

Genes Gone Wild

The Biology of Human Cancer

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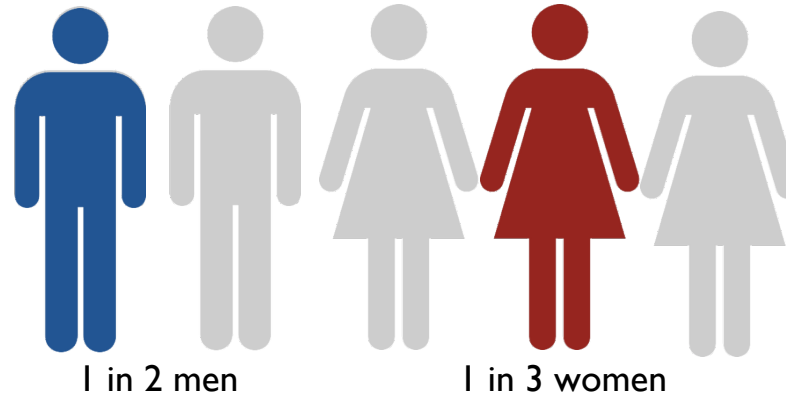
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Roadmap for the talk

1. Introduction to the biology of cancer
2. Cancer in the clinic

I. Introduction to the Biology of Cancer

Cancer impacts nearly all of our lives

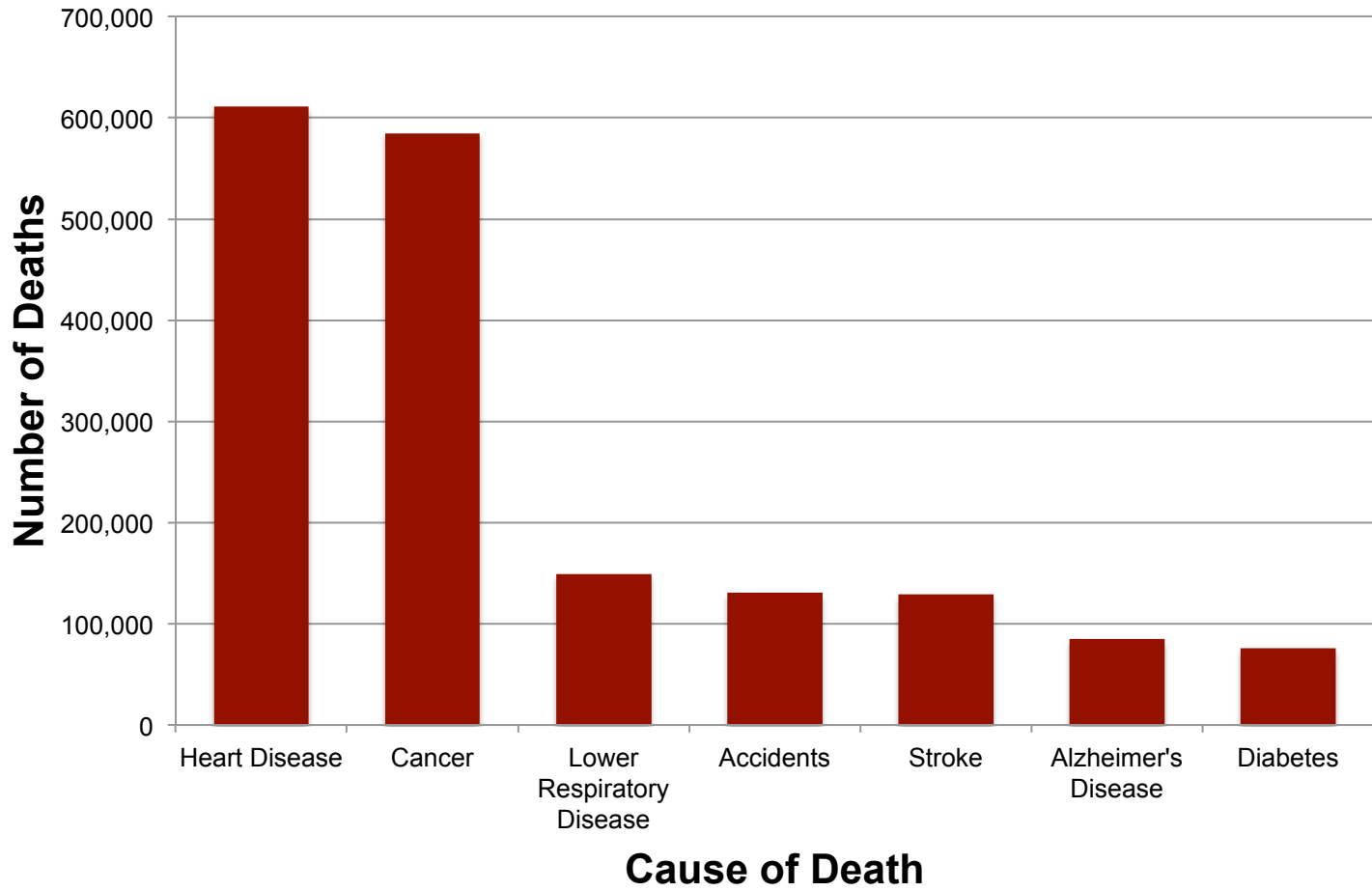


1,658,370 estimated new cases in 2015

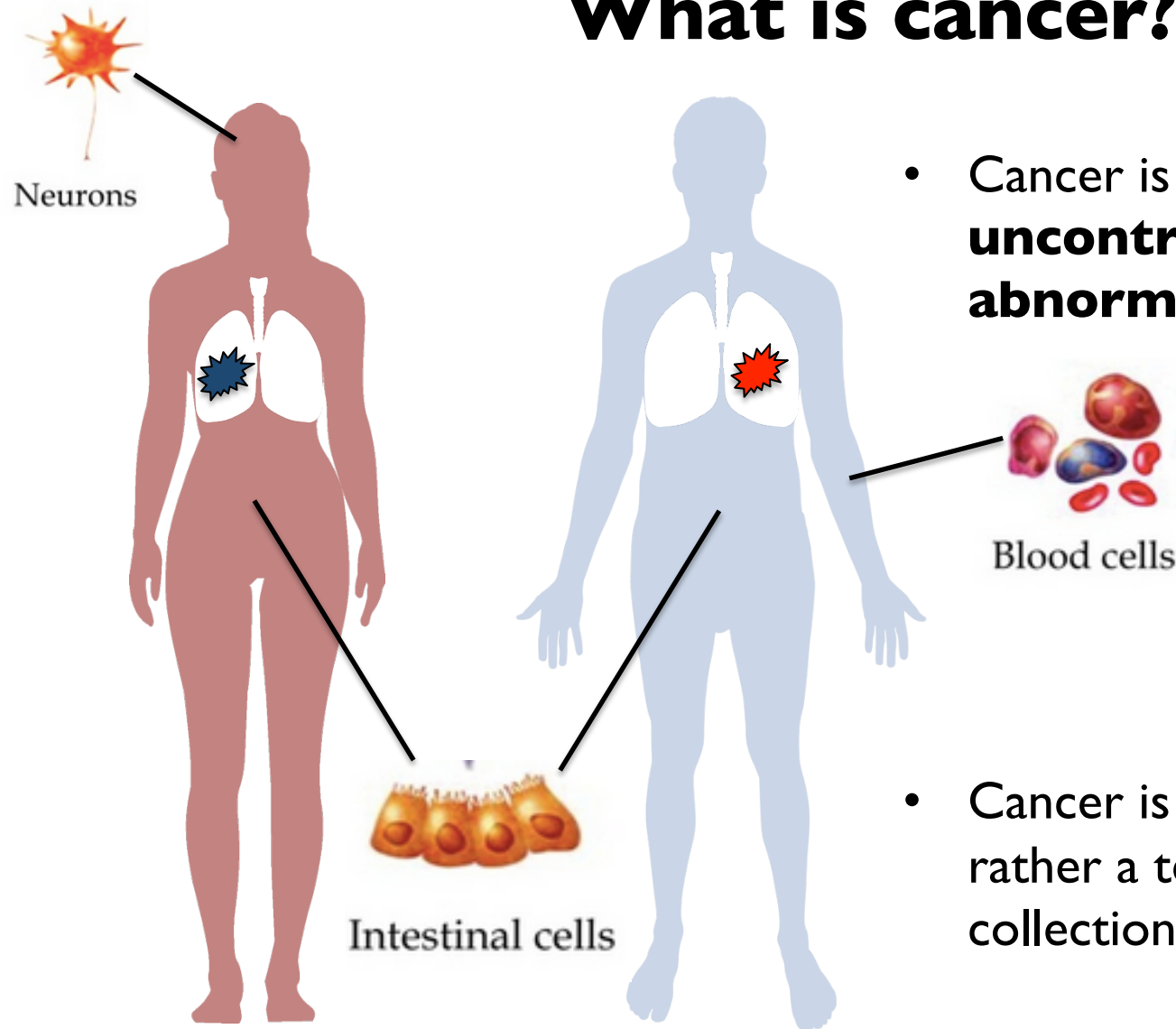
589,430 estimated deaths in 2015

Cancer is the second leading cause of death in the US

Leading Causes of Death in the US in 2013



What is cancer?



- Cancer is characterized by the **uncontrolled growth** of **abnormal** cells

- Cancer is not a single disease but rather a term that refers to a collection of **many** diseases

Cancer and tumor are not synonymous

Tumor: a mass of tissue lacking normal function

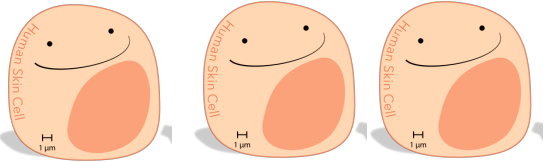
Benign: localized and does not spread to other parts of the body (cannot metastasize)

Malignant: invades nearby tissues and spreads to other parts of the body (can metastasize)

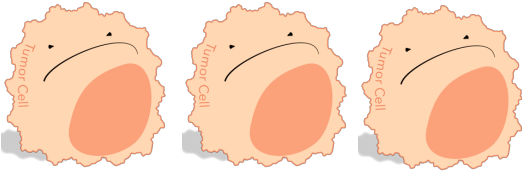
Cancer!

