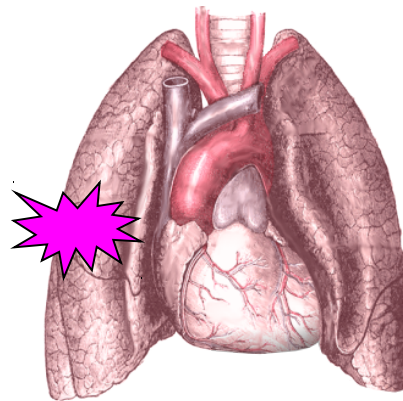
Uncontrolled cell division  
and DNA replication

# There are many diverse types of cancer

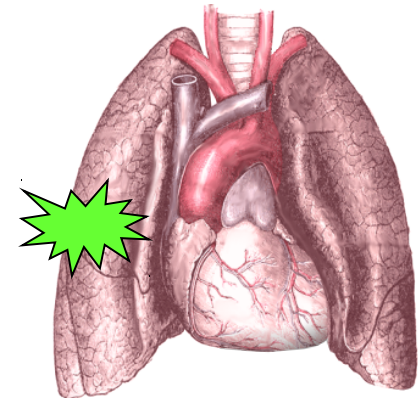
- Depending on mutation, different signaling pathways are affected



Signaling  
Pathway A



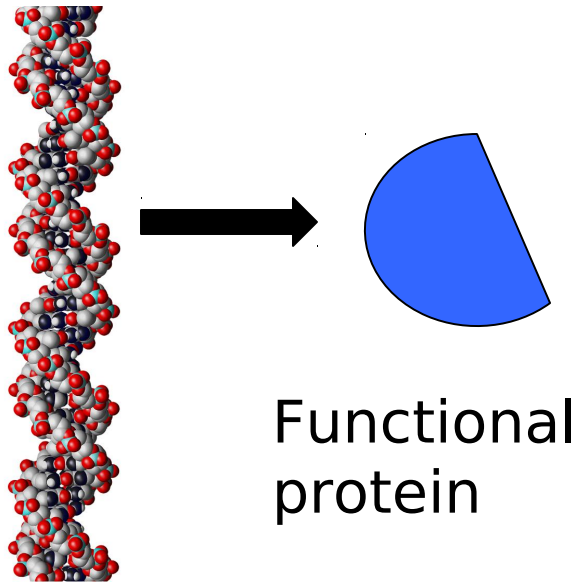
Signaling  
Pathway B



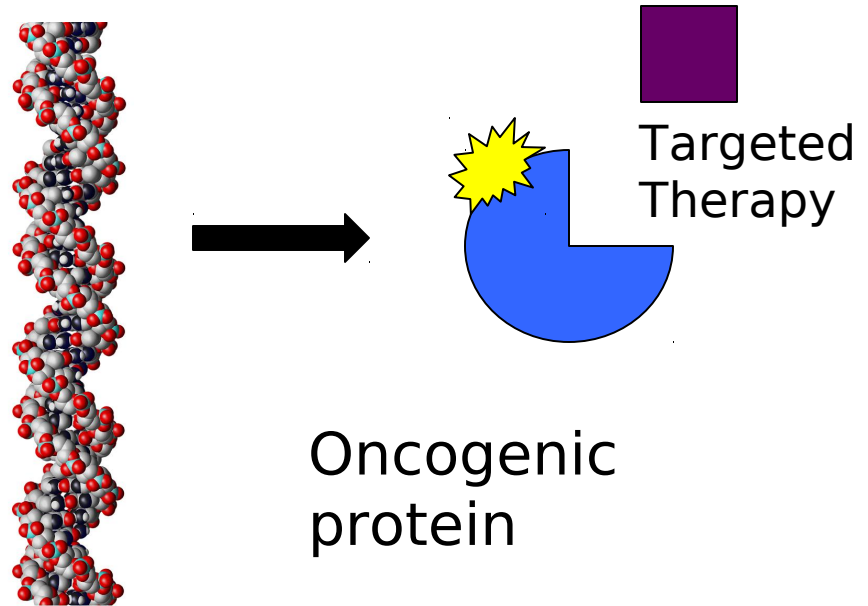
Signaling  
Pathway C



“Targeted therapies” are medicines that interfere with specific mutated proteins necessary for tumor growth

