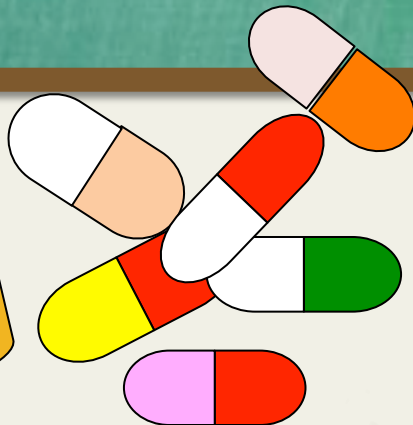
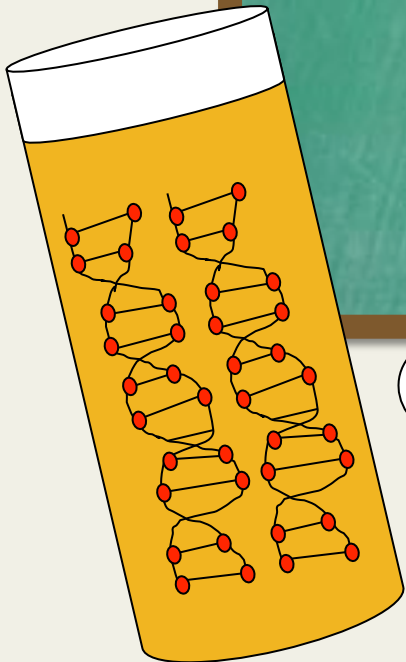


NC DNA DAY

Pharmacogenomics



What is DNA?



What is DNA Day?

What is DNA Day?



April 1953

Drs. James Watson and
Francis Crick determined
the **structure of DNA**
(*double helix*)

What is DNA Day?



April 1953

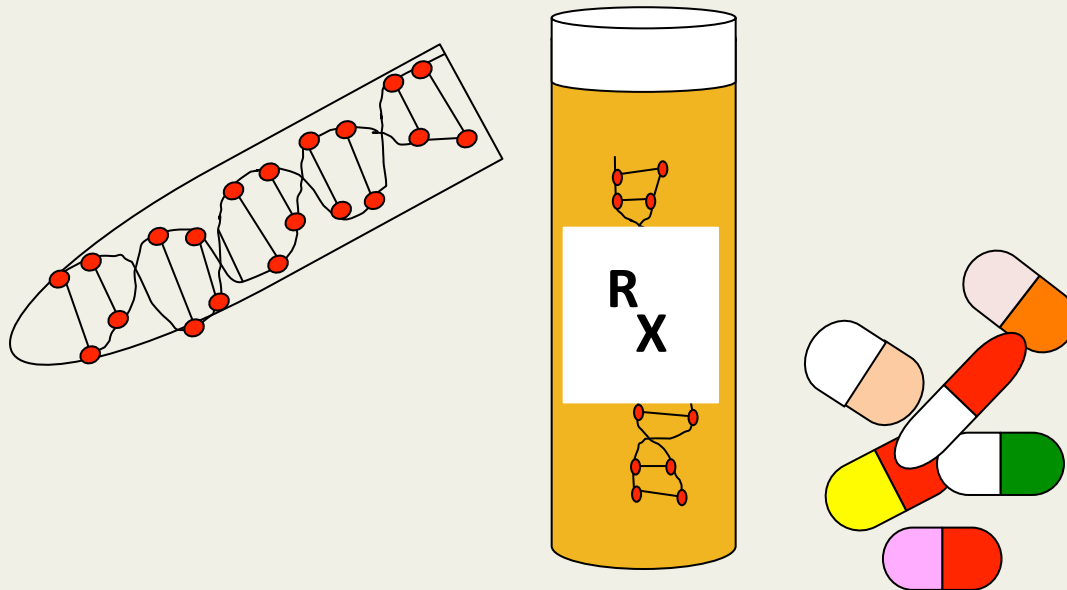
Drs. James Watson and Francis Crick determined the **structure of DNA** (*double helix*)



April 2003

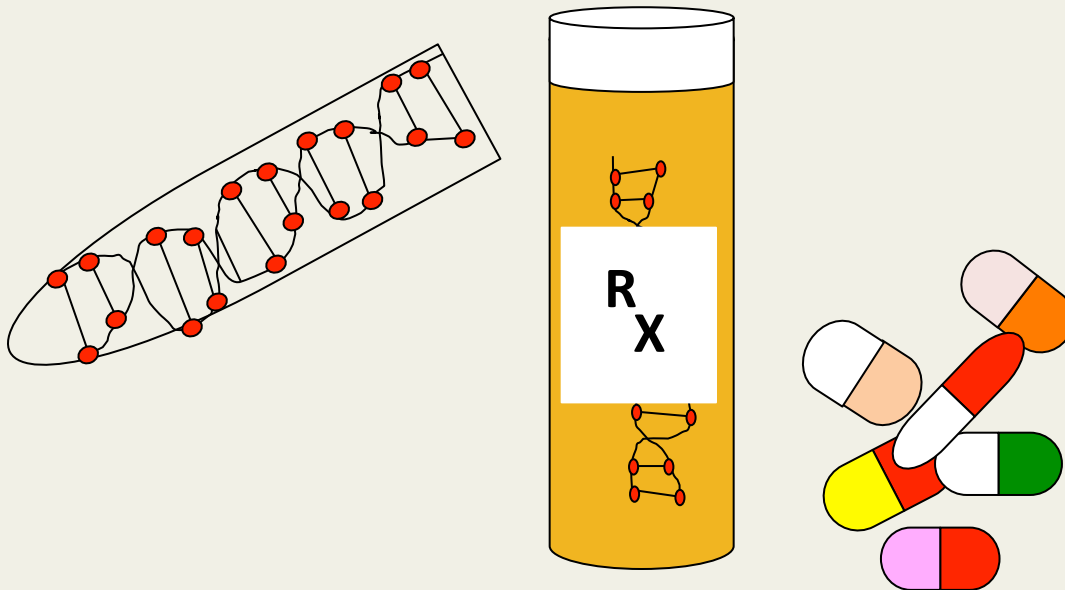
Human Genome Project determined the **entire DNA sequence of a human** (*3 billion letters*)

What is Pharmacogenomics?



What is Pharmacogenomics?

Pharma = drug or medicine
Genomics = the study of genes

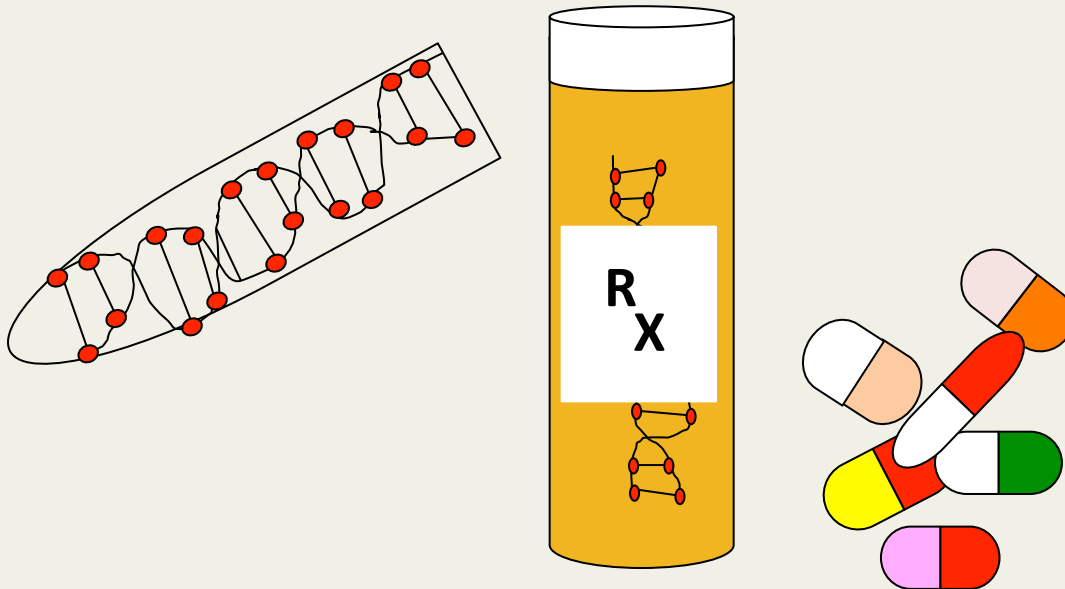


What is **Pharmacogenomics**?

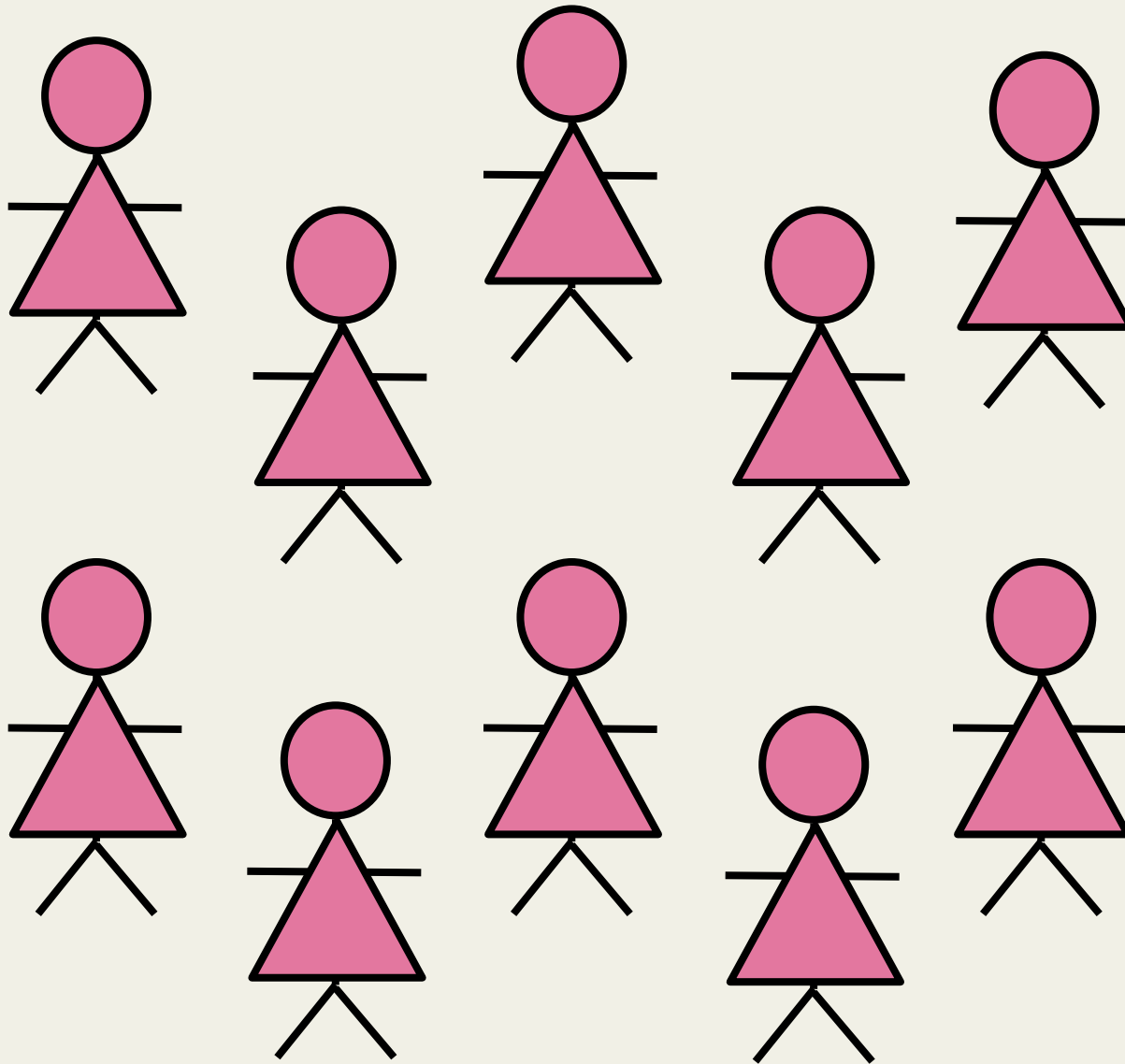
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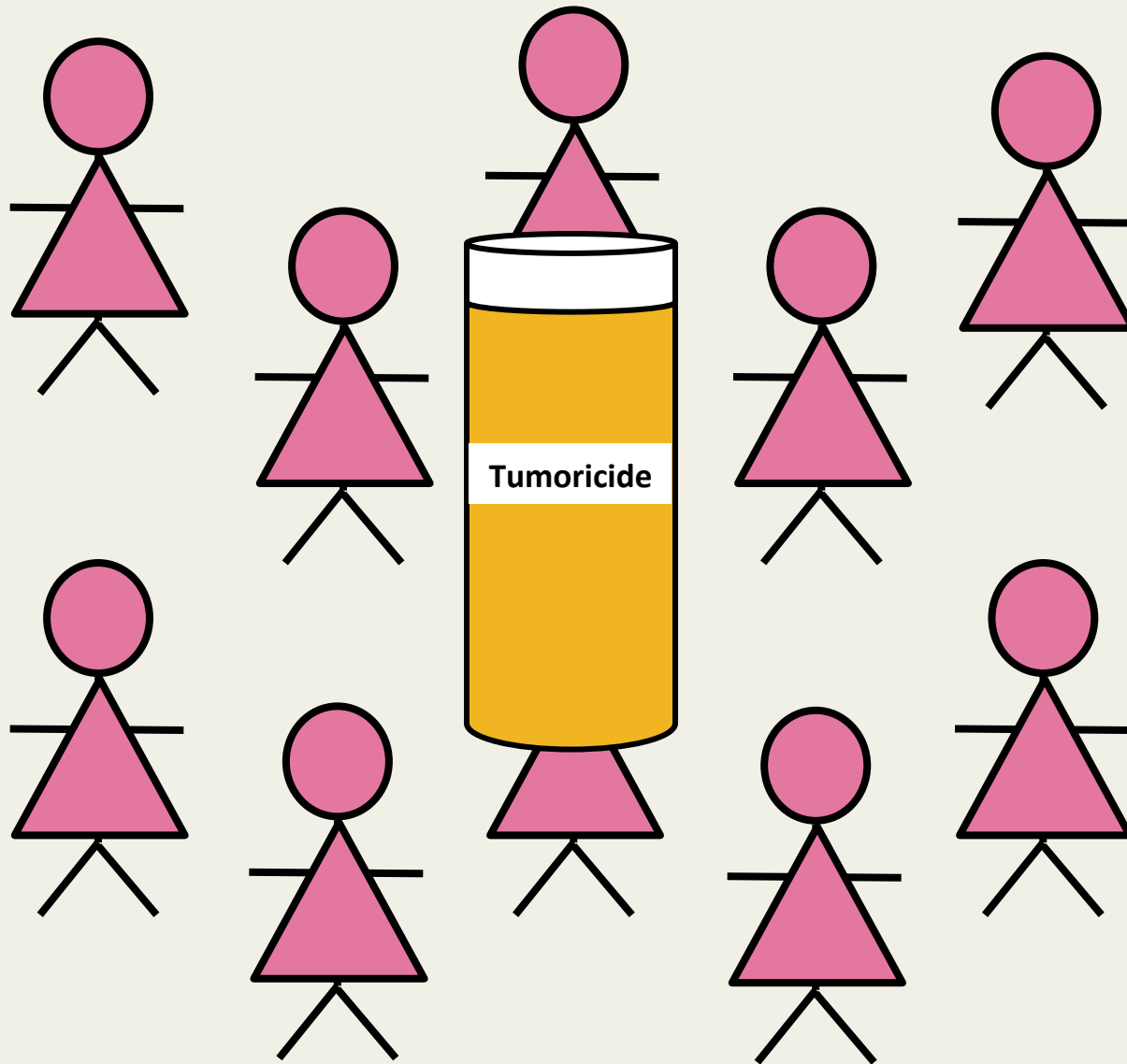
Personalized medicine tailored to your genes