Cancer cells are different from normal cells

Normal Cells

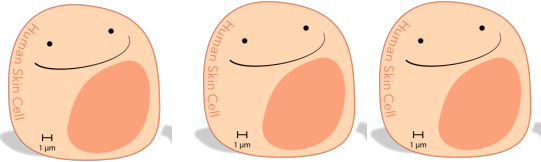


Cancer Cells

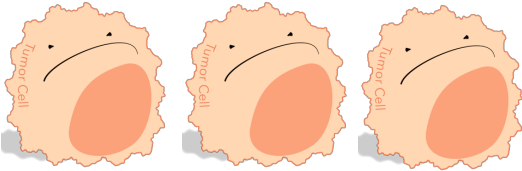


Cancer cells are different from normal cells

Normal Cells



Cancer Cells



Grow and divide in an orderly fashion	Grow and divide uncontrollably
Die when they become old or damaged	Resist death and continue to grow
Carry out specialized functions	Lose ability to carry out specialized functions
Stick together in the right place in the body	Invade other tissues

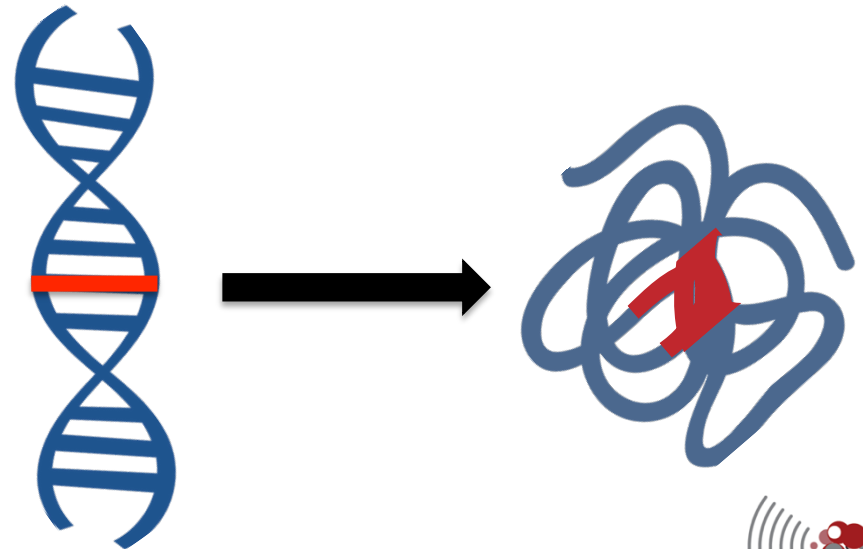
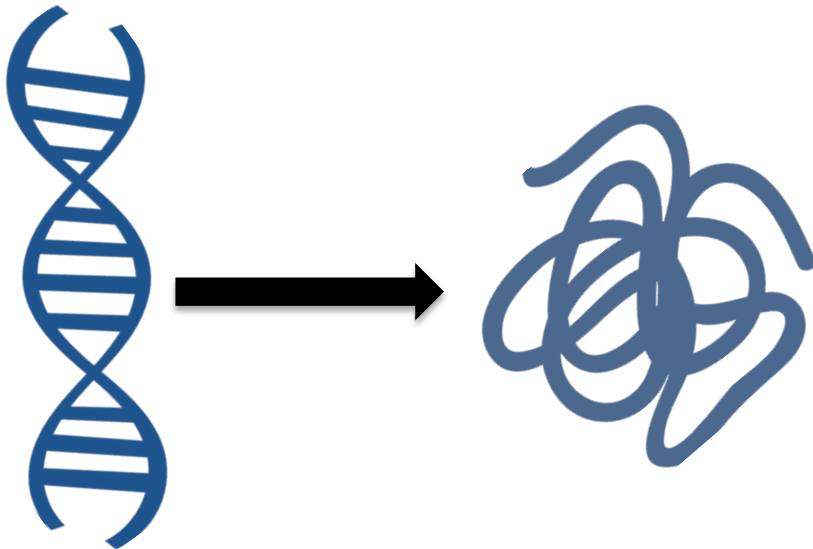
Questions?

What causes cancer?

Accumulation of **genetic mutations**



Changes in production or activity level of **proteins**



Cancer is a genetic disease

- **Acquired** mutations are the result of damages to the DNA of a cell accrued over a person's life and are not heritable

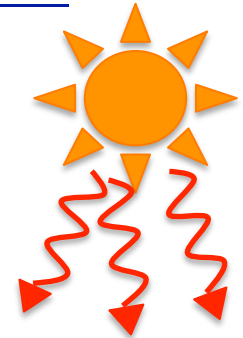


1) Environmental factors

Chemical carcinogens



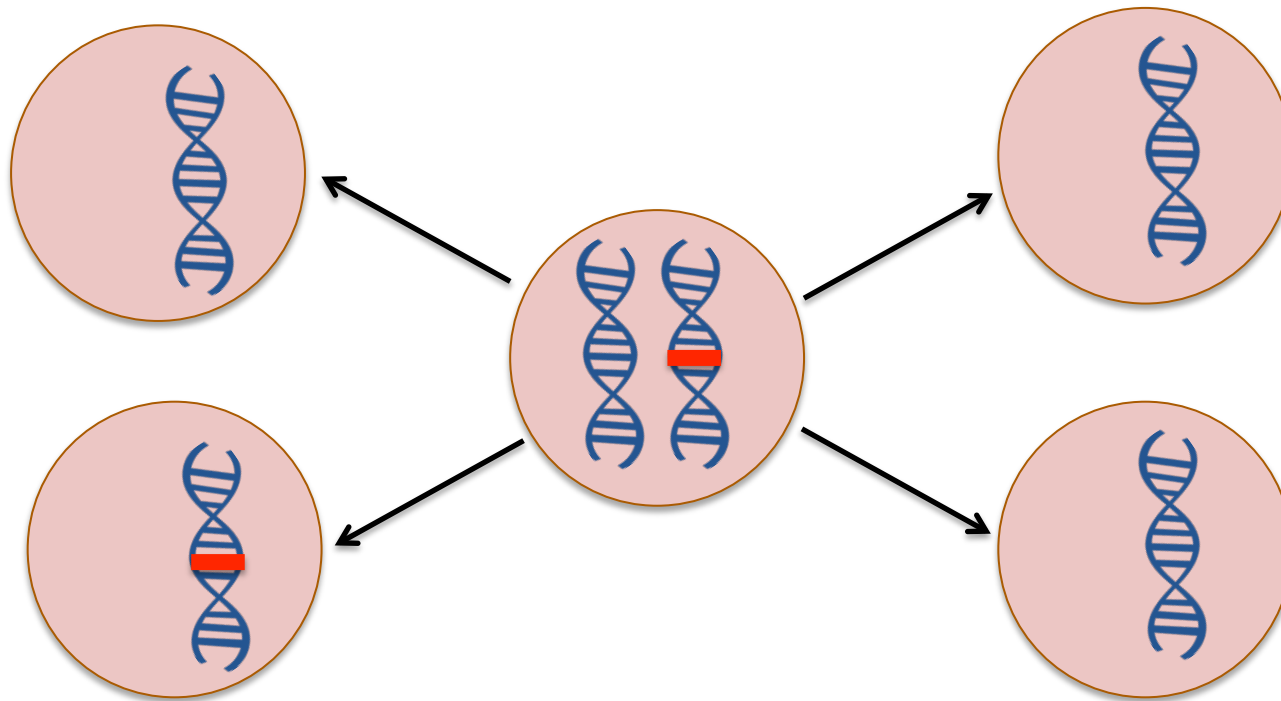
Radiation



Cancer is a genetic disease

2) Errors in DNA replication

~3 billion base pairs of DNA in the cell



~1 mutation per 10 billion base pairs that are replicated

Cancer is a genetic disease

- **Acquired** mutations: damages to the DNA of a cell accrued over a person's life and are not heritable
 - 1) Environmental factors
 - 2) Errors in DNA replication
- **Inherited mutations:** mutations present in your parents that you receive in every cell of your body

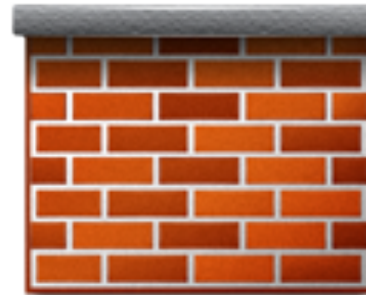
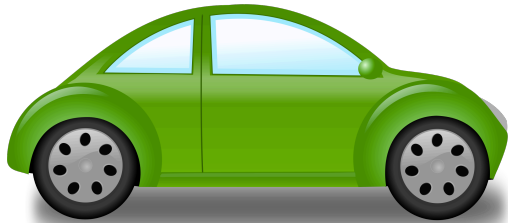
What kind of mutations are associated with cancers?

We have ~20,000 protein coding genes in our DNA. Mutations in most of these genes will not cause cancer.

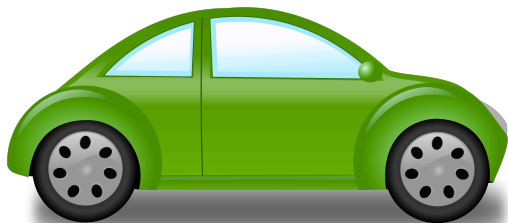
Cancer is caused by mutations in two classes of genes: **oncogenes** and **tumor suppressor genes**.