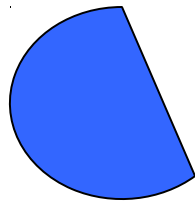
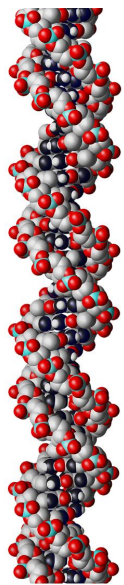


AGCGTAT**G**TGTCAC  
Normal sequence



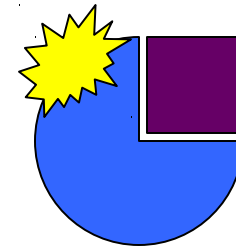
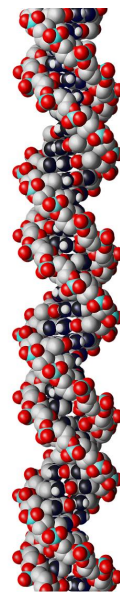
AGCGTAT**C**TGTCAC  
Mutated sequence

“Targeted therapies” are medicines that interfere with specific mutated proteins necessary for tumor growth



Functional  
protein

AGCGTAT**G**TGTCAC  
Normal sequence

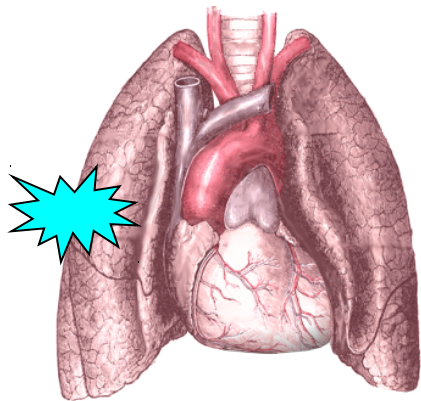


Oncogenic protein  
**blocked**

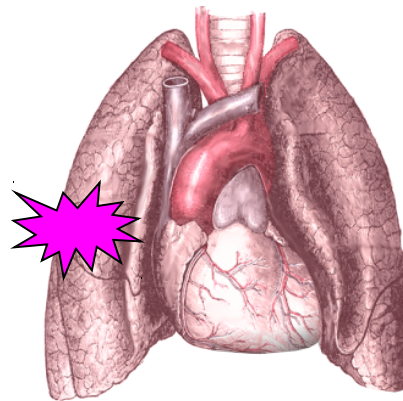
AGCGTAT**C**TGTCAC  
Mutated sequence

# Targeted therapies only work for patients with the correct mutation

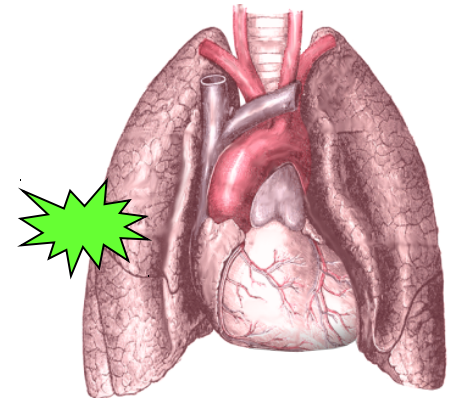
- Patients must be tested for the targeted mutation before treatment