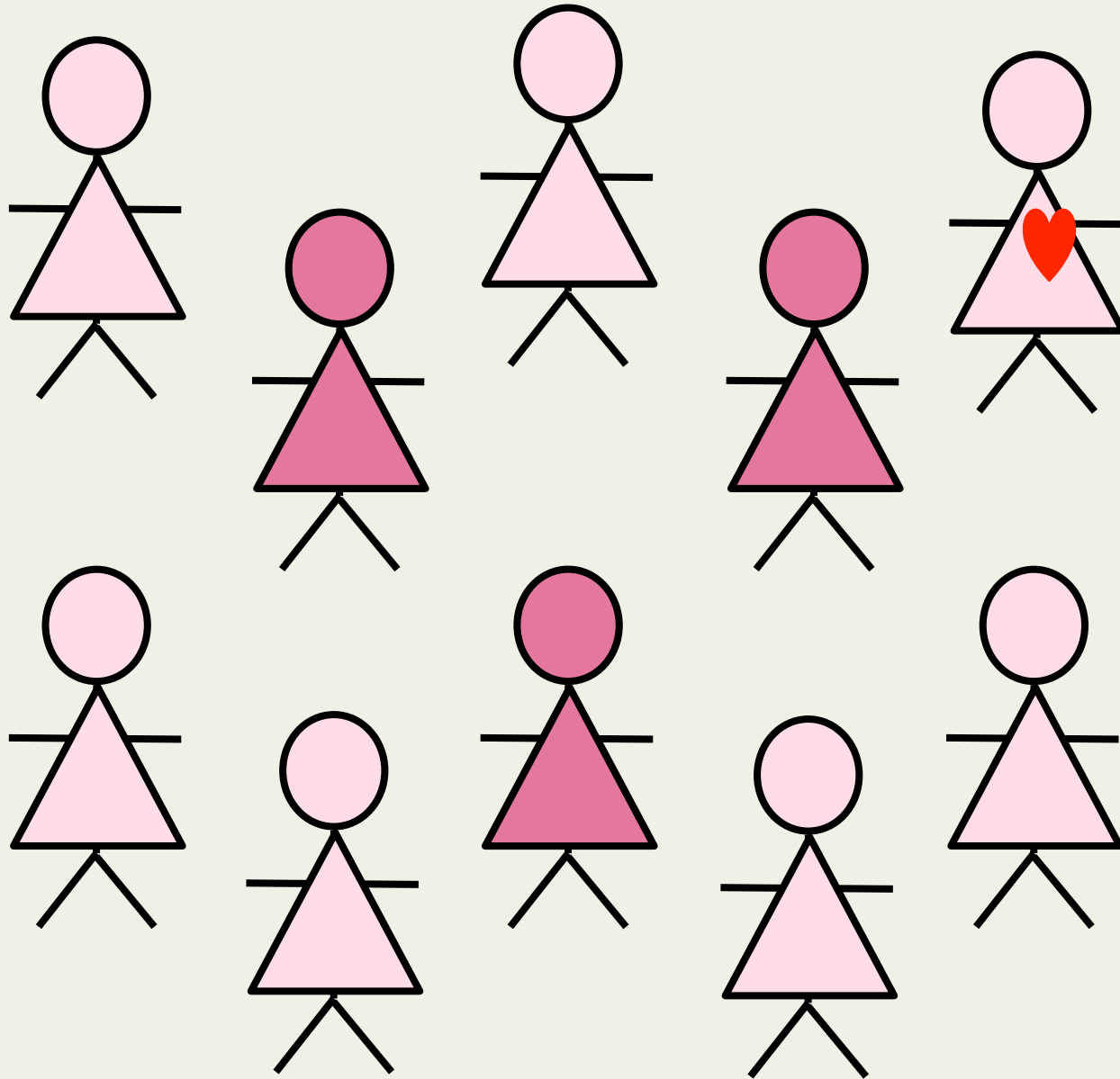
Case Study – Breast Cancer Patients



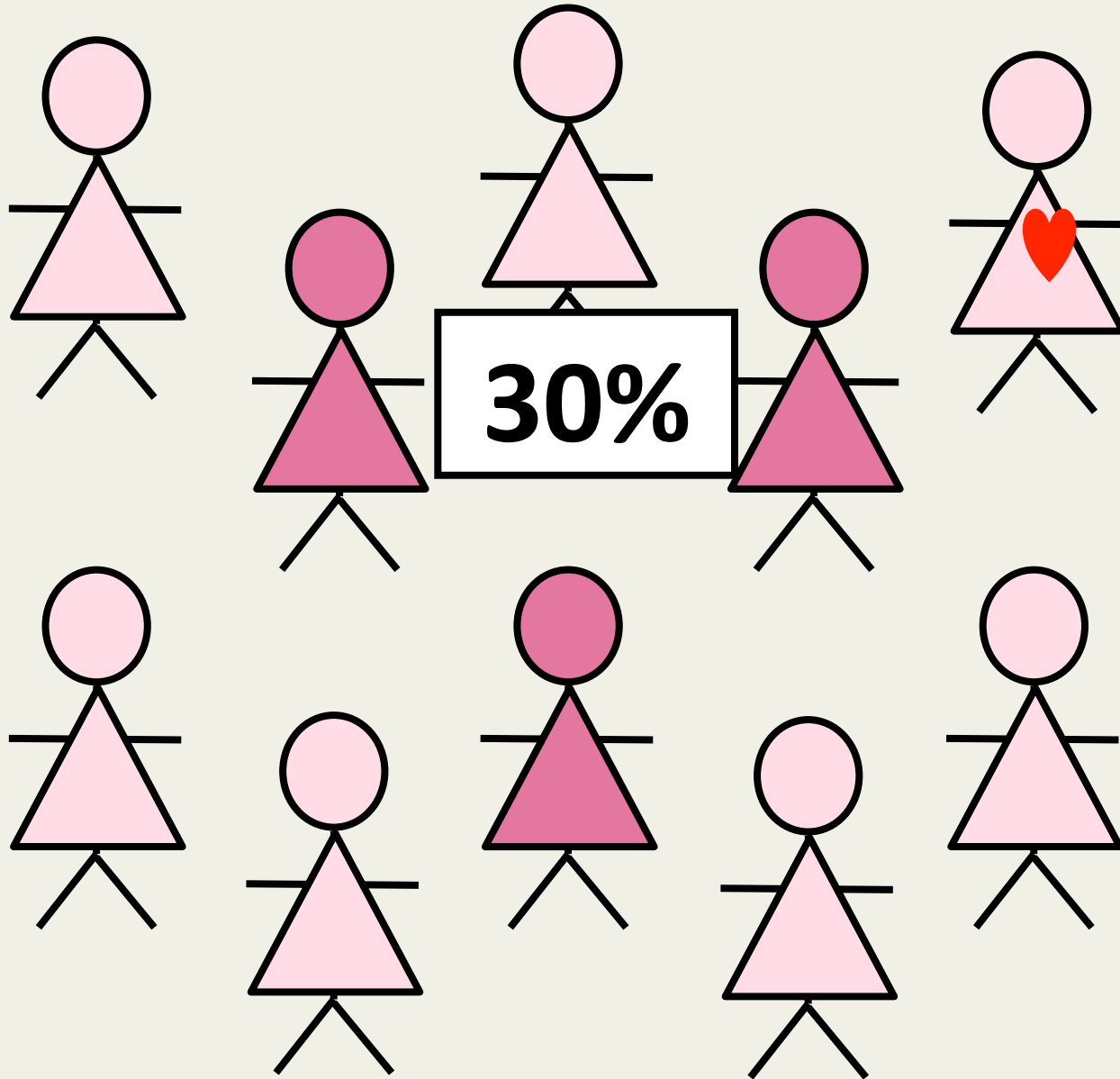
Case Study – Breast Cancer Patients



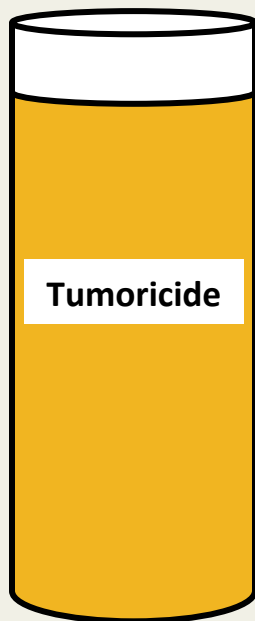
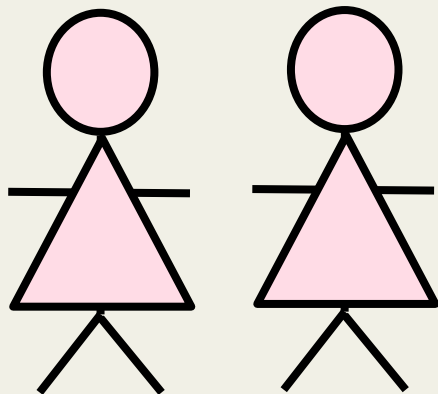
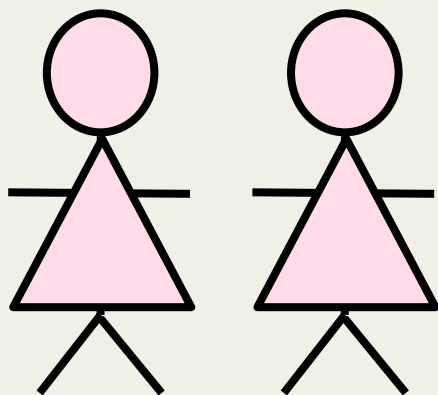
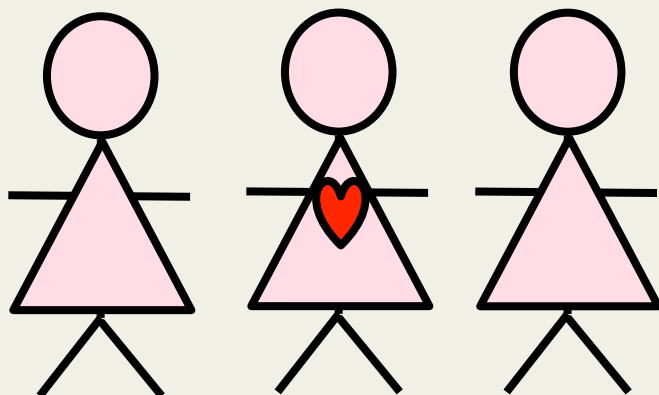
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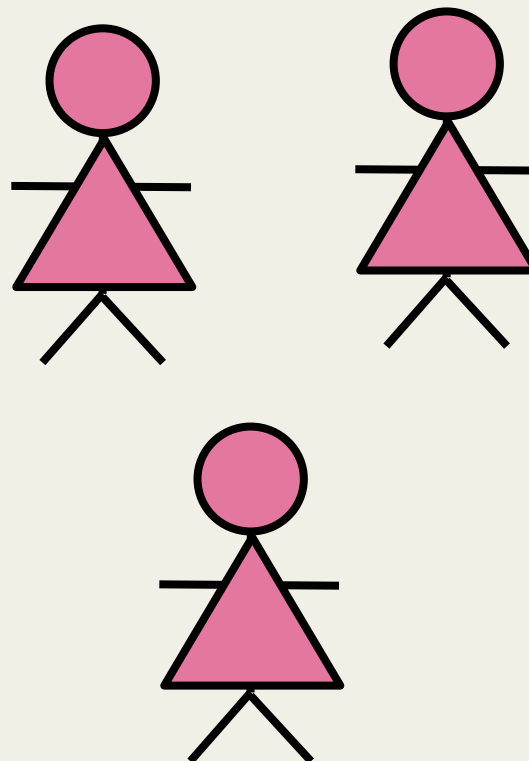
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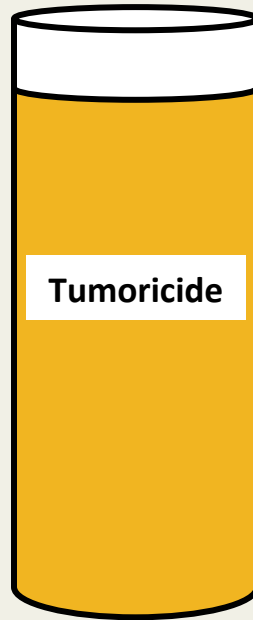
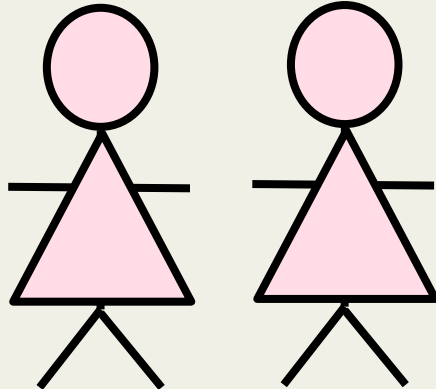
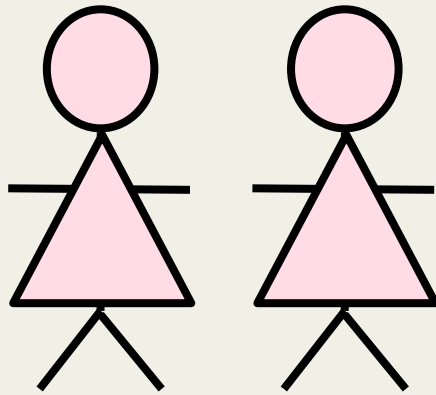
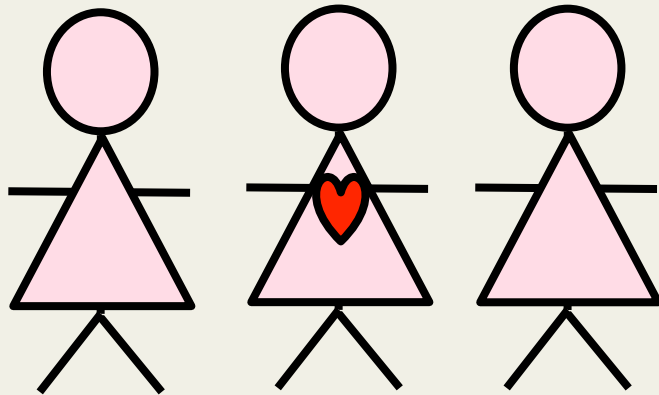
No Effect/Hurt



Helped

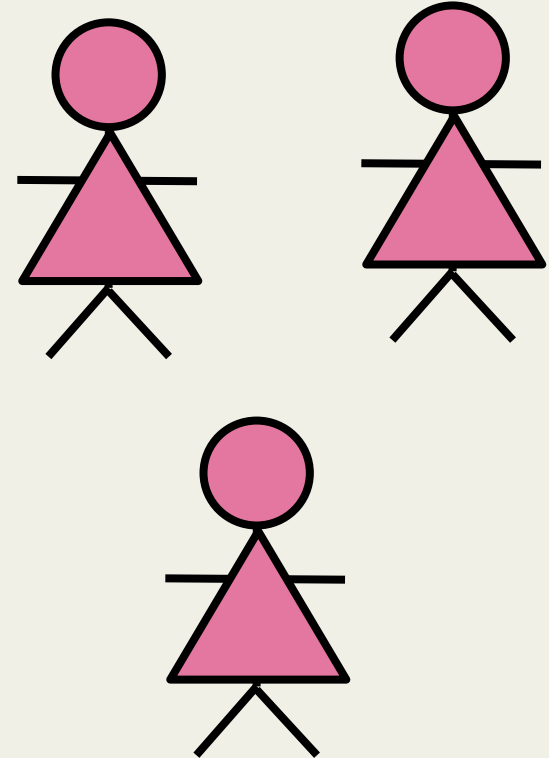


No Effect/Hurt



Why?

Helped

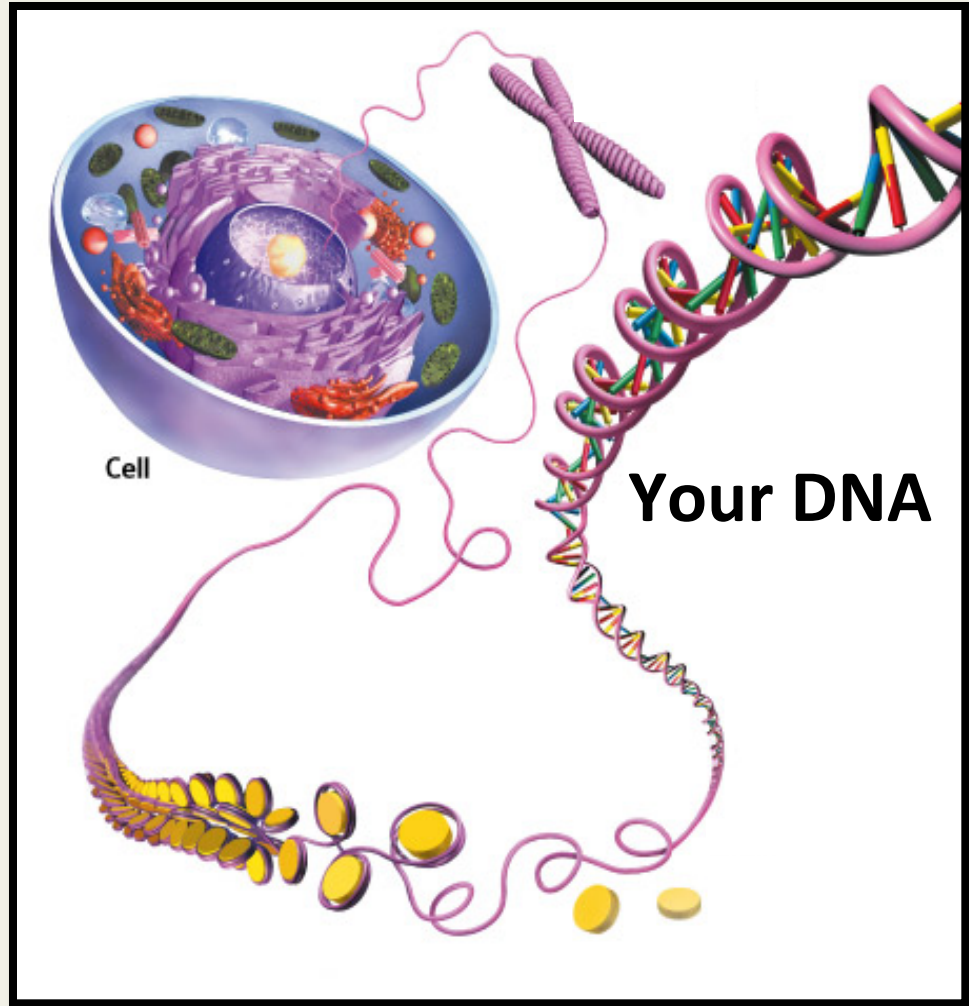


How do scientists make personalized medicine?

You



Your cells



How do scientists make personalized medicine?

You

Your cells

**It's all about what makes
YOUR genetic code *UNIQUE***

Genetic Code: DNA

DeoxyriboNucleic Acid (DNA) contains all the information necessary to make a complete organism

DNA is composed of a combination of 4 **nucleotides**

Genetic Code: DNA

DeoxyriboNucleic Acid (DNA) contains all the information necessary to make a complete organism

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Adenine

Genetic Code: DNA

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DNA is composed of a combination of 4 **nucleotides**



Adenine



Thymine

Genetic Code: DNA

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Adenine



Thymine

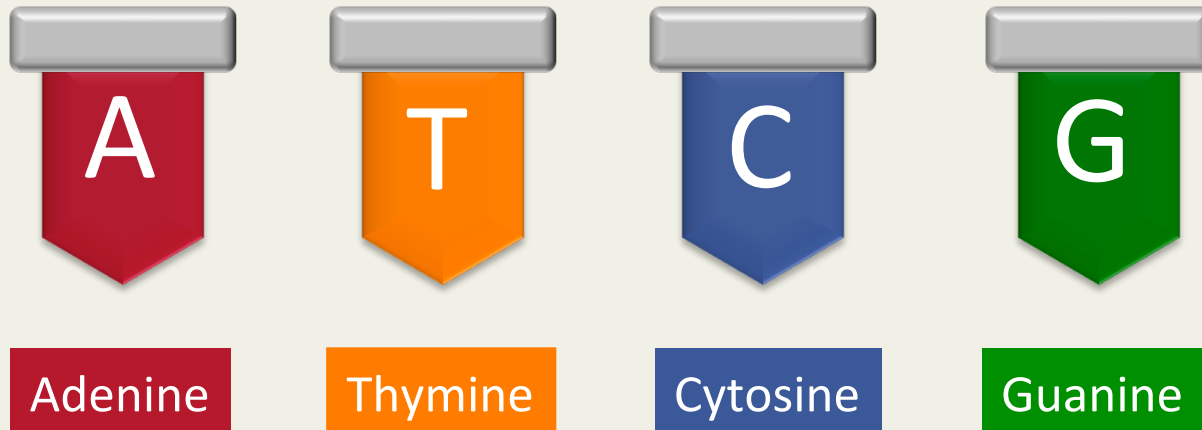


Cytosine

Genetic Code: DNA

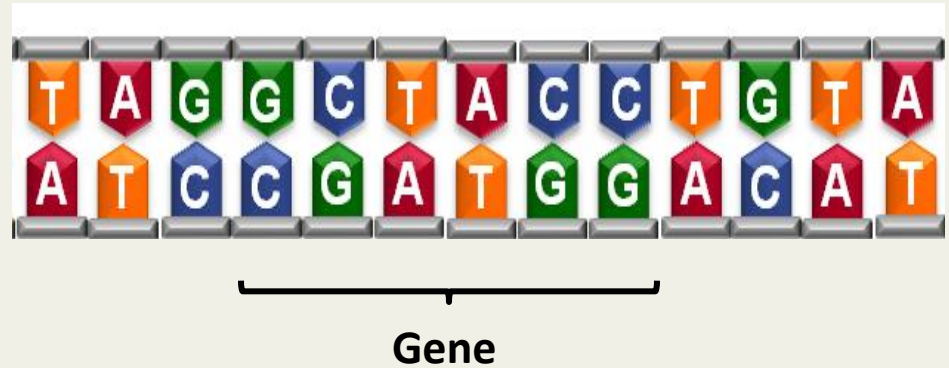
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DNA is composed of a combination of 4 **nucleotides**



The Central Dogma: DNA→RNA→Protein

DNA: A long double-stranded string of nucleotides that encode for many genes.



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DNA: A long double-stranded string of nucleotides that encode for many genes.



RNA: A single-stranded copy of one gene.