Analogy: cells must control their growth like cars control their speed

Oncogenes drive cancer when inappropriately turned on like how a stuck gas pedal accelerates a car

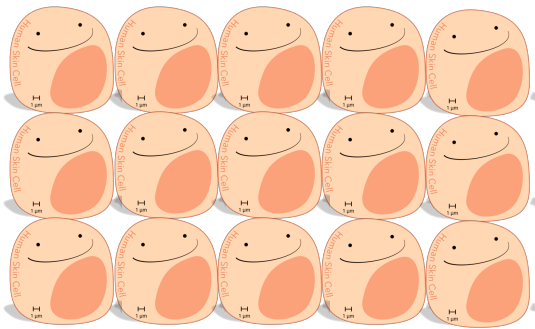


Tumor suppressor genes drive cancer when inappropriately turned off like how a broken brake pedal cannot slow down a car

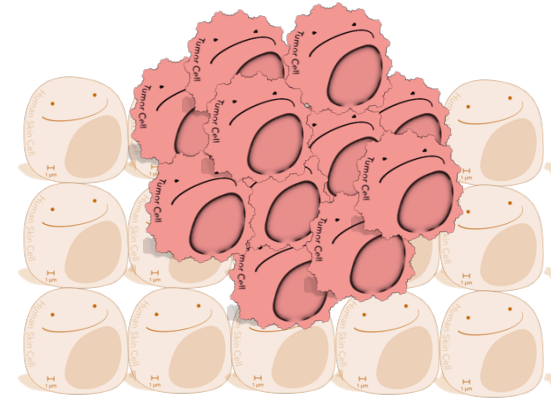


Oncogenes and tumor suppressors in normal cells and cancer cells

Normal Cells



Cancer Cells



Genes which help cells grow appropriately by being turned on at the right time

Oncogenes

Mutations cause the gene to be permanently turned on or activated

Genes which help

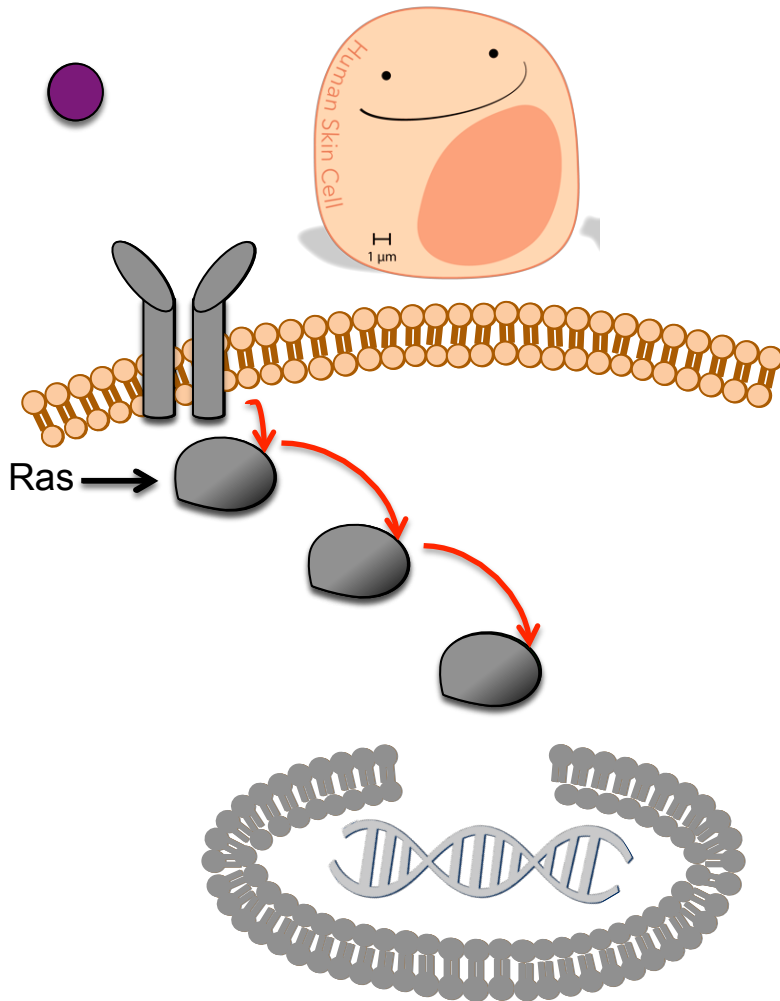
- 1) prevent growth
- 2) repair DNA damage

Tumor Suppressors

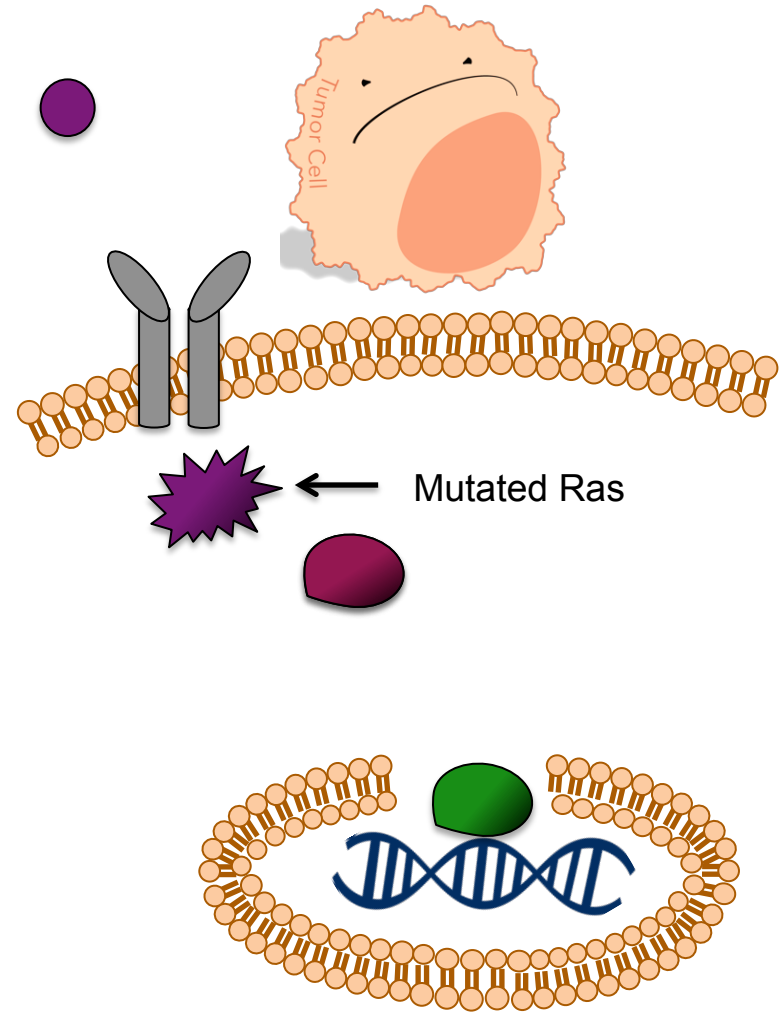
~~Mutations cause the gene to be permanently turned off or inactivated~~

Oncogene

Ras: transmits the signal to grow



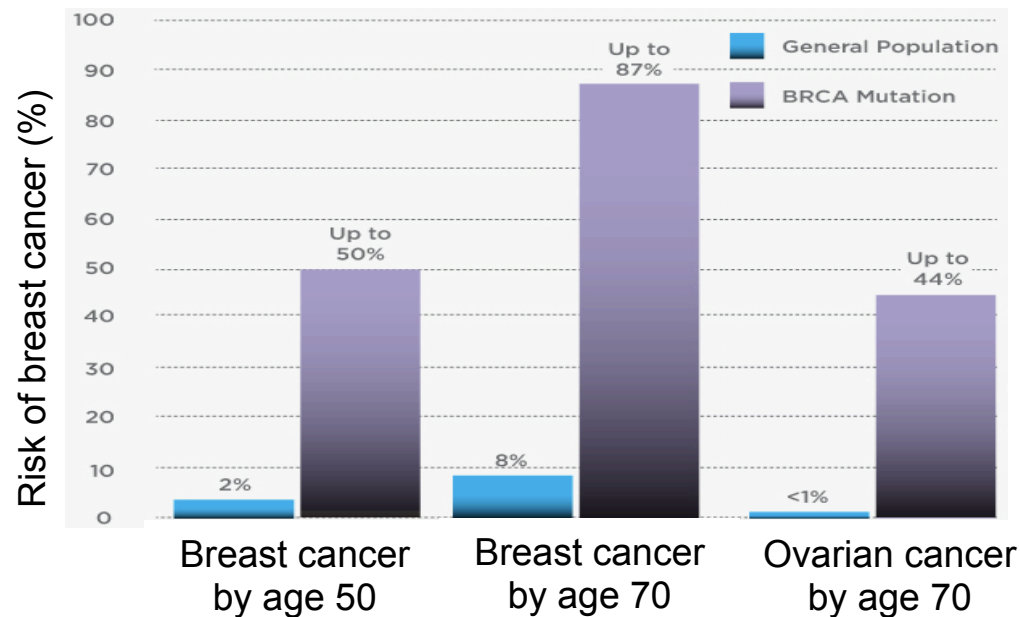
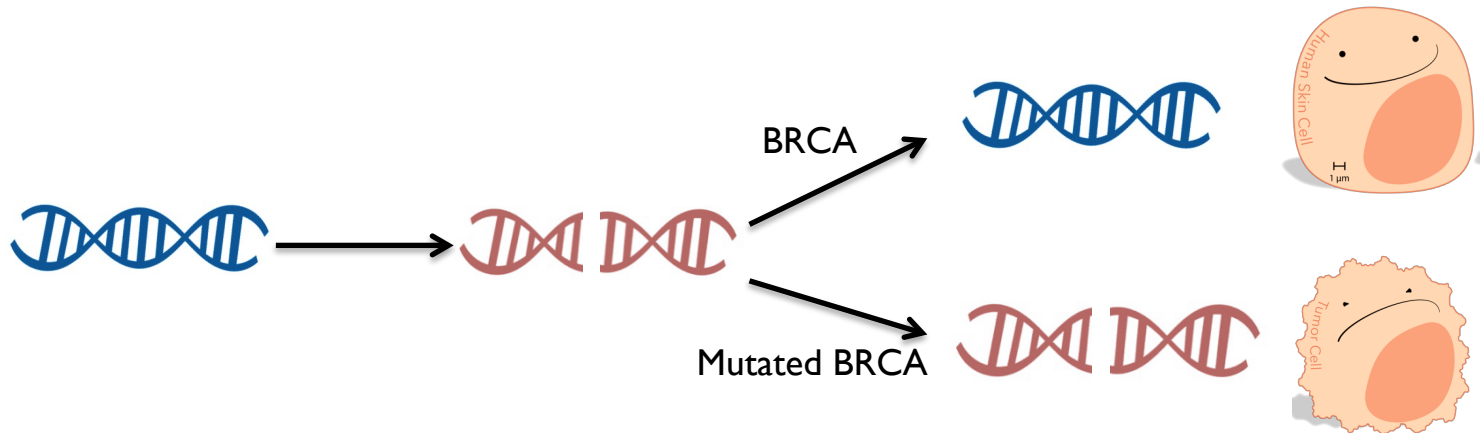
Signal \rightarrow Growth



Growth Always On



Tumor Suppressor BRCA: helps repair DNA damage

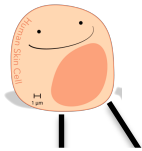


Questions?