Targeted Therapy  
A



Targeted Therapy  
B

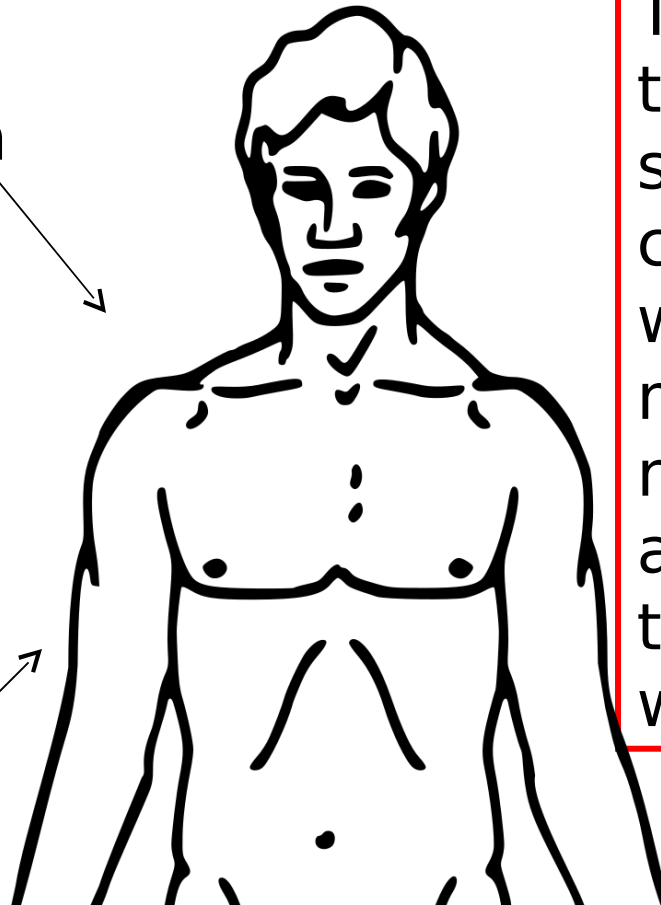


Targeted Therapy  
C

# Targeted Therapies have fewer side effects

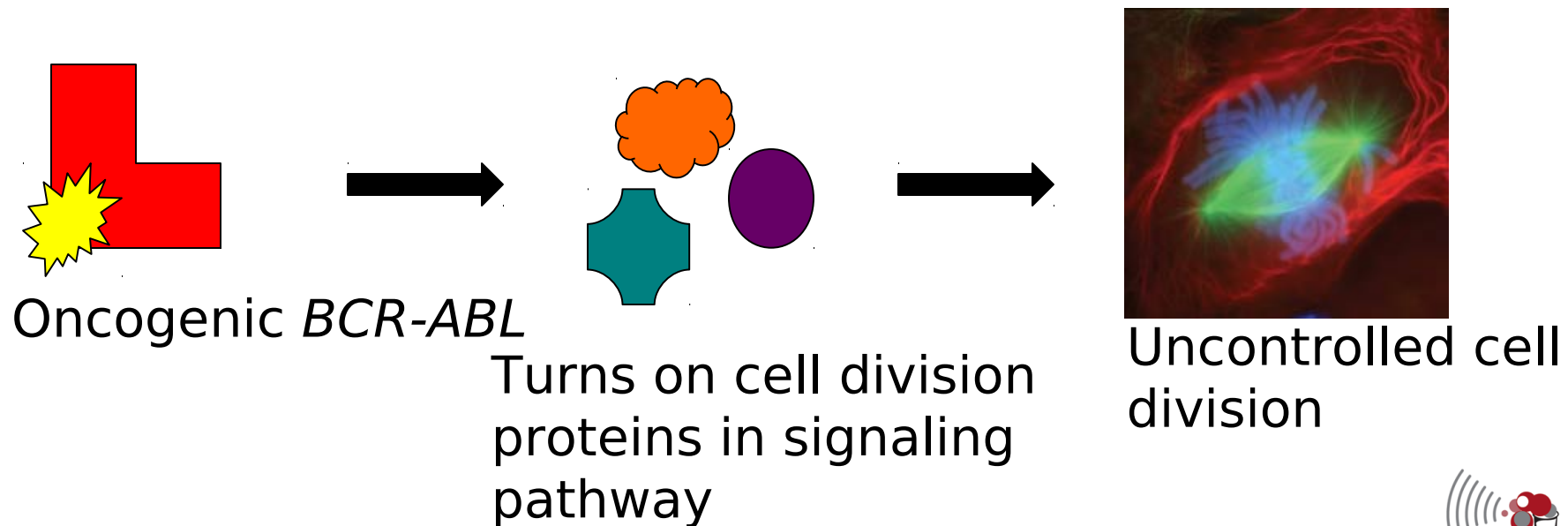
Joint pain, fatigue, skin lesions, for PLX4032