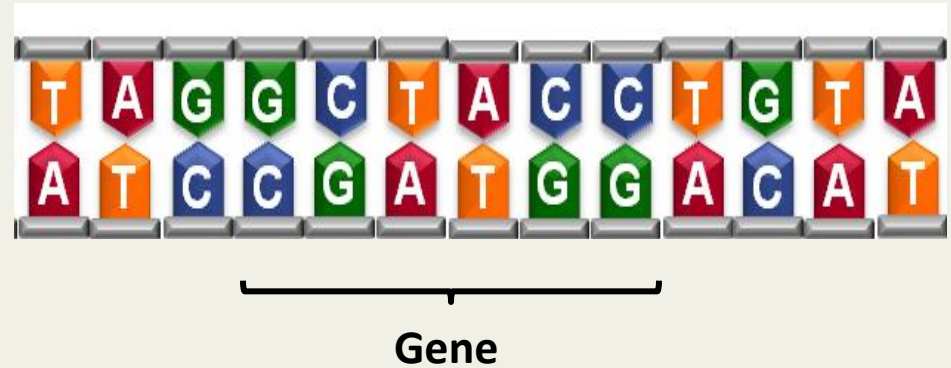
Gene



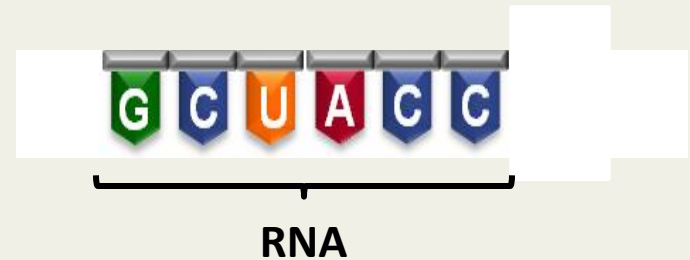
RNA

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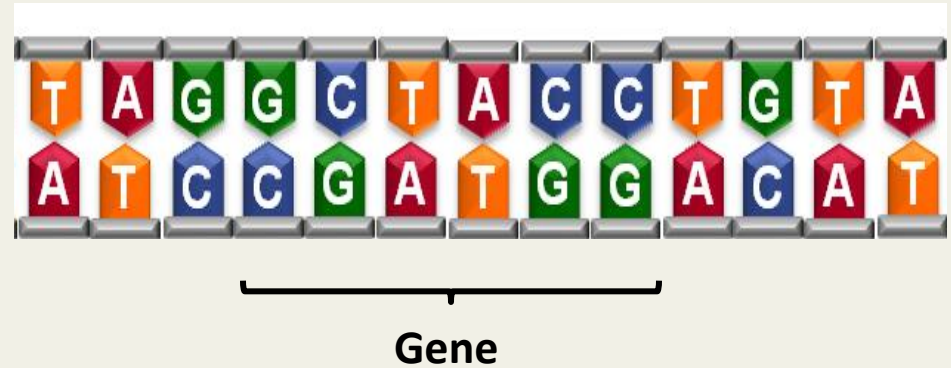
RNA: A single-stranded copy of one gene.



Protein: Proteins are composed of amino acids. Amino acids are made from triplets of nucleotides called codons.

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↓

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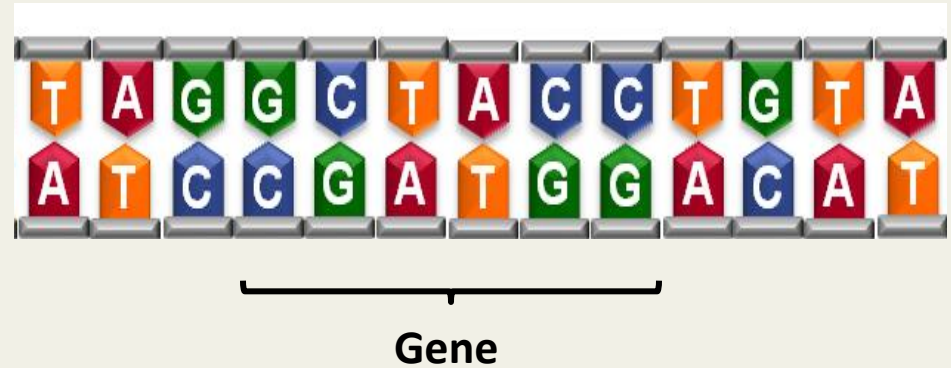


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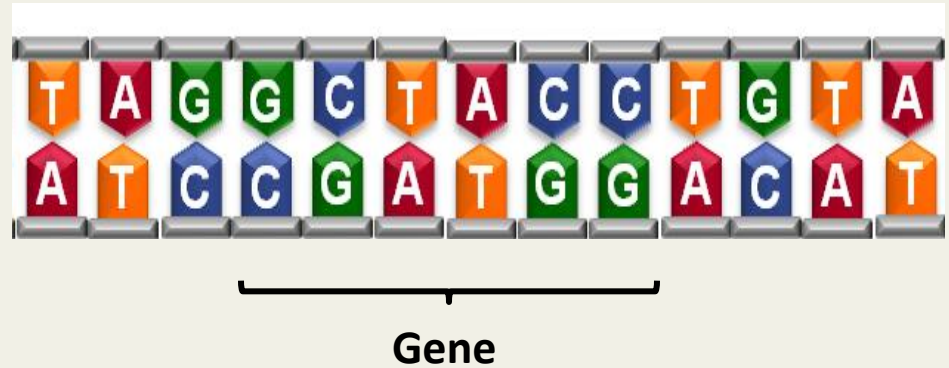
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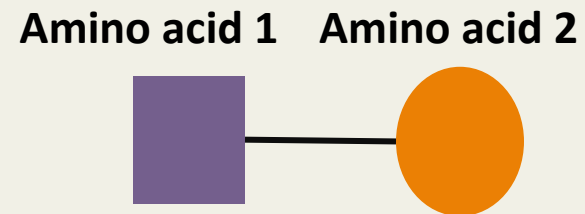
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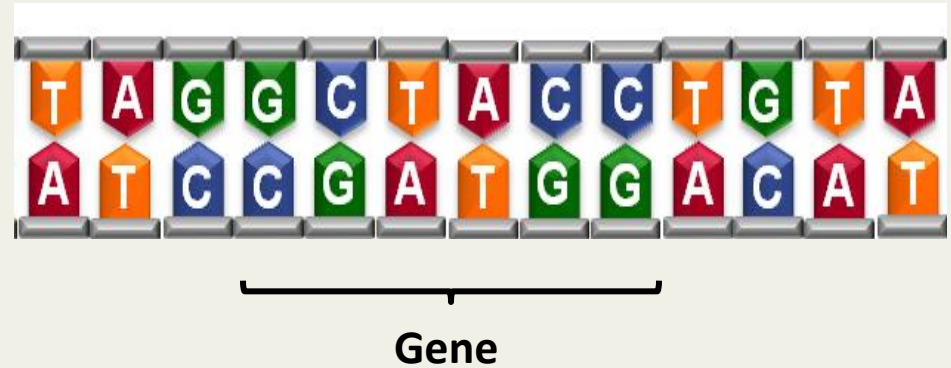


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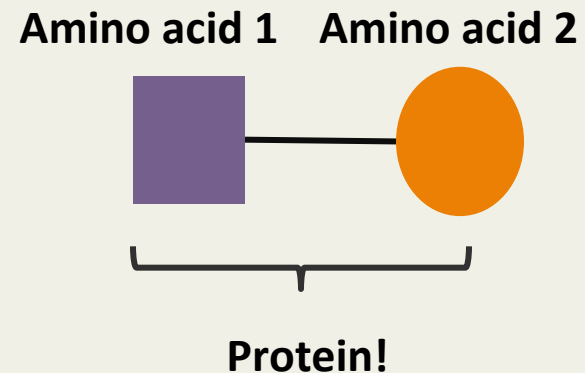
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A small change in the gene sequence can result in a
very different protein

DNA: ATG GTG CTG TCT CCT

A small change in the gene sequence can result in a very different protein

DNA:

ATG

GTG

CTG

TCT

CCT

Amino Acids/Protein:

Met

A small change in the gene sequence can result in a very different protein

DNA:

ATG

GTG

CTG

TCT

CCT

Amino Acids/Protein:

Met	Val
-----	-----

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GTG

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TCT

CCT

Amino Acids/Protein:

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-----	-----	-----

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-----	-----	-----	-----	-----

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ATG

GTG

CTG

TCT

CCT

Amino Acids/Protein:

Met

Val

Leu

Ser

Pro

DNA:

ATG

GTG

CTG

TCT

ACT

A small change in the gene sequence can result in a very different protein

DNA:

ATG

GTG

CTG

TCT

CCT

Amino Acids/Protein:

Met

Val

Leu

Ser

Pro

DNA:

ATG

GTG

CTG

TCT

ACT

Amino Acids/Protein:

Met

Val

Leu

Ser

Thr

A small change in the gene sequence can result in a very different protein

DNA: ATG GTG CTG TCT CCT

Amino Acids/Protein:

Met	Val	Leu	Ser	Pro
-----	-----	-----	-----	-----

Words: Tom and Sam are bad

DNA: ATG GTG CTG TCT **ACT**

Amino Acids/Protein:

Met	Val	Leu	Ser	Thr
-----	-----	-----	-----	-----

A small change in the gene sequence can result in a very different protein

DNA: ATG GTG CTG TCT CCT

Amino Acids/Protein:

Met	Val	Leu	Ser	Pro
-----	-----	-----	-----	-----

Words: Tom and Sam are bad

DNA: ATG GTG CTG TCT ACT

Amino Acids/Protein:

Met	Val	Leu	Ser	Thr
-----	-----	-----	-----	-----

Words: Tom and Sam are sad

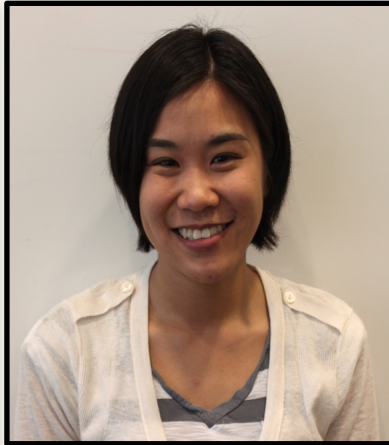
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Words:	Tom	and	Sam	are	bad

DNA:	ATG	GTG	CTG	TCT	ACT
Amino Acids/Protein:	Met	Val	Leu	Ser	Thr
Words:	Tom	and	Sam	are	sad

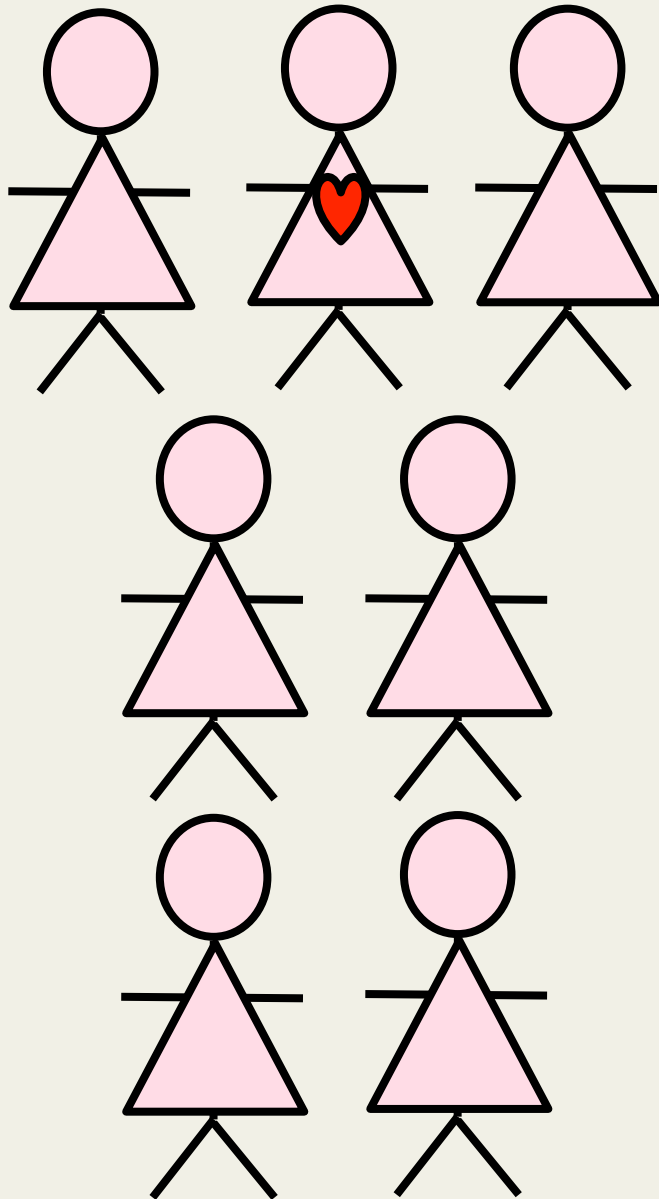
Changes in DNA are called variations or mutations

Variations in the DNA (**genotype**) can cause observable changes (**phenotype**) in individuals

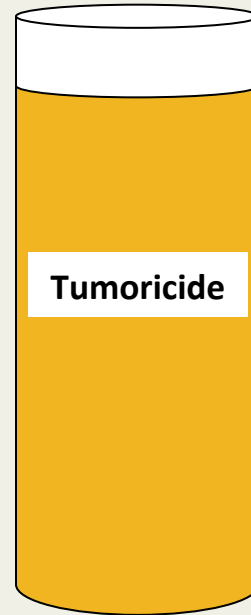
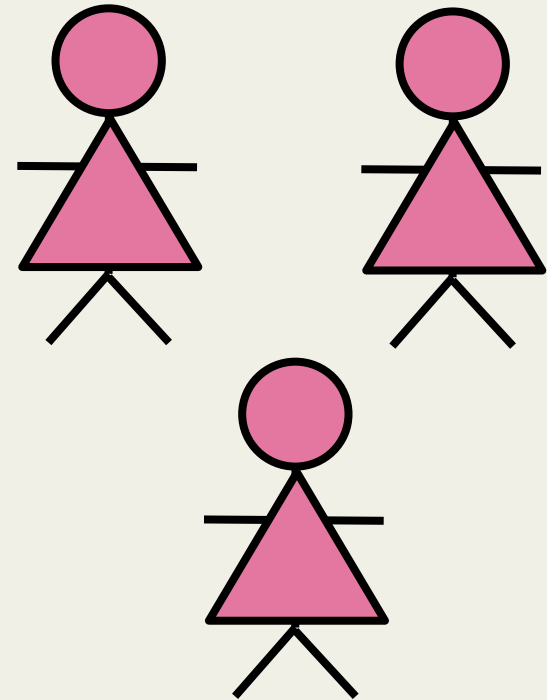