Is a single mutation enough to develop cancer?

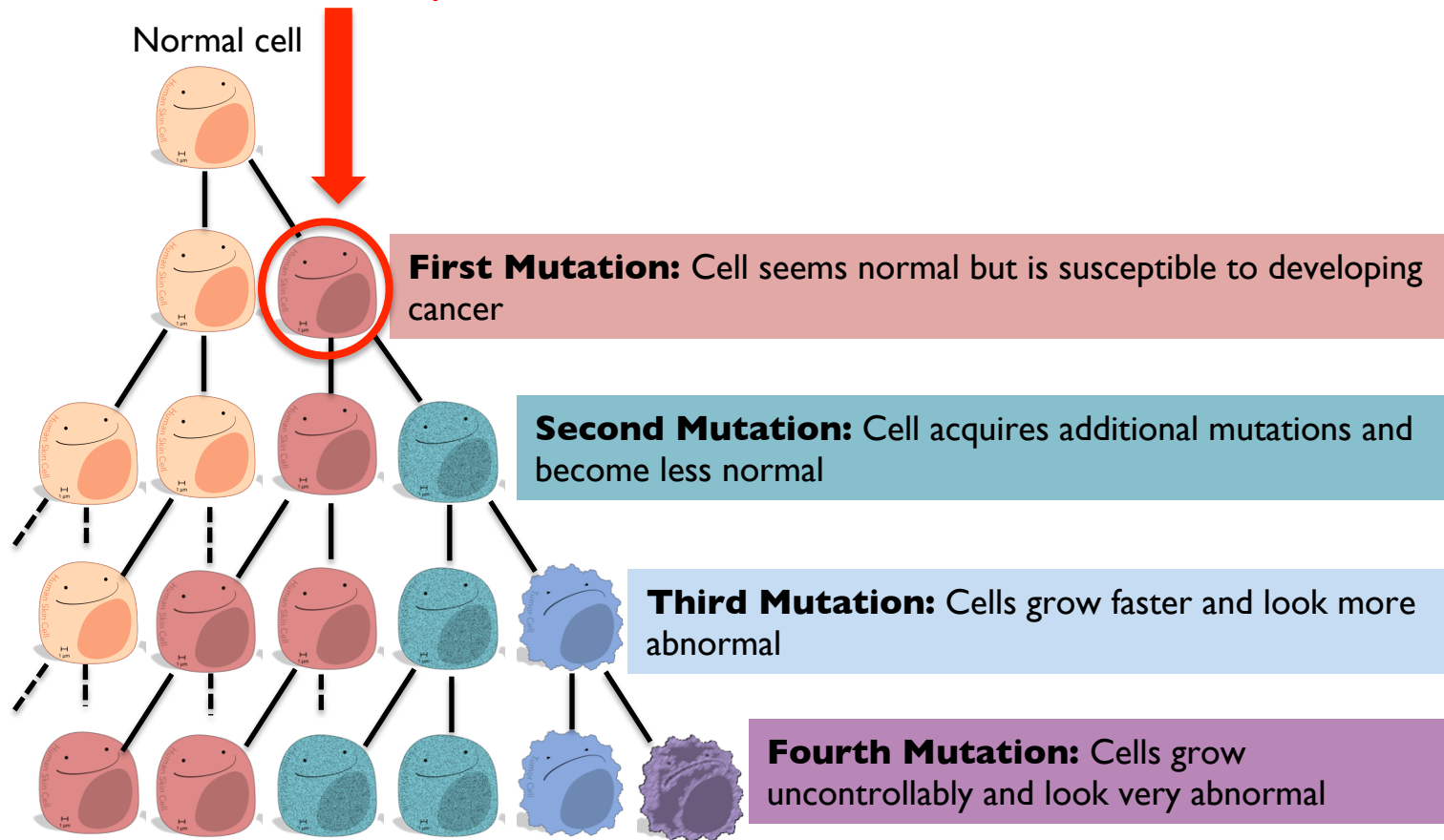
- It generally takes more than one mutation for cancer to develop
- Cancer causing mutations build upon one another

Normal cell



Individuals with inherited genetic mutations are more susceptible to developing cancer

Individuals with inherited mutations begin here in every cell of the body



Researchers are using cancer genome sequencing to understand cancer

- Some Goals
 - Identify driver mutations
 - Weed out passenger mutations
 - Advance personal medicine
- Findings
 - Certain genes are recurrently mutated in particular cancers
 - Analysis of 4,742 samples from 21 tumor types yielded 33 new genes
 - We still have more genes to find!
- Significance: huge number of potential new targets for cancer research and therapy



Summary

- Cancer is a collection of diseases that are characterized by **uncontrolled growth of abnormal cells**
- Cancer is a genetic disease caused by acquired or inherited mutations
- Mutations that cause cancer occur in **oncogenes** and **tumor suppressor genes**
- Typically more than one mutation is necessary before cancer develops, and each cancer is unique
- **Cancer genome sequencing** is identifying large numbers of potential new targets for cancer research and therapy

Questions?

2. Cancer in the Clinic

Disclaimer: All information provided here is for educational purposes only. **I am not a medical doctor** and I am in no way providing medical advice. While I hope that this information may be helpful to any patients or family members of patients, please discuss all medical decisions with a physician.

How does cancer harm the body?

Tumor: a mass of tissue lacking normal function

Tumors, whether benign or malignant, cause **disease** by interfering with normal function of neighboring tissues

Malignant tumors can **metastasize**, or spread to other parts of the body, causing more disease and making treatment more difficult

Melanoma is a very dangerous skin cancer

Cancer Type	New U.S. Cases (2015)	U.S. Deaths (2015)
All Skin Cancers	3,500,000	12,000

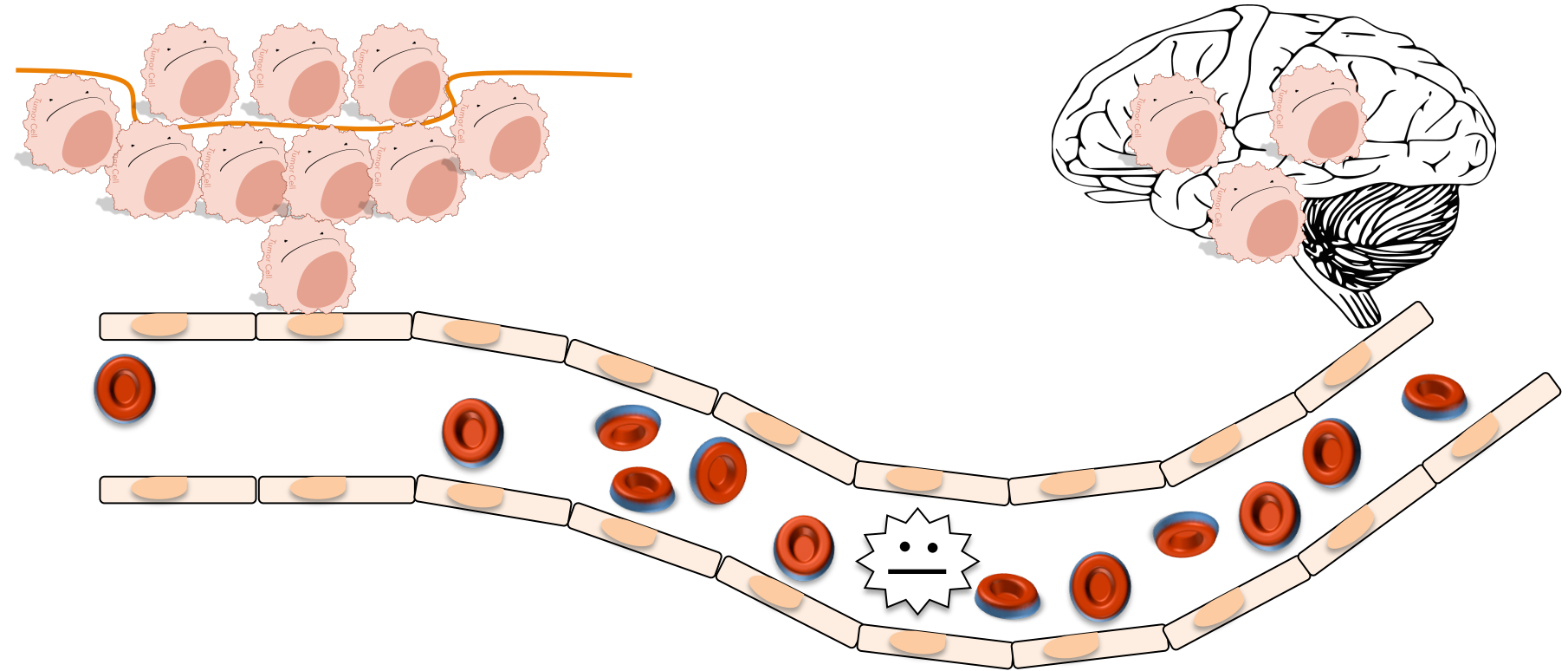
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Cancer Type	New U.S. Cases (2015)	U.S. Deaths (2015)
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Melanoma	73,870	