“minimal” side effects: nausea, muscle pain, diarrhea with Gleevec

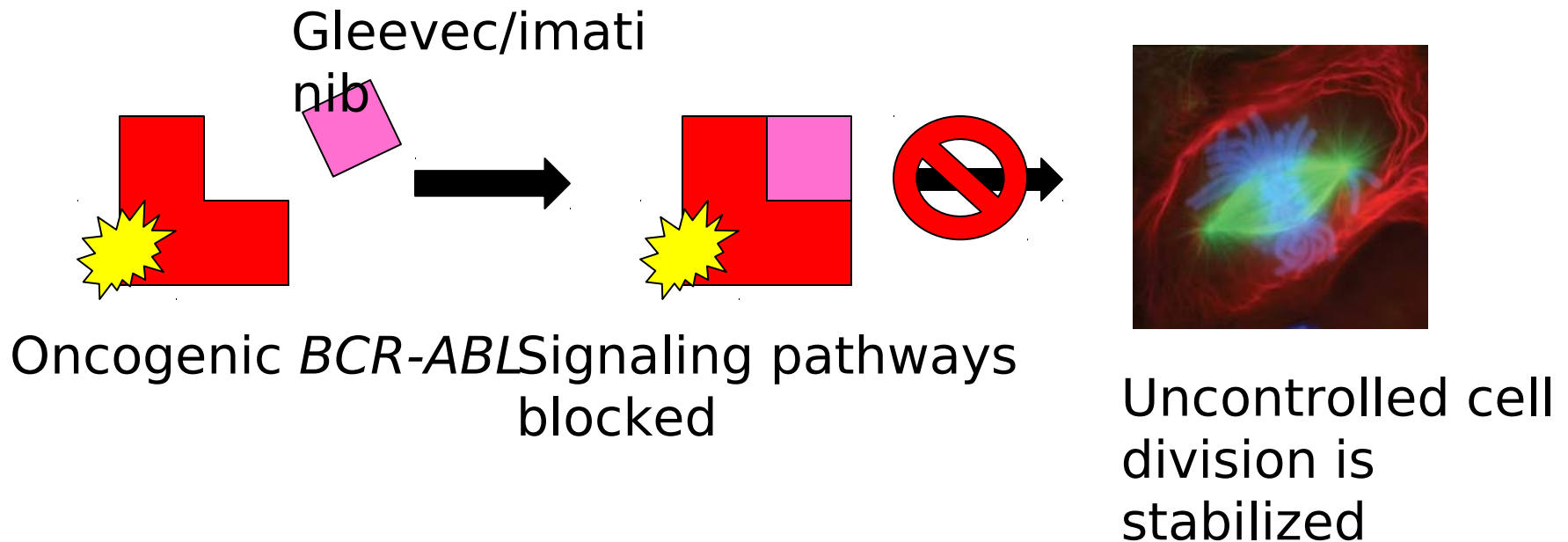


Targeted therapies specifically target cancer cells which have the mutations and not normal cells and have a wider therapeutic window

# Chronic myelogenous leukemia (CML) is a cancer of white blood cells



# Chronic myelogenous leukemia is a cancer of white blood cells

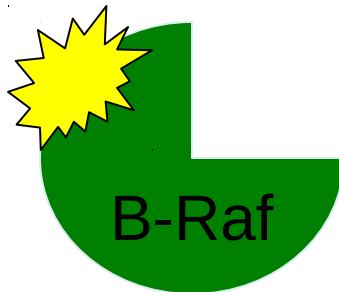


- CML currently has 89% 5-year survival rate compared to 23% in 1975

- Gleevec can be used for other cancers that have

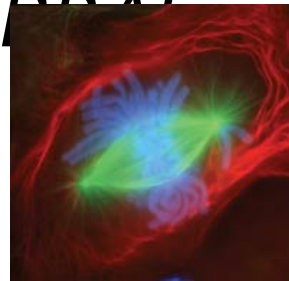
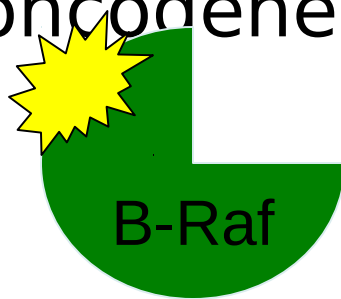
# BRAF inhibitors for melanoma

- Melanoma, a type of skin cancer, is resistant to chemotherapy and radiation
- 68,000 new cases and 8,700 deaths/year in U.S.
- 40-60% of melanomas have a driver oncogene called *BRAF*