**Variations
in our
DNA
make us
UNIQUE!**

No Effect/Hurt



Helped

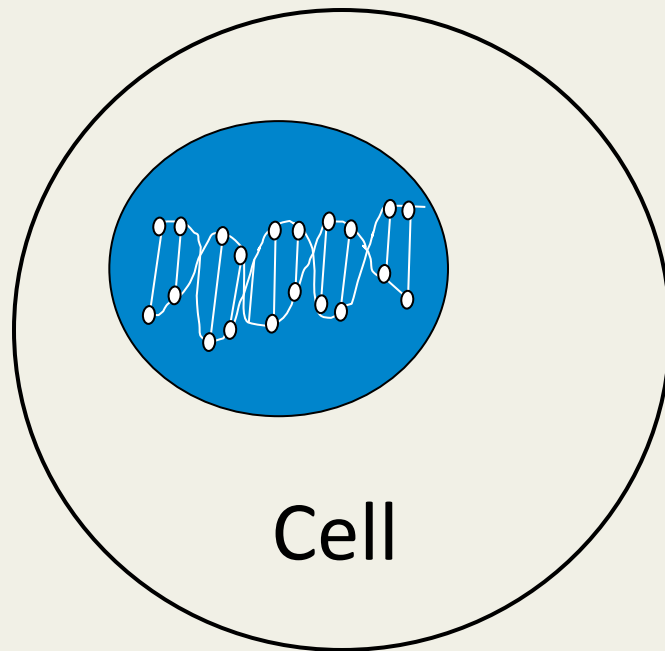


**Why does Tumoricide work
on some patients but not
on others?**

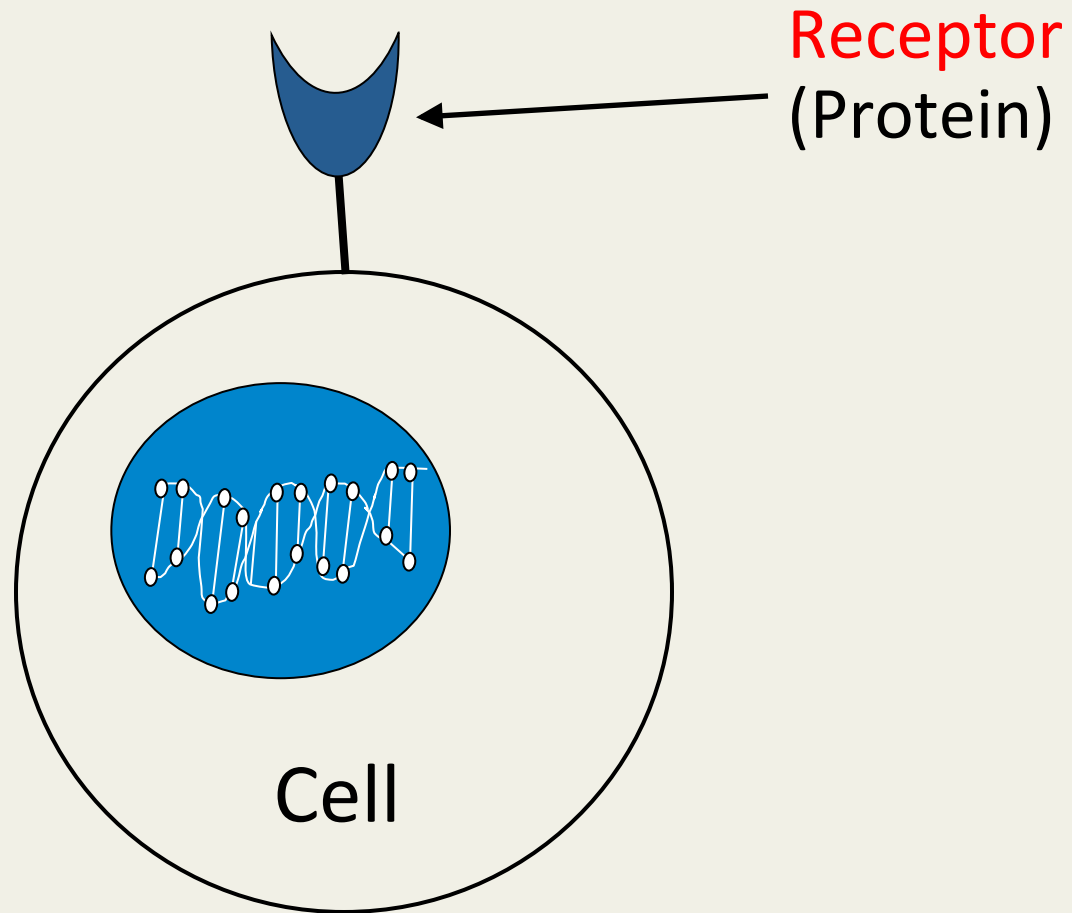
What are the reasons a person would react differently to drugs?

1. Having the receptor (protein) to recognize the drug
2. Other physiological traits that enable you to respond to a drug
3. How your body processes the drugs after receiving it