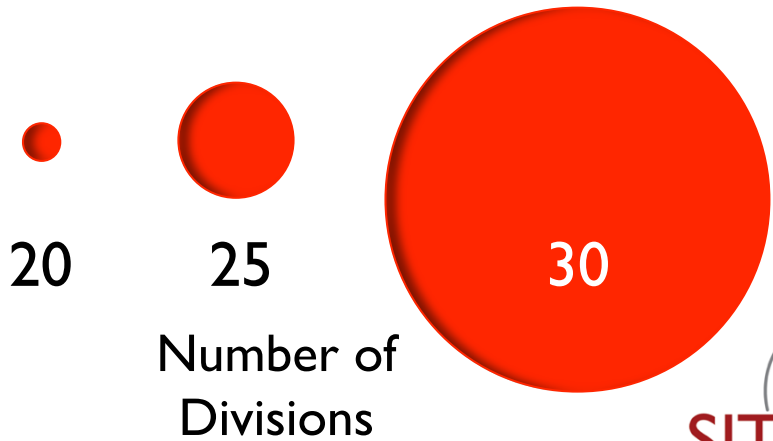
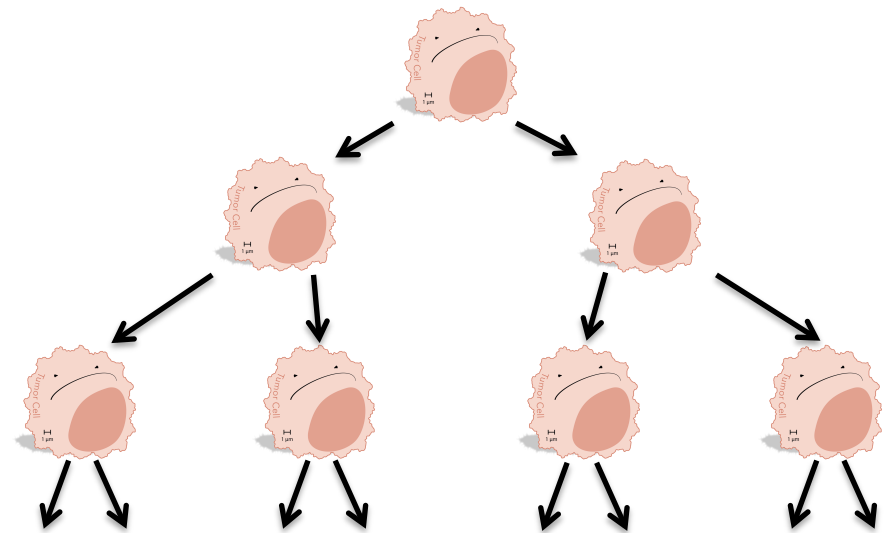
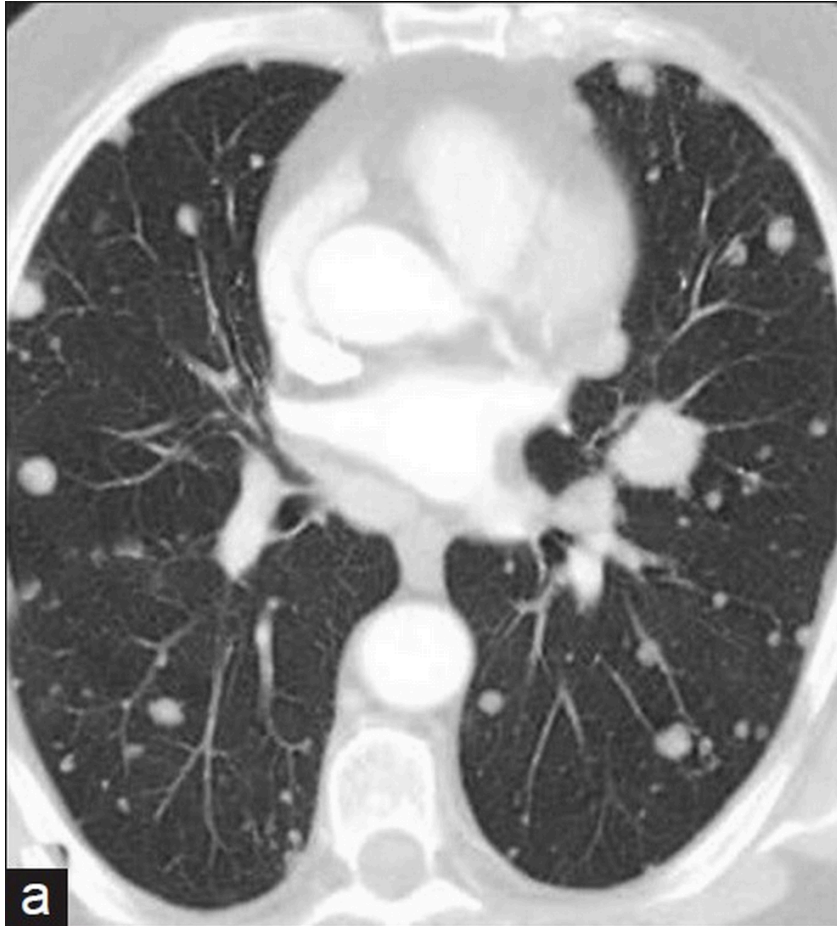
Melanoma is a very dangerous skin cancer

Cancer Type	New U.S. Cases (2015)	U.S. Deaths (2015)
All Skin Cancers	3,500,000	12,000
Melanoma	73,870	9,940

Metastasis is a difficult, rare process



Metastasis Detection



Cancer Staging

- Staging is the categorization of cancers by severity
- Staging guides treatment, prognosis, clinical trials, and research

Considerations include:

- Tumor Size
- Regional Lymph Node Involvement
- Presence of Distant Metastasis

Cancer Staging

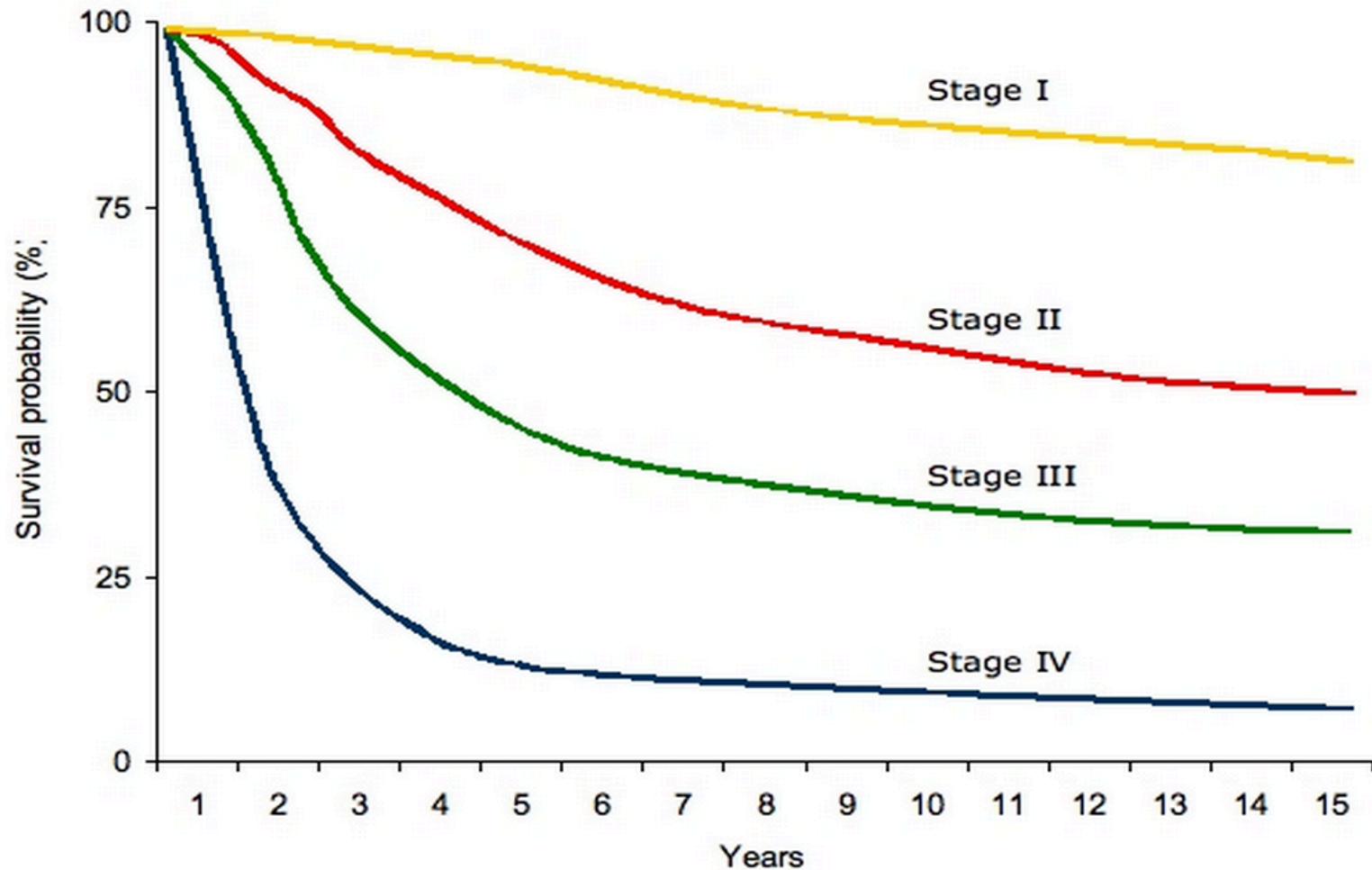
- Staging is the categorization of cancers by severity
- Staging guides treatment, prognosis, clinical trials, and research

Considerations include:

- **T**umor Size
- Regional Lymph **N**ode Involvement
- Presence of Distant **M**etastasis

- Different cancers often have their own staging systems (usually I to IV)

Melanoma Stage is Highly Predictive of Survival Probability



Summary (Part I)