# BRAF inhibitors for melanoma

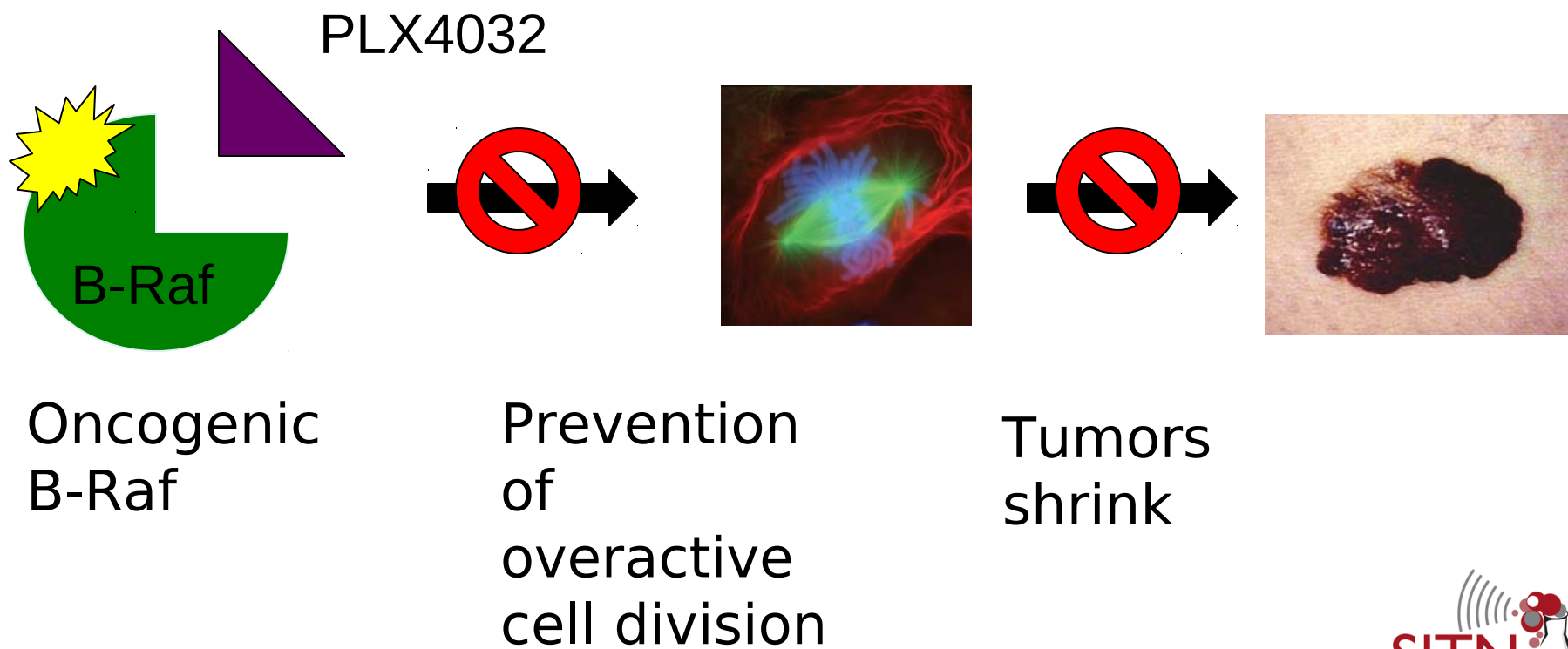
- Melanoma, a type of skin cancer, is resistant to chemotherapy and radiation
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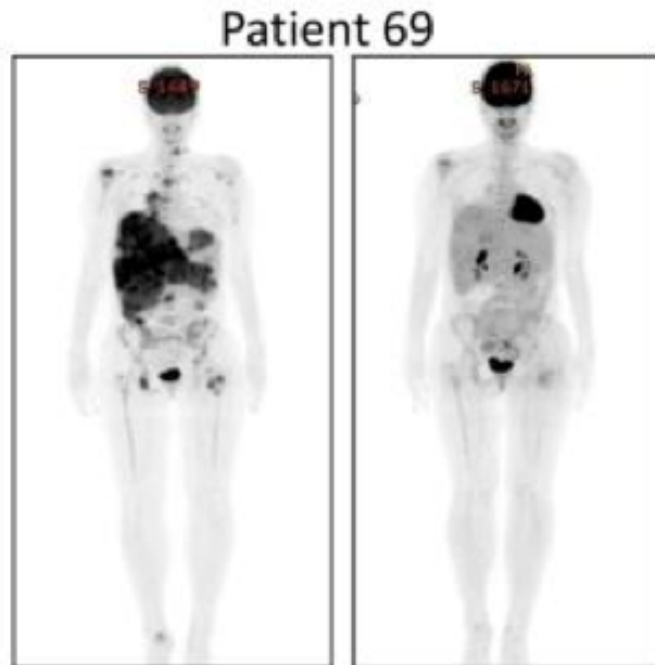
Over-activate signaling pathways for cell division