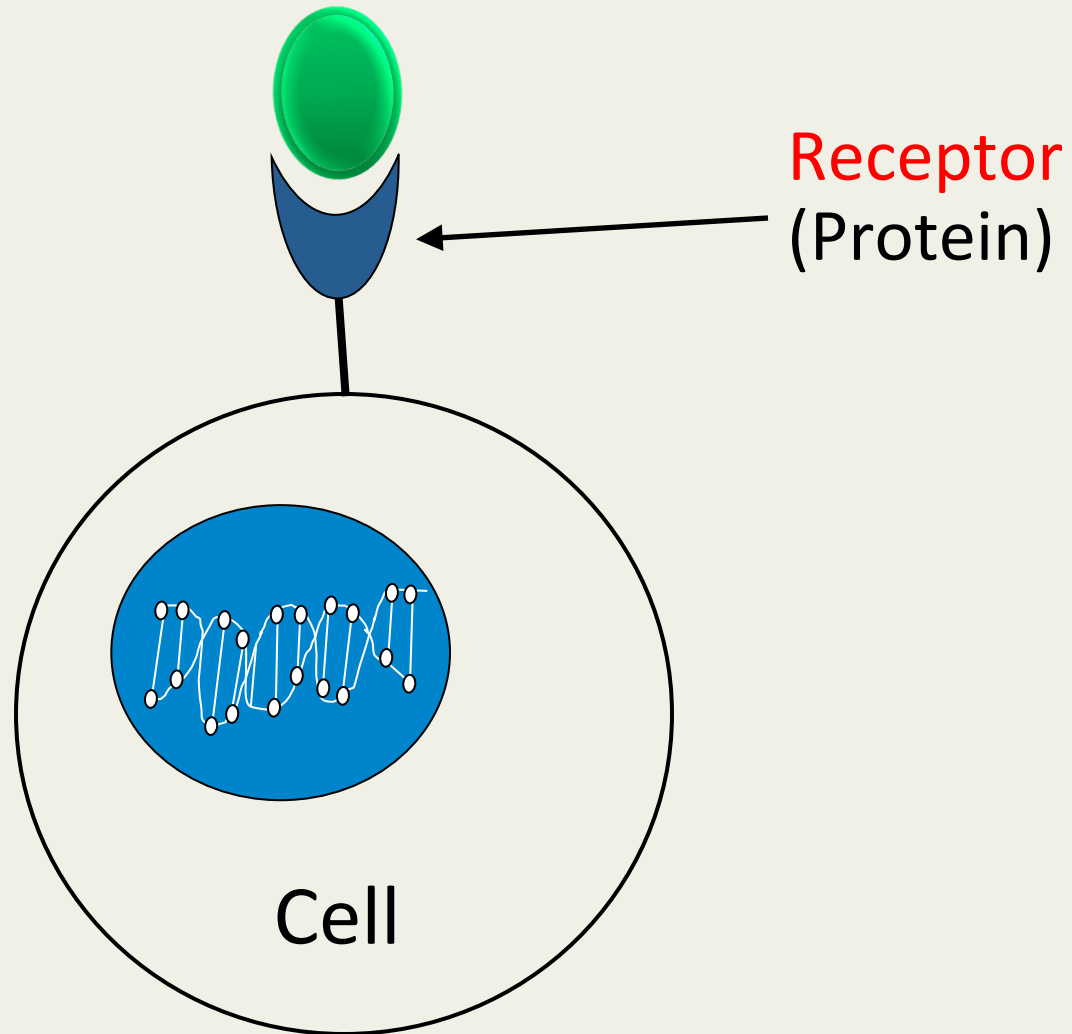
Drugs and Receptors



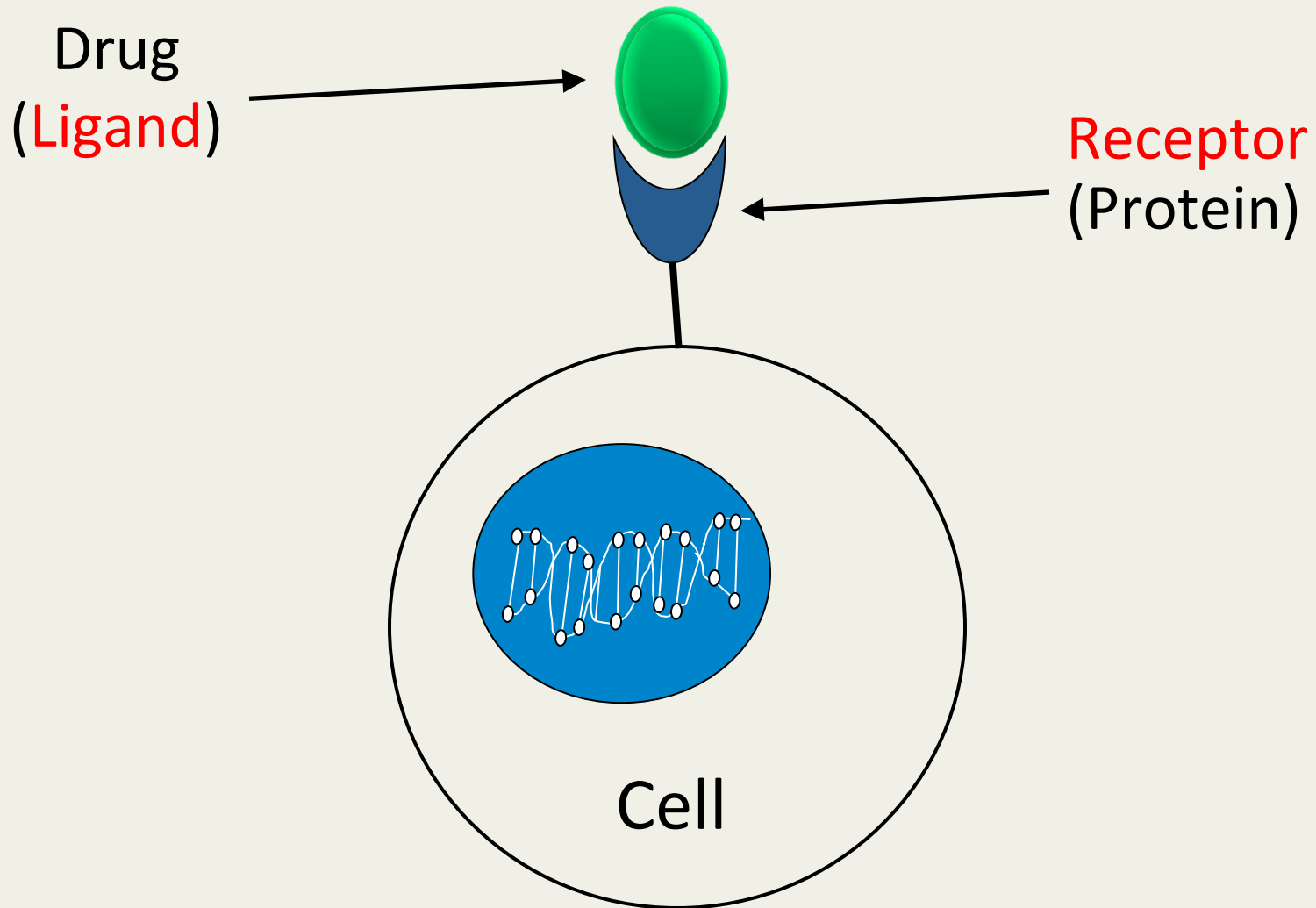
Drugs and Receptors



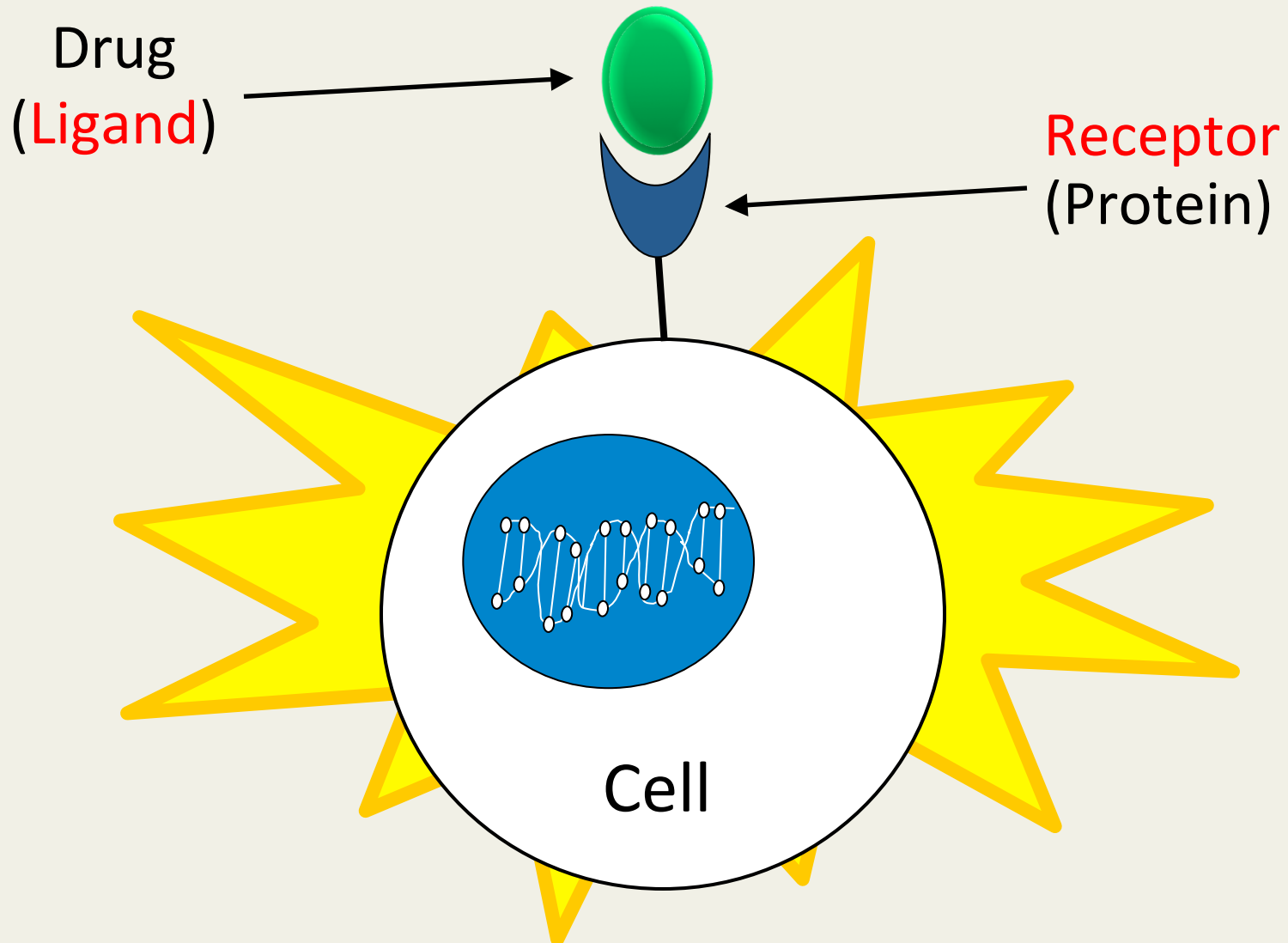
Drugs and Receptors



Drugs and Receptors

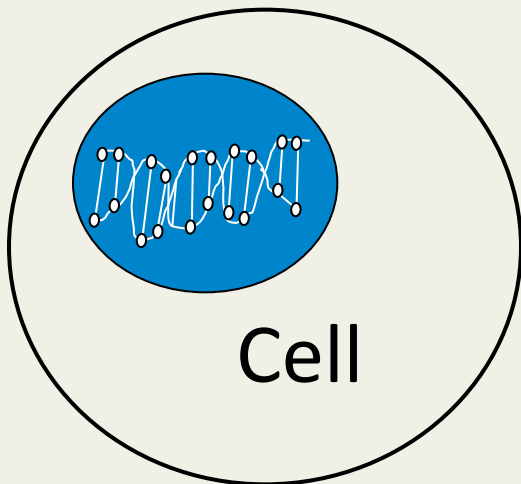


Drugs and Receptors



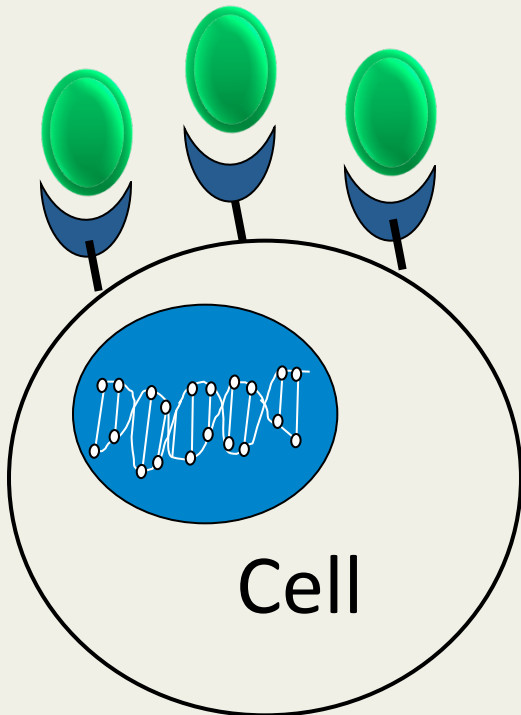
Your DNA and Drugs

Variation in genes can cause variation in receptors