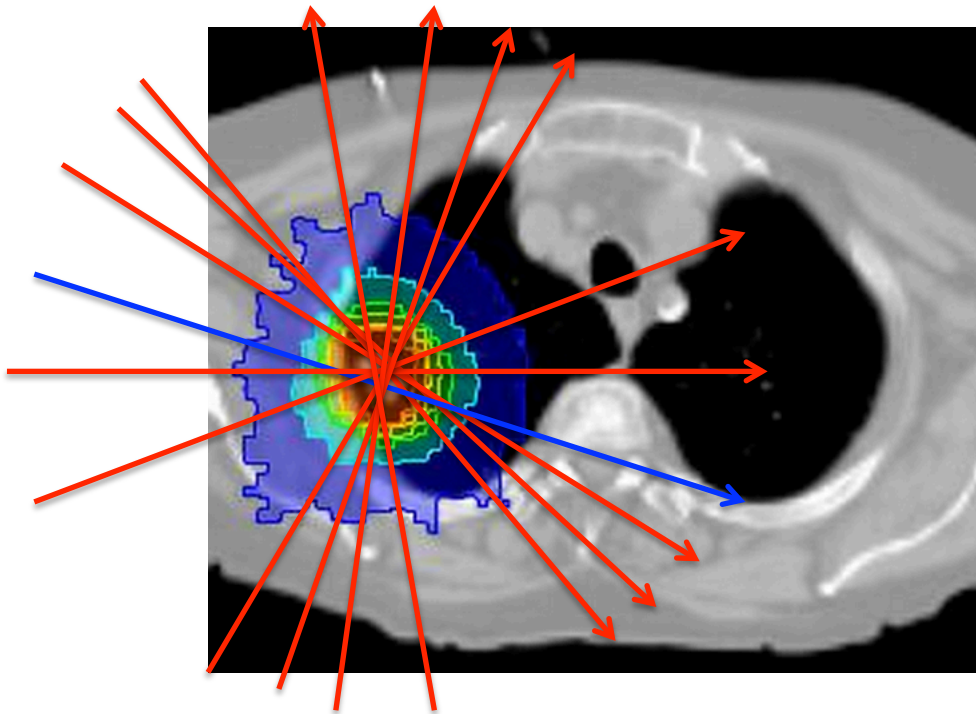
- Tumors cause disease by interfering with neighboring, normal tissues
- Malignant tumors can metastasize
- Just because a tumor *can* metastasize doesn't mean it already *has*
- Staging allows us to categorize cancers by severity
- Presence of metastases defines highest stages

Questions?

Surgery is Very Effective for Localized Tumors

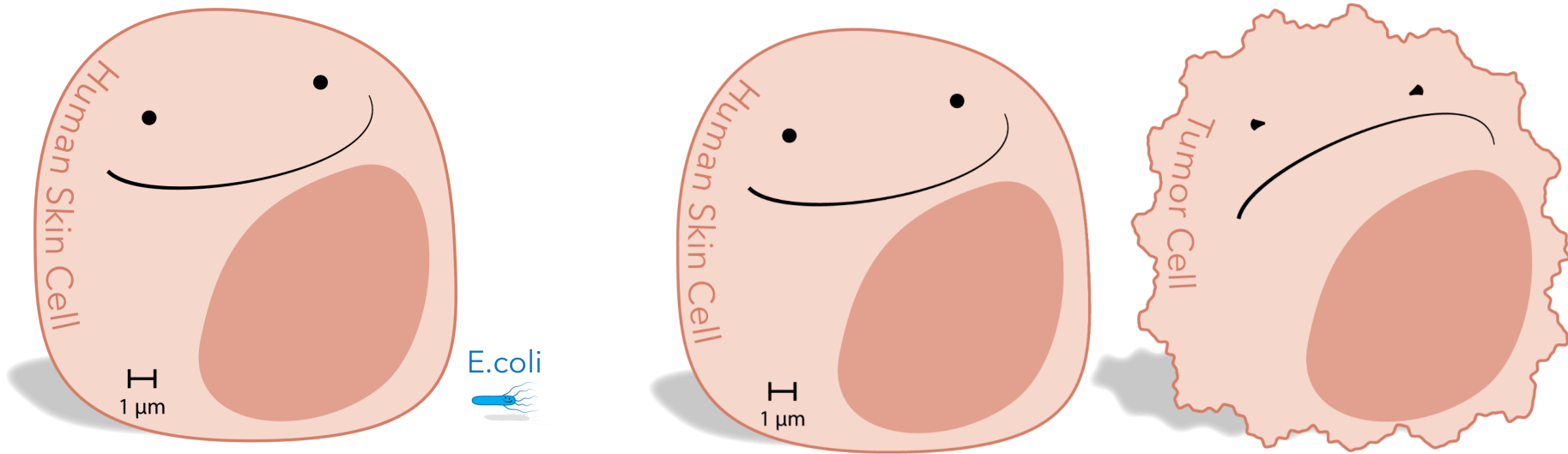
- Where is the tumor?
- How big is the tumor?
- Can we remove appropriate margins?
 - **Margins:** surrounding tissue removed with a tumor
- Ideally, remove **all** cancerous cells

Radiation Therapy- Local Treatment, Less Invasive



- But wait! I thought radiation caused cancer?

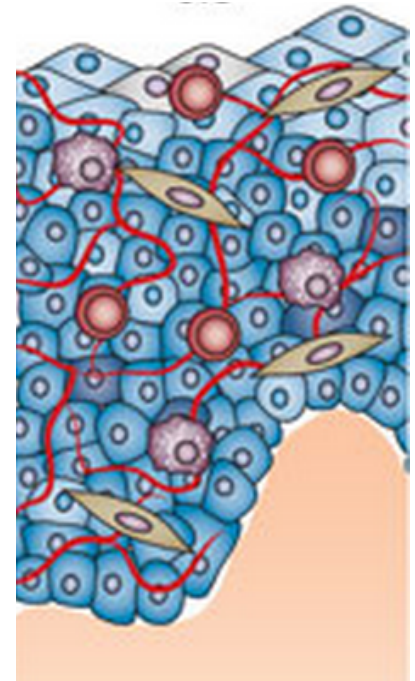
Chemotherapy- Treatment for the Whole Body



- Drugs that target rapidly dividing cells
 - Prevent cells from copying DNA
 - Inhibit cell division
- Side effects: lose normal, rapidly dividing cells

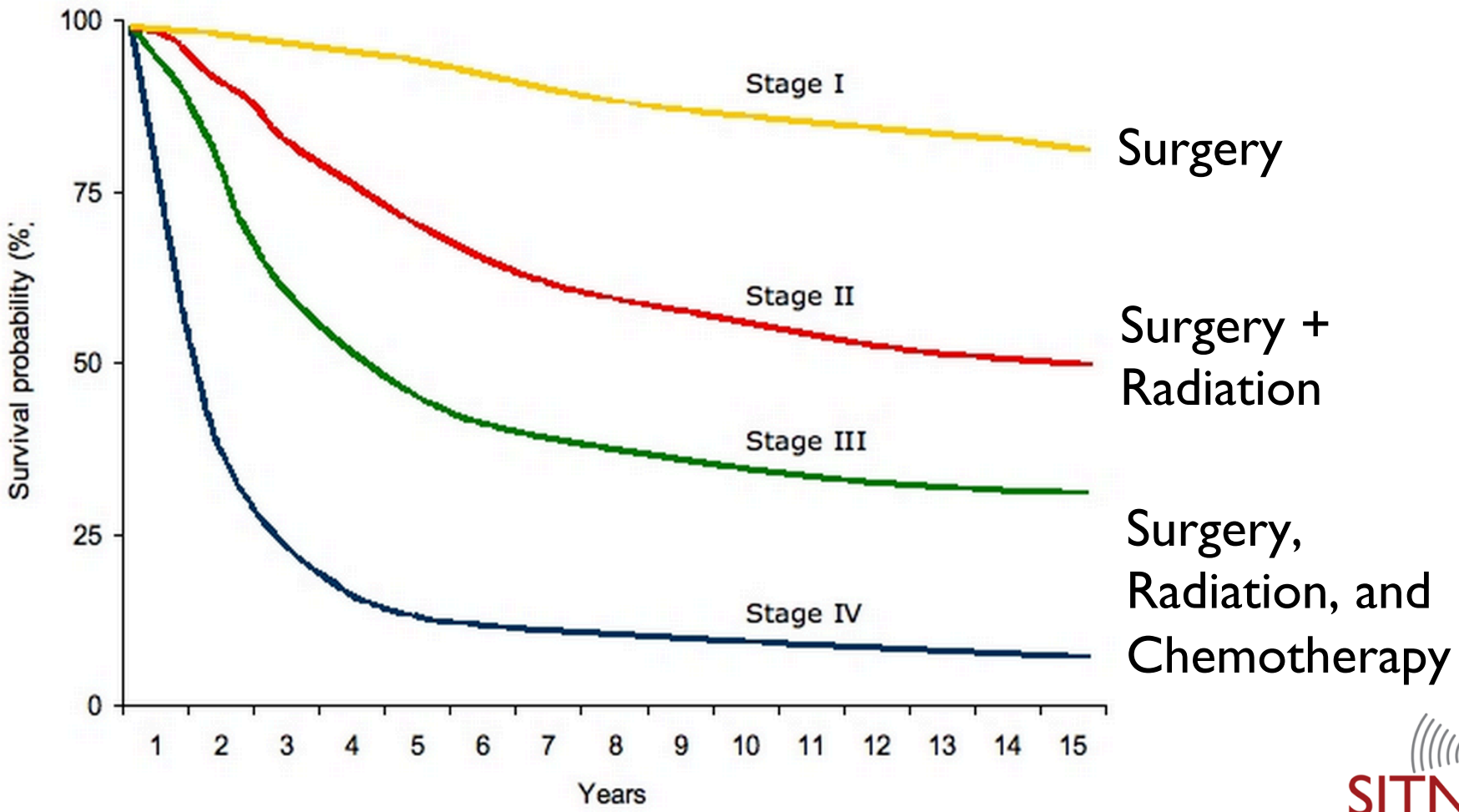
Resistance to Chemotherapy

- Tumors are made up of a diverse group of cells
- Cancerous cells are always gaining more mutations
- Chemotherapy can actually *cause* more mutations
- Only need one cell to mutate to survive therapy