# PLX4032/vemurafenib inhibits oncogenic *BRAF*

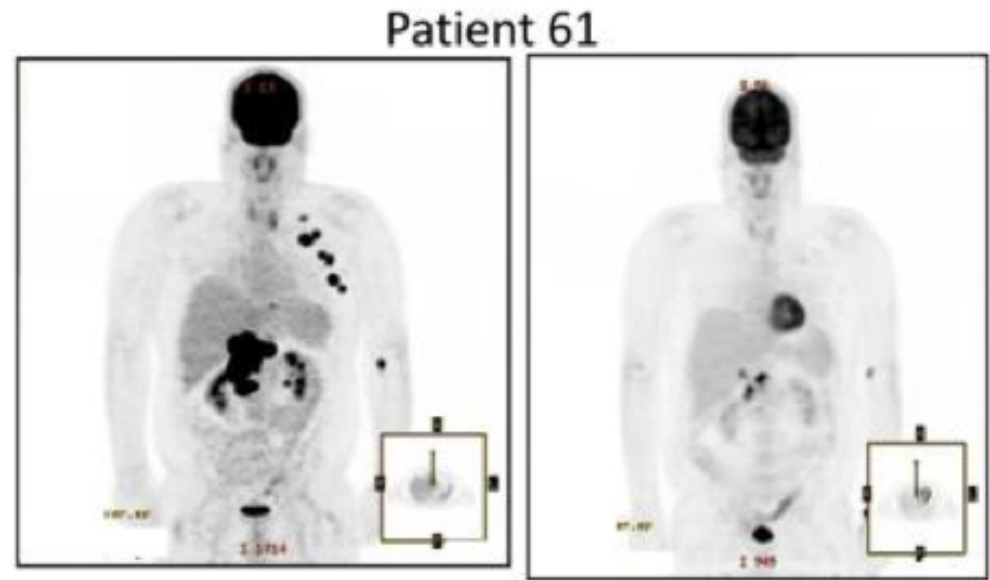


# Examples of PLX4032 effectiveness during clinical trials



Before

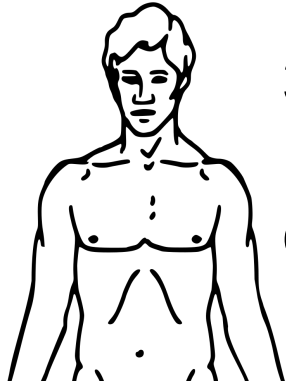
After



Before

After

# PLX4032 randomized clinical trial

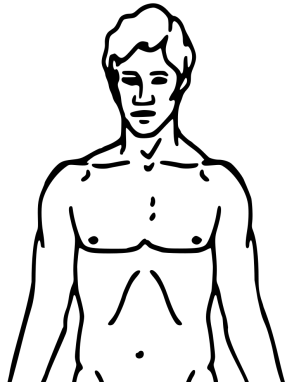


336 patients with  
BRAF oncogene  
on PLX4032



63% less risk  
of death

6 months



336 patients with  
BRAF oncogene  
on chemotherapy



Chemotherapy  
group given  
opportunity to  
try PLX4032

# Summary: Cancer Therapies

- Chemotherapy and radiation therapy attack general features of cancer cells
  - effective treatment for many, but not all types of cancer, and lead to side effects due to small therapeutic window
- Targeted therapies attack specific features (mutations ) of cancer cells
  - Cancers with those mutations respond very well with fewer side effects
- Understanding the genetics of cancer is important for developing therapies