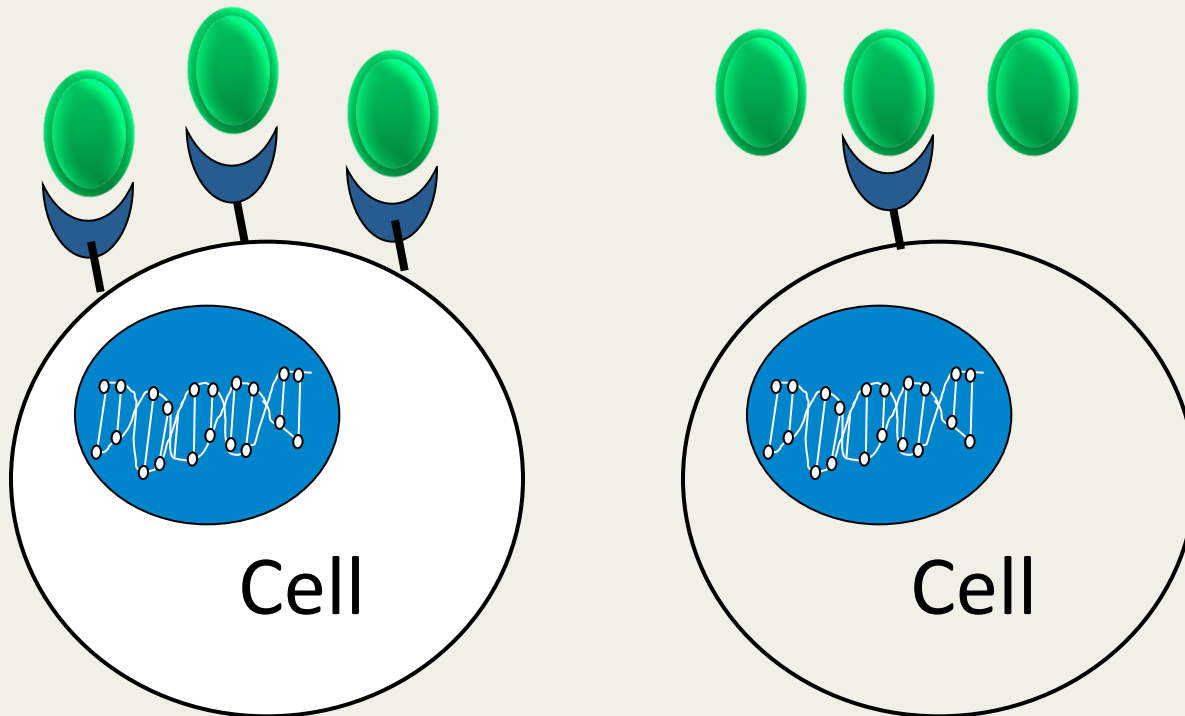
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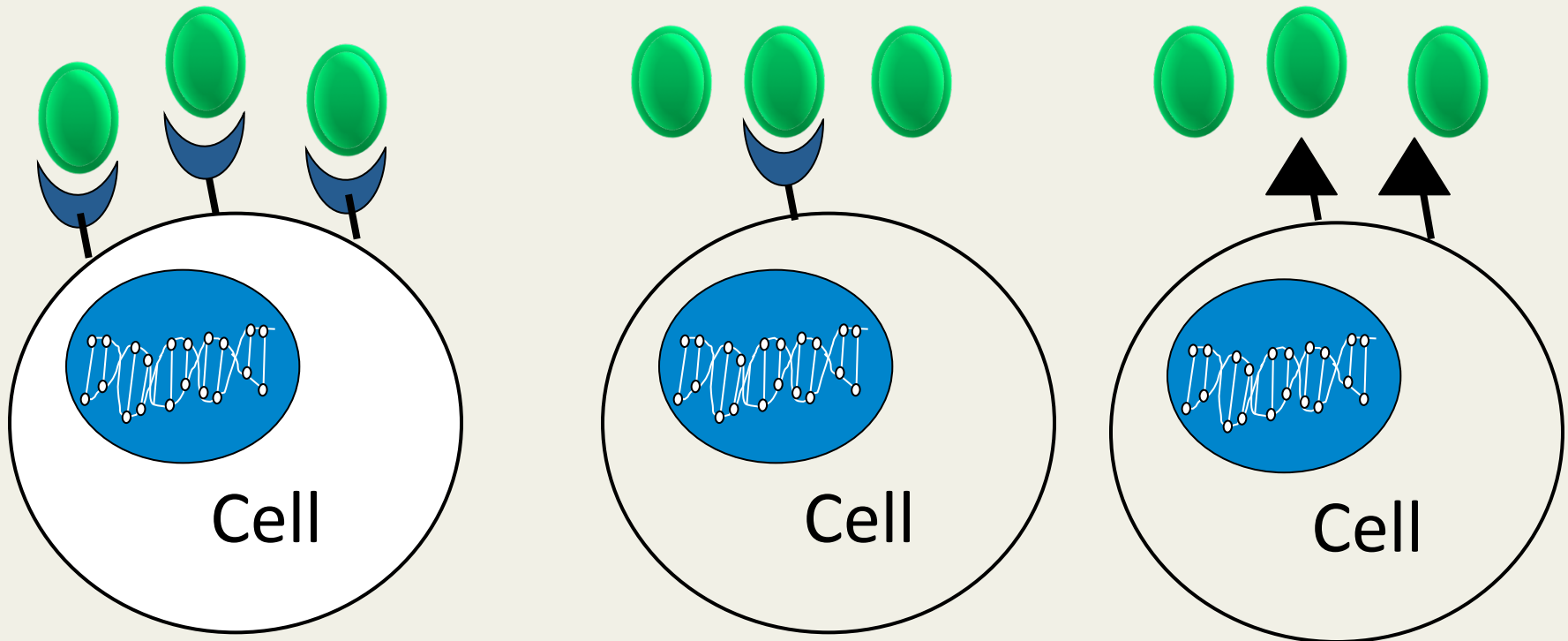
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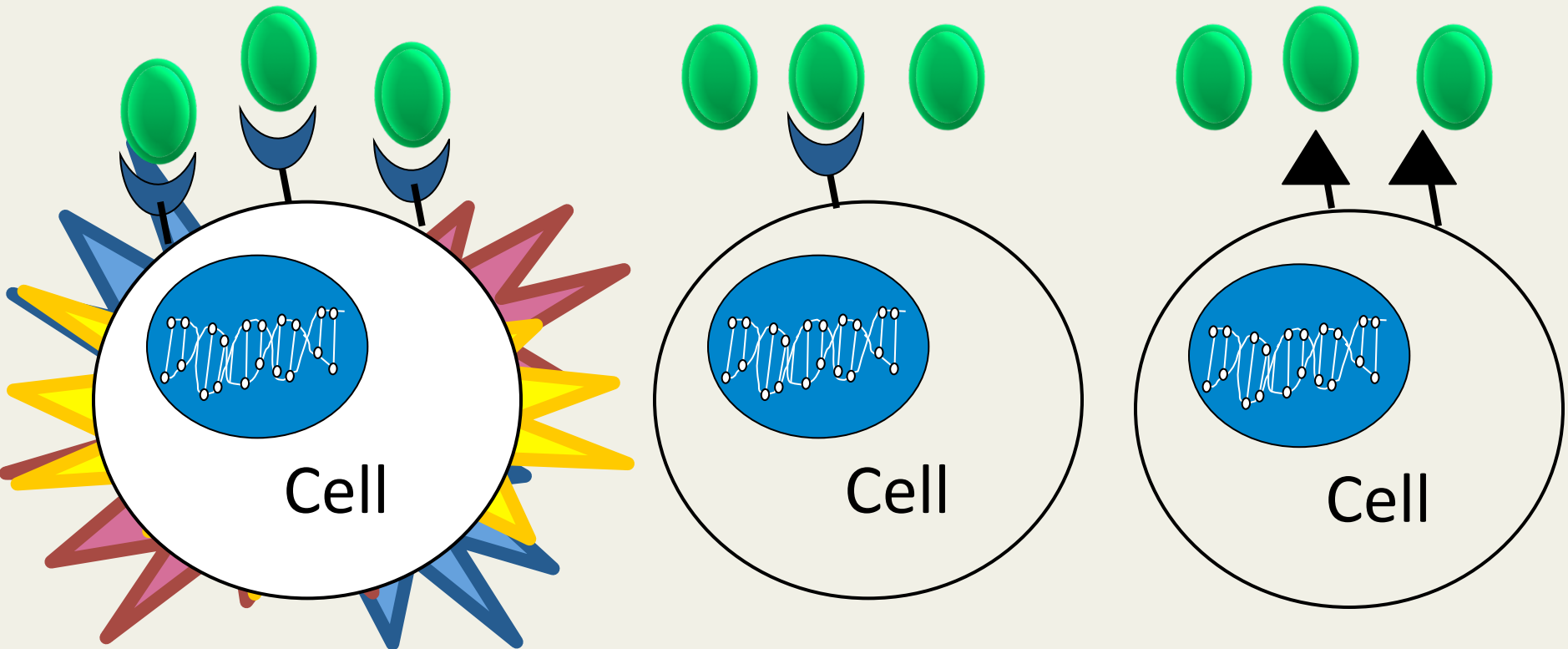
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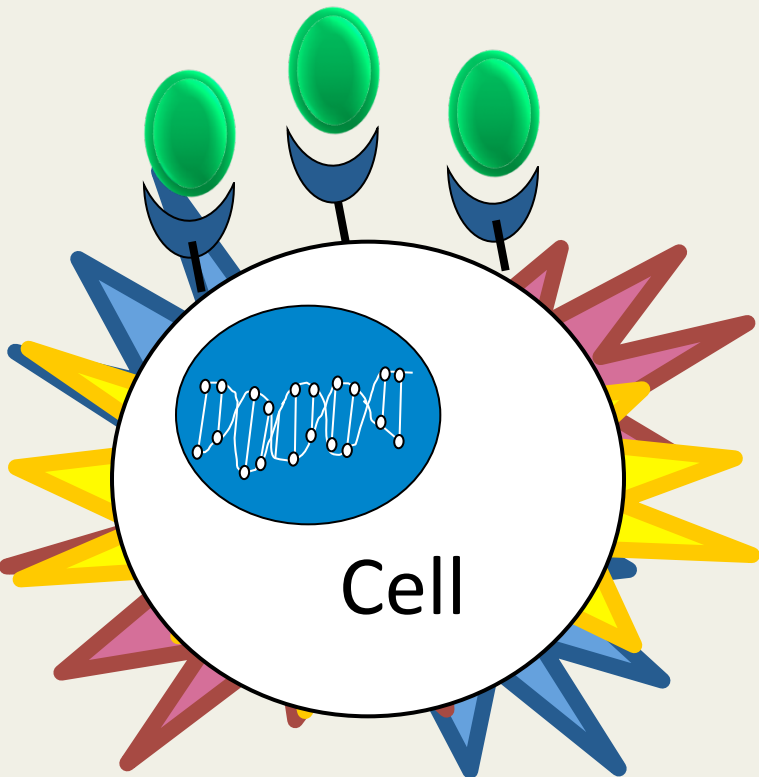
Too Many
(hypersensitive)