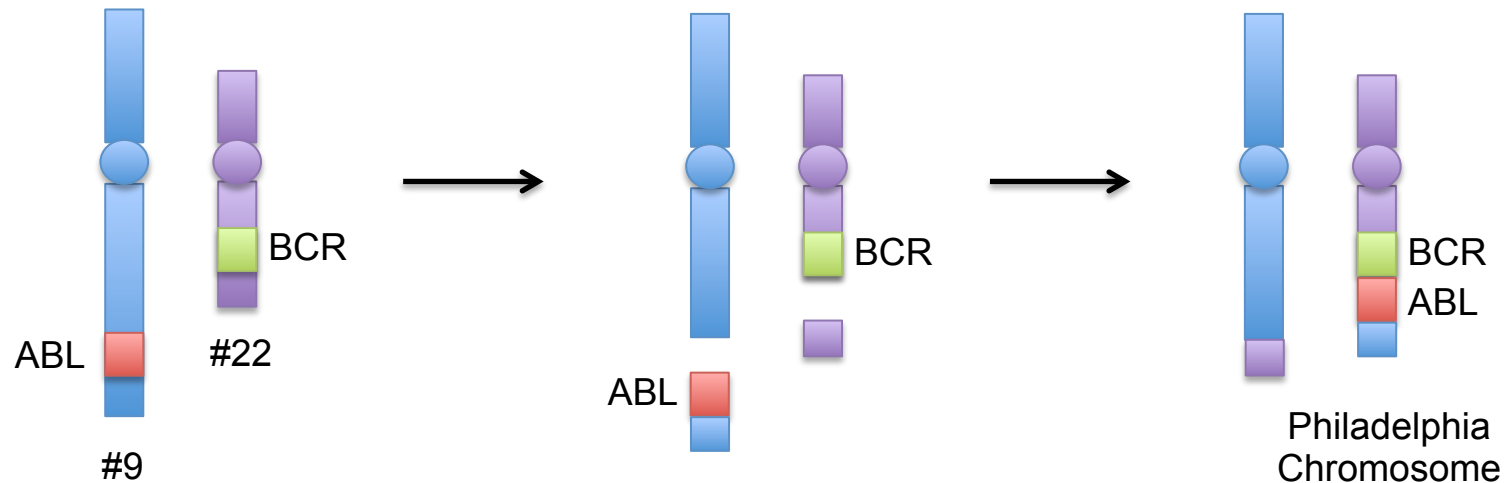


1 in 1,000,000 → 1 in 1,000,000,000,000

Melanoma Treatment Differs by Stage, but is Usually Aggressive

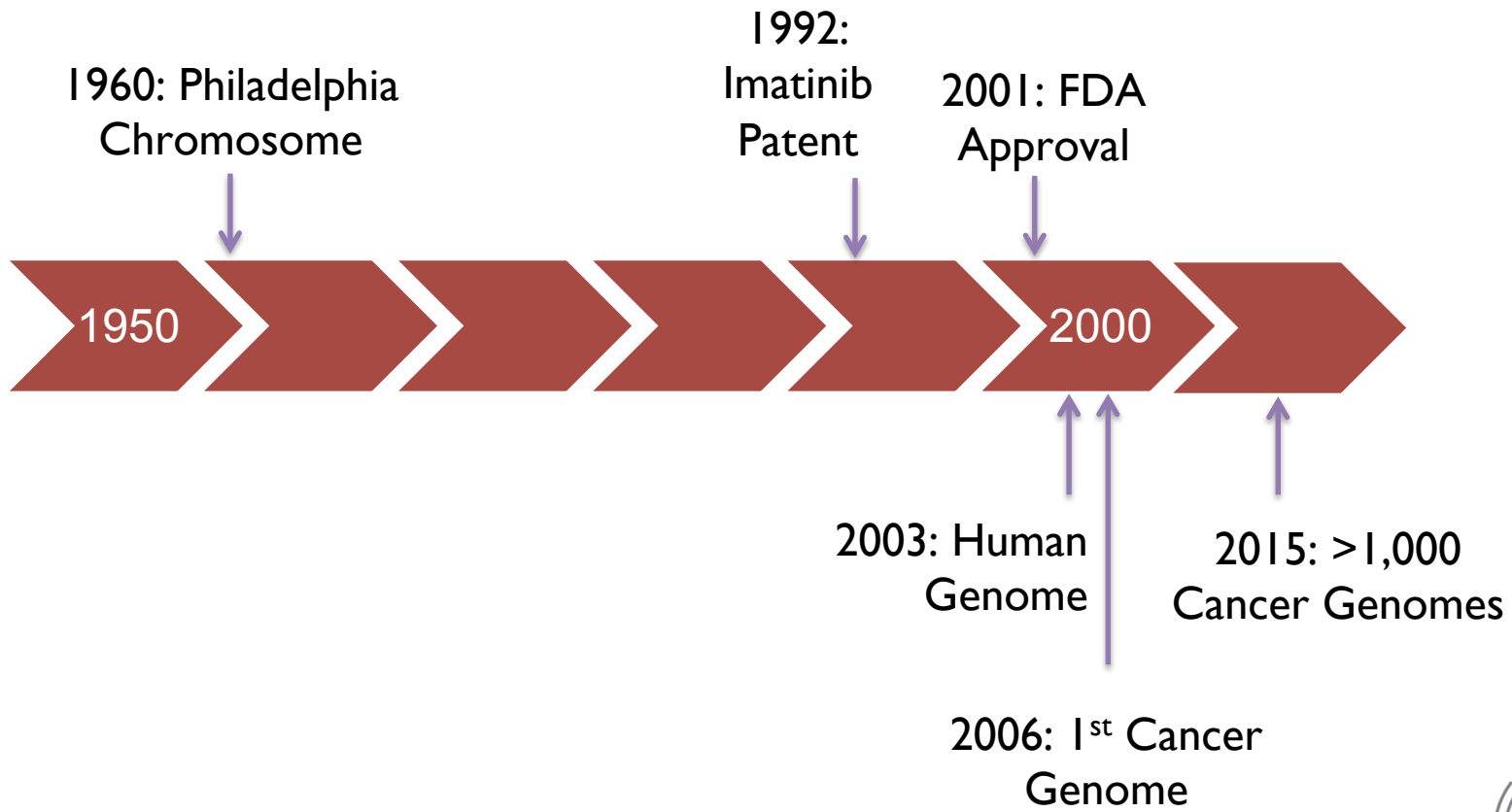


Targeted Therapies: the Future

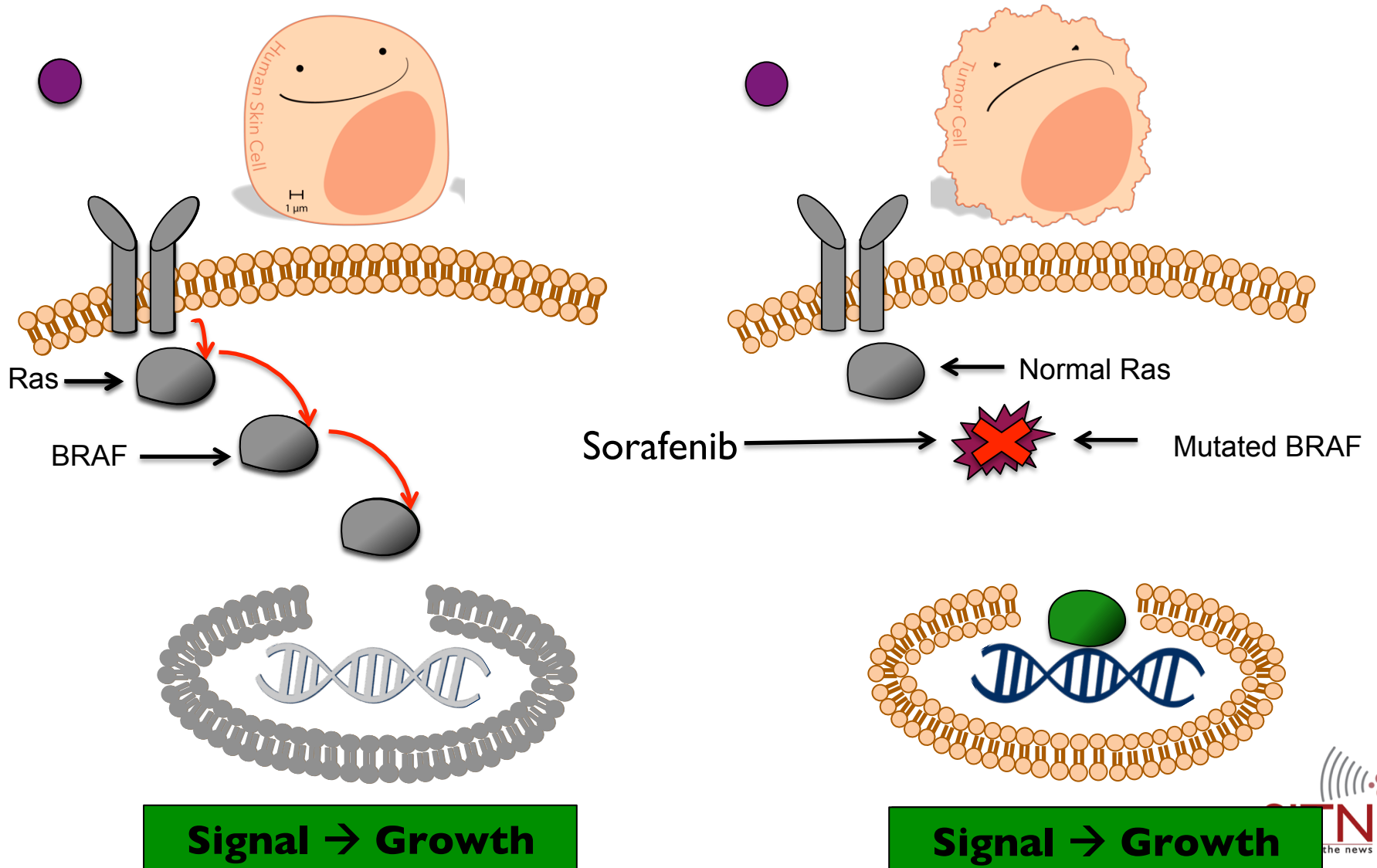


- Chronic Myelogenous Leukemia (CML)
- Imatinib specifically inhibits BCR-ABL

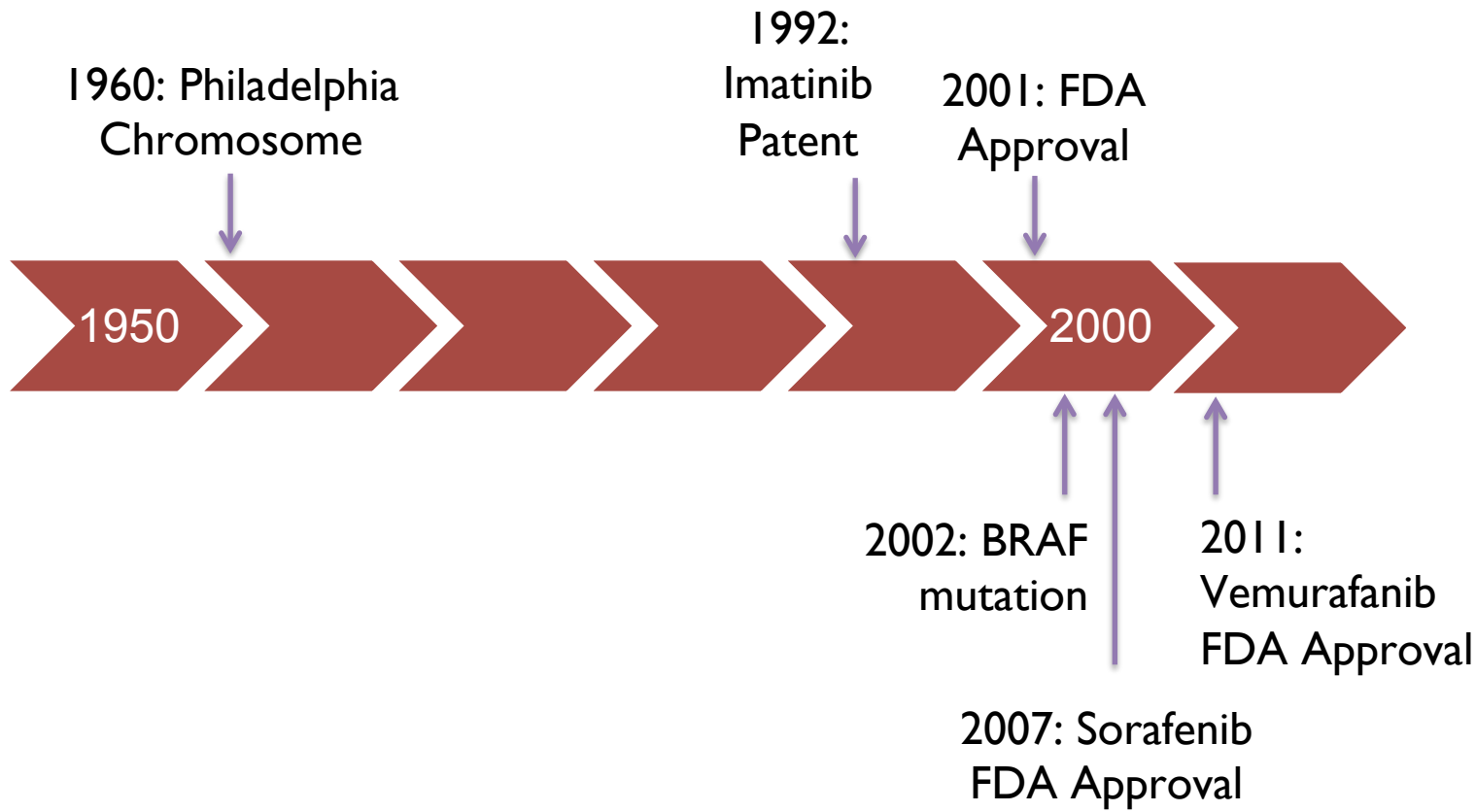
Targeted Therapies are becoming easier to develop



BRAF Oncogene- 50% of Melanomas



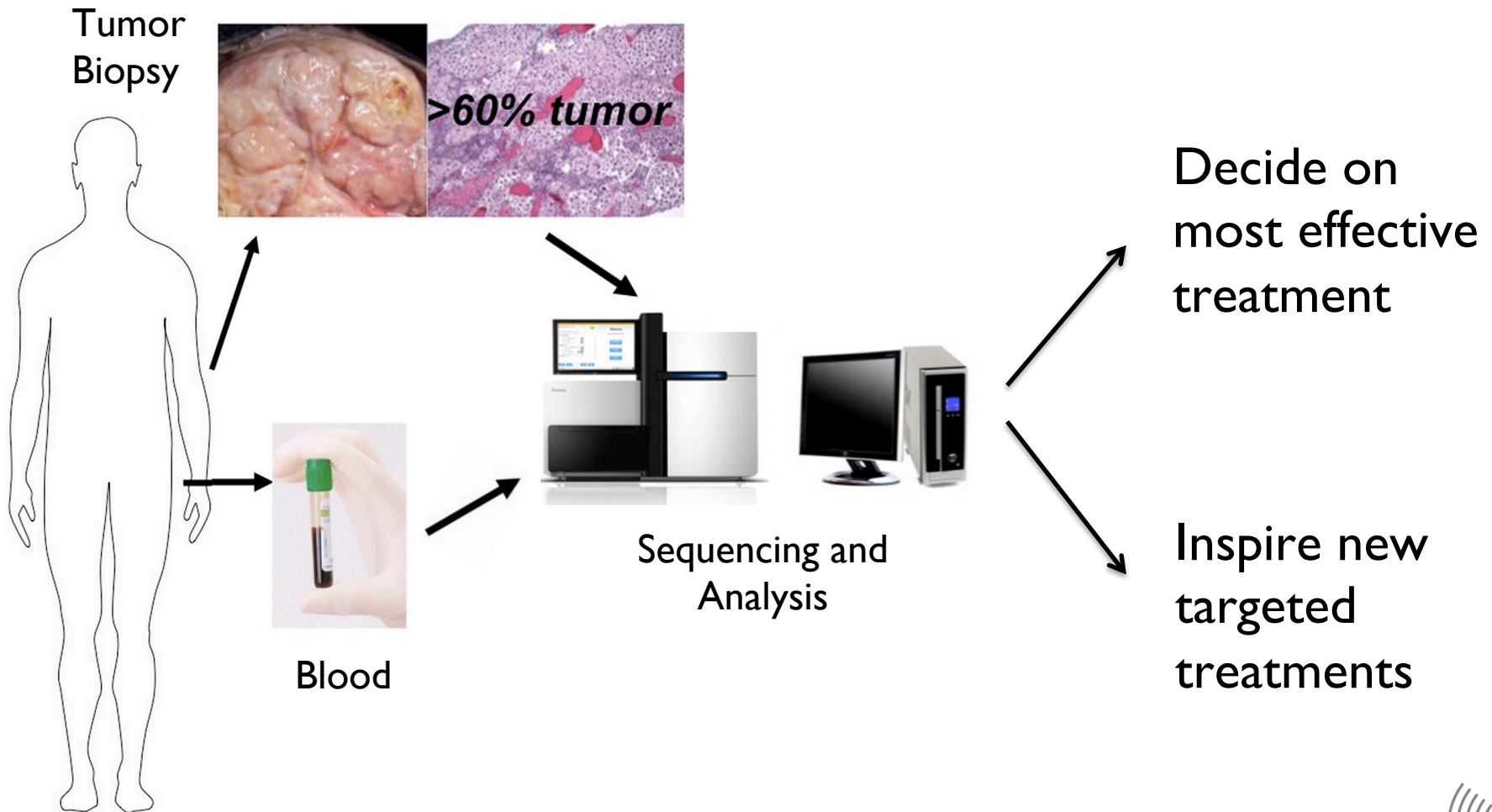
Targeted Therapies are becoming easier to develop



More Targeted Therapies are Rapidly Becoming Available

Drug	Cancer Type	Target	Year Approved
Tamoxifen (and related)	Breast	ER	1977
Trastuzumab (Herceptin)	Breast, Stomach	HER-2	1998
Imatinib (Gleevec)	CML, Stomach	BCR-ABL	2001
Bevacizumab (Avastin)	Colon, Lung, Renal, Ovarian, Brain	VEGF-A	2004
Everolimus (Zortress)	Renal, Pancreatic, Breast	mTOR	2009
Vemurafenib (Zelboraf)	Melanoma	BRAF	2011
Vismodegib (Erivedge)	Skin	SMO	2012