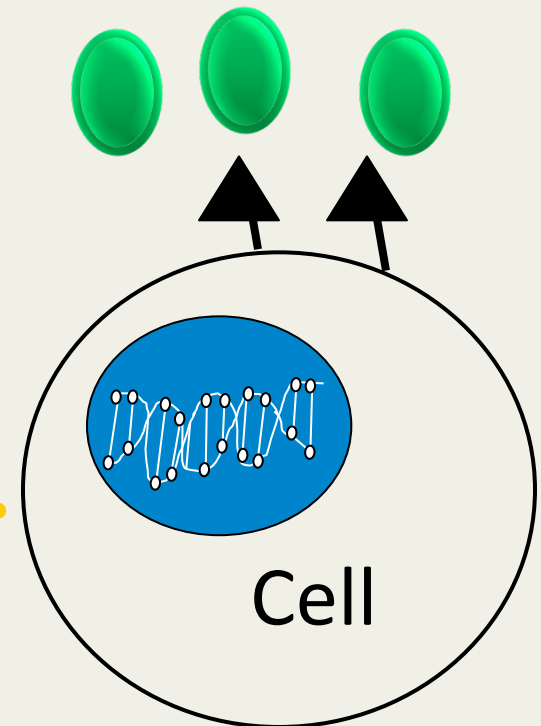
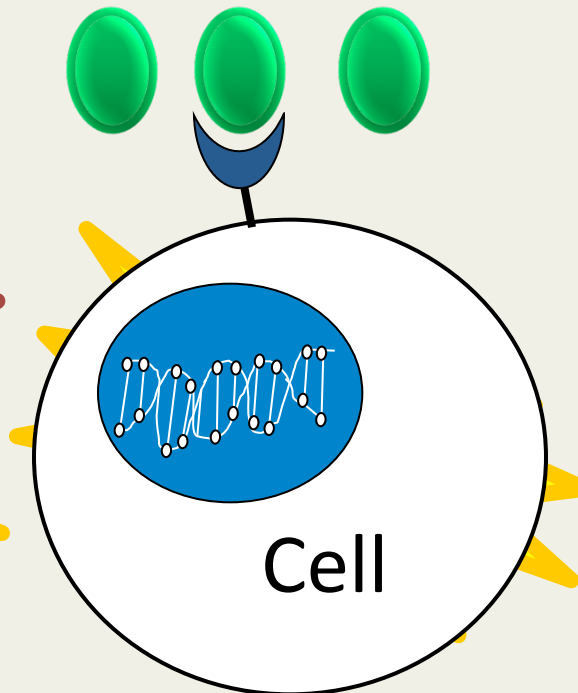
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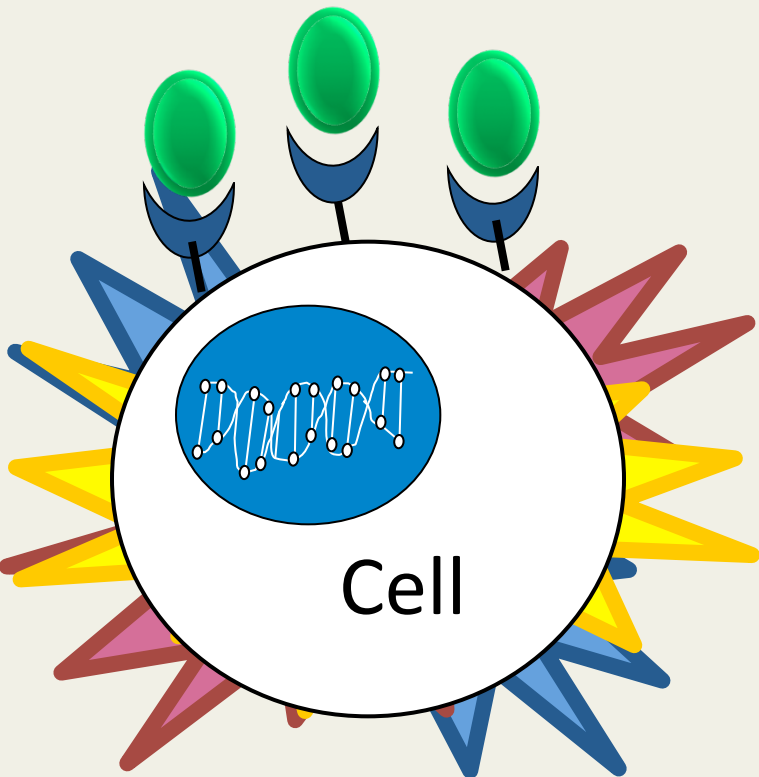
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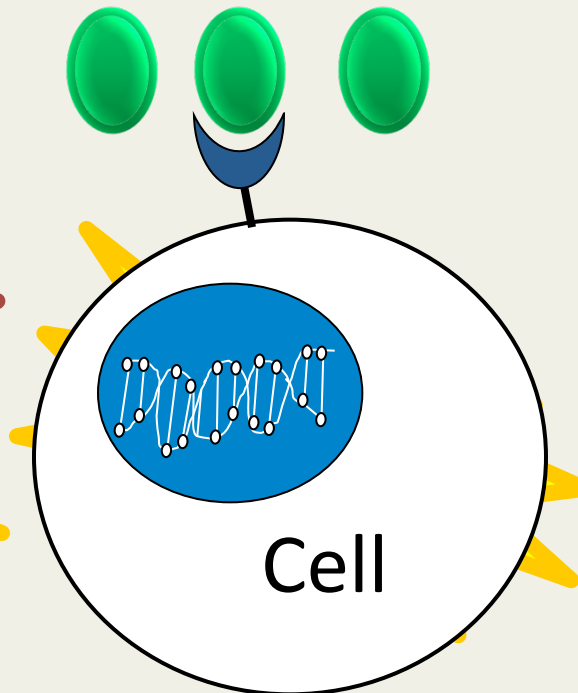
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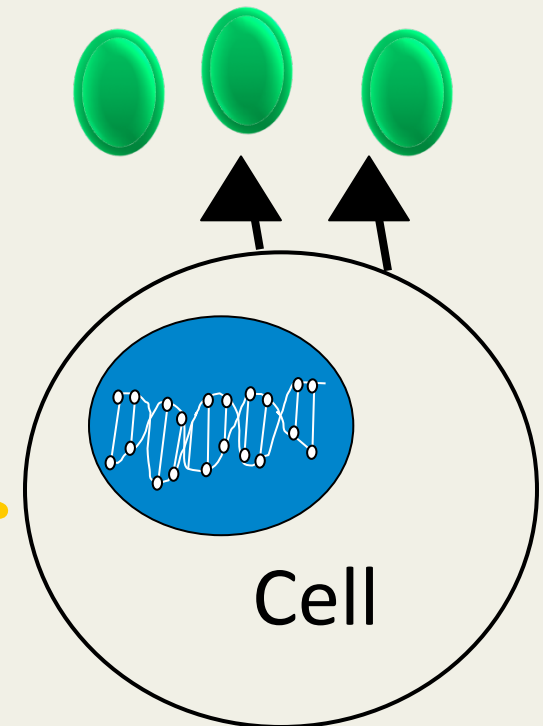
Too Many
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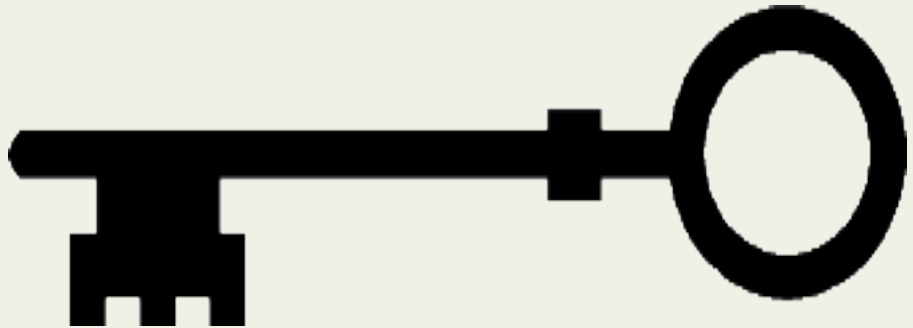
Too Few
(**hyposensitive**)



Mutated
(**insensitive**)



Where Drugs “Fit” In



Lock = Receptor

Key = Drug

Let's do a class case study!

Let's do a class case study!

- Taste the PTC strip

(This won't hurt you - not a toxic chemical)

What do you taste?

Let's do a class case study!

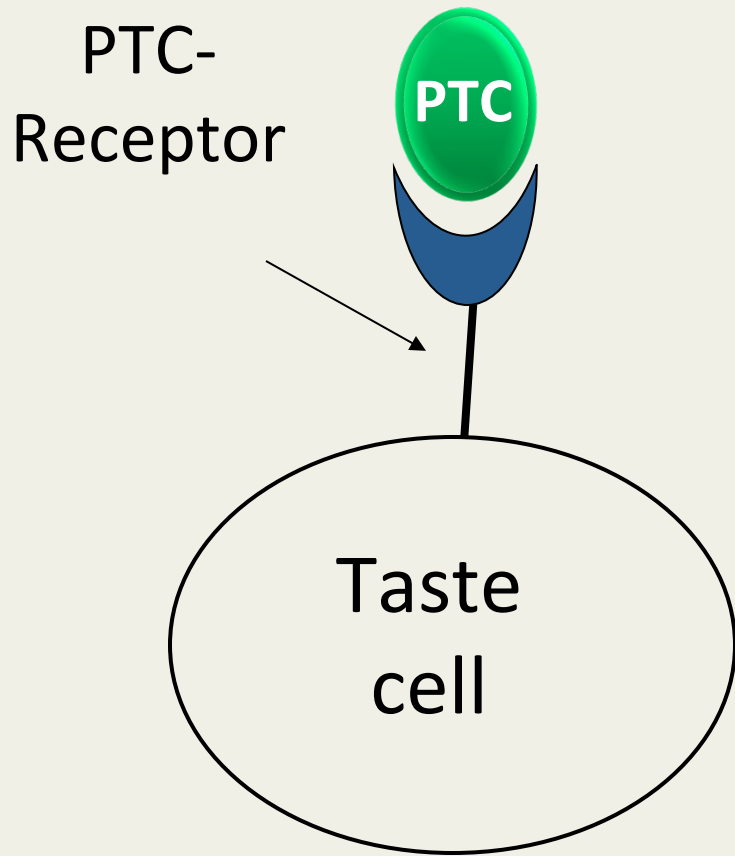
- Taste the PTC strip
(This won't hurt you - not a toxic chemical)

What do you taste?

Why does the strip taste bitter to some
and have no taste for others?

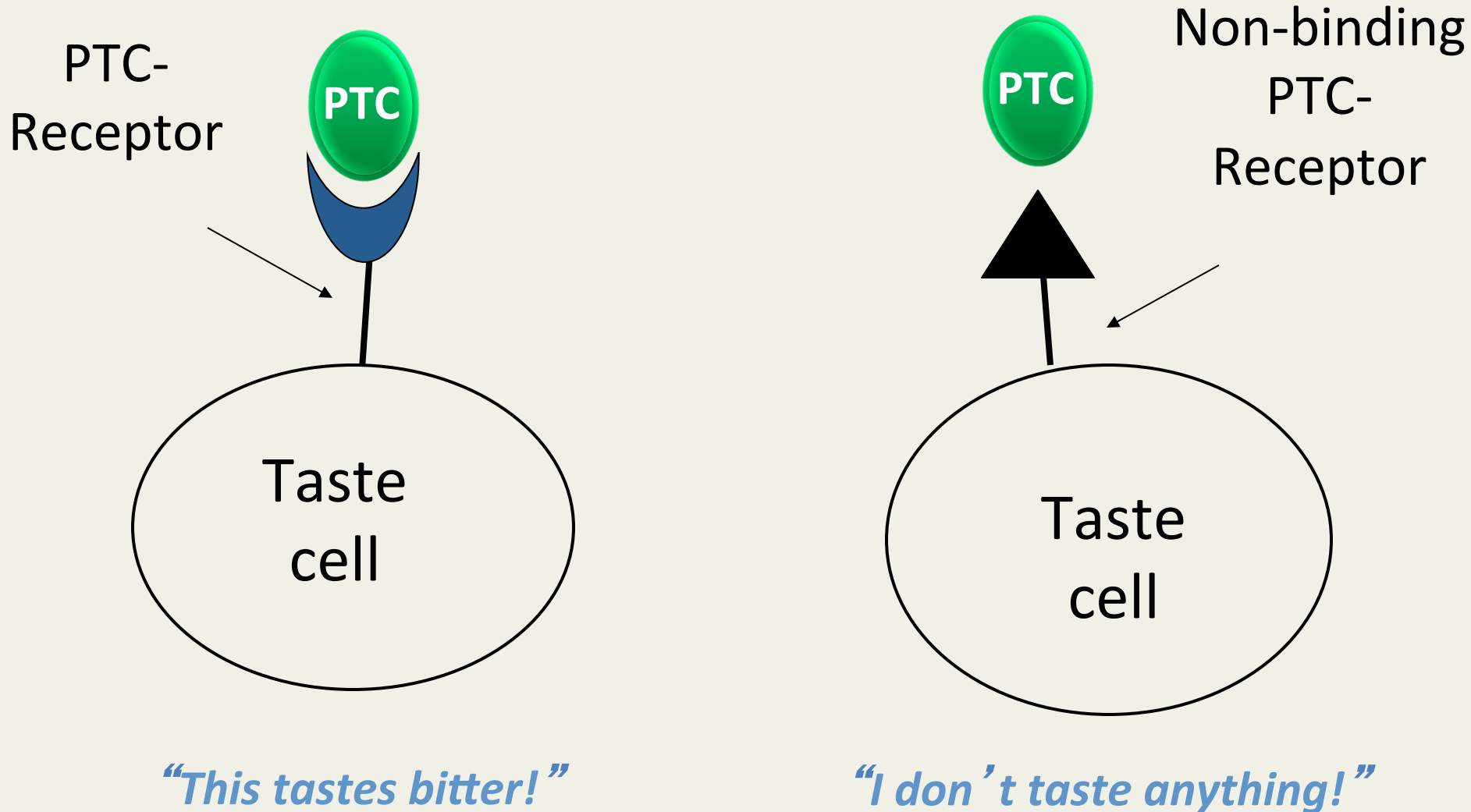
What is your hypothesis?

Why can some people taste PTC and others can't?



“This tastes bitter!”

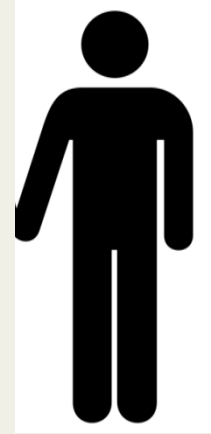
Why can some people taste PTC and others can't?



Where does tasting PTC come from?



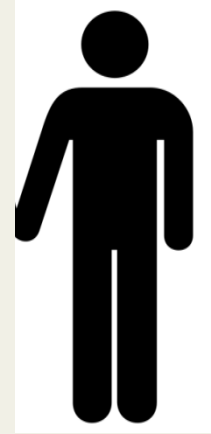
You have two copies of every gene:
one from Mom
and
one from Dad



Where does tasting PTC come from?



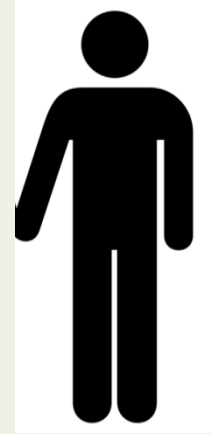
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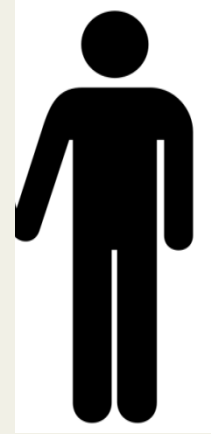
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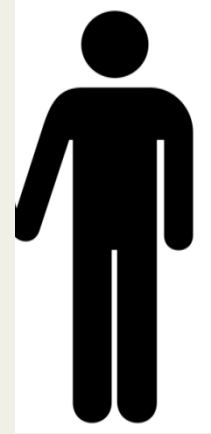


- Your two genes are the **genotype**

Where does tasting PTC come from?



You have two copies of every gene:
one from Mom
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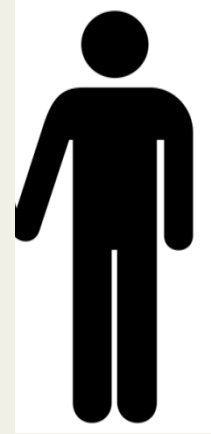


- Your two genes are the **genotype**
- A gene can be **dominant** or **recessive**

Where does tasting PTC come from?

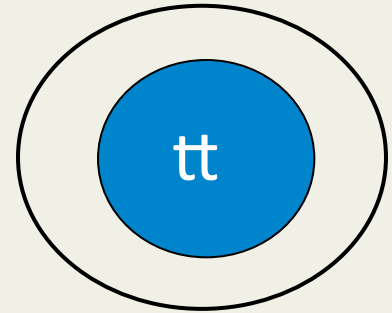
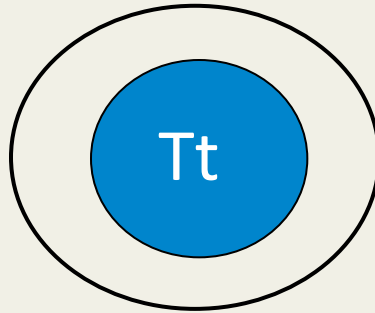
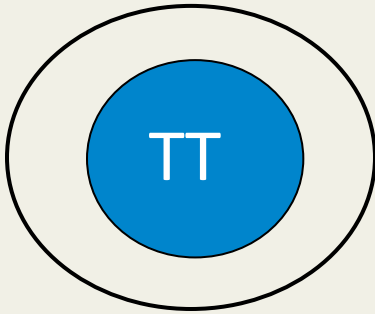


You have two copies of every gene:
one from Mom
and
one from Dad

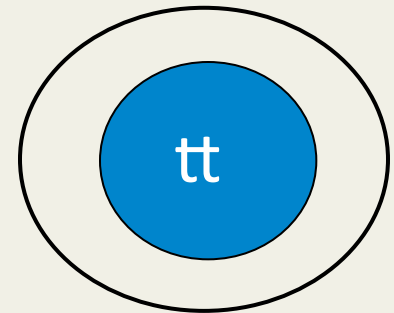
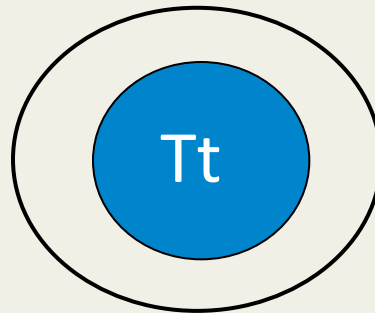
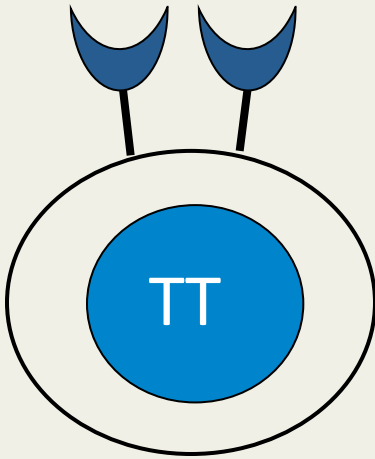


- Your two genes are the **genotype**
- A gene can be **dominant** or **recessive**
- The expressed trait is a **phenotype**

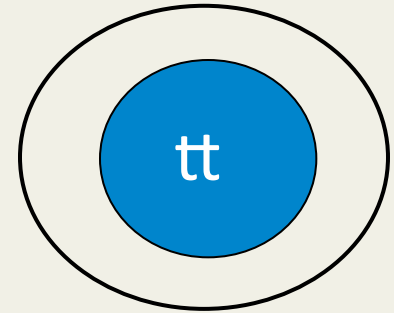
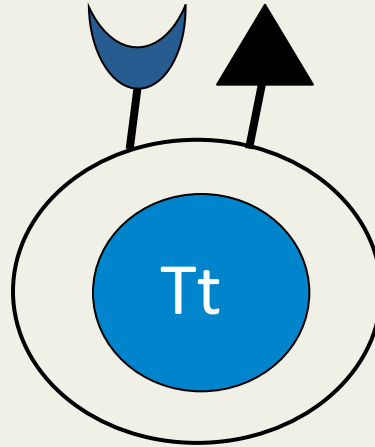
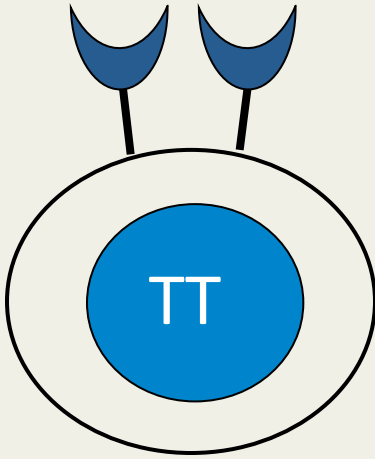
Tasting PTC is **dominant** (T) over inability taste PTC which is **recessive** (t)



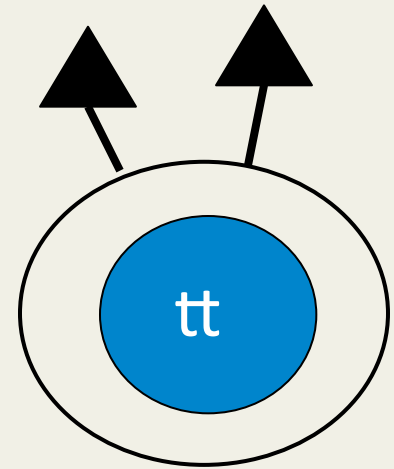
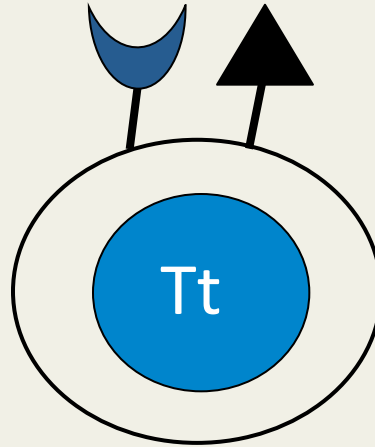
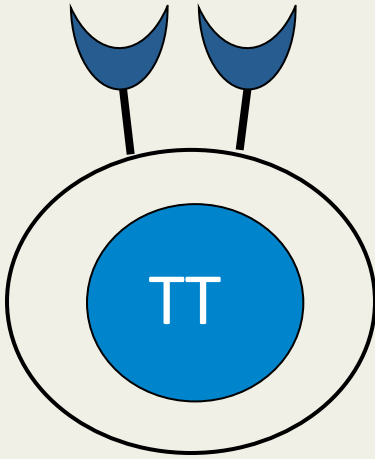
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