Ramucirumab (Cyramza)	Stomach	VEGFR2	2014

Personalized Medicine



Summary (Part 2)

- Surgery is effective at removing a single, localized tumor
- Radiation helps with localized tumors that we cannot surgically remove
- Traditional chemotherapies target rapidly dividing cells throughout the body
- Targeted therapies are being inspired by our rapidly increasing knowledge

Take Home Conclusions

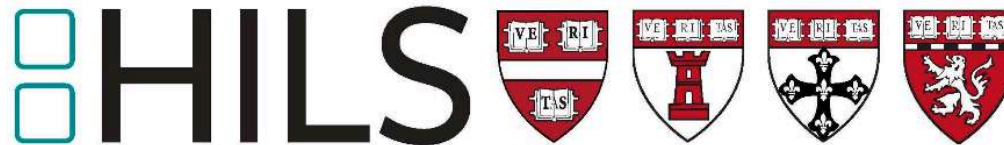
- Cancer is a genetic disease caused by DNA mutations
- Cancer progression is tied to more mutations
- Metastasis is the spread of cancer to other tissues
- Surgery, radiation, and chemotherapies are our major current treatments
- Targeted therapies are becoming more numerous and allow us to attack the underlying causes of cancer

Questions?

Thank you!

SITN would like to acknowledge the following organizations for their generous support of this event.

Harvard Integrated Life Sciences



The nonprofit plasmid repository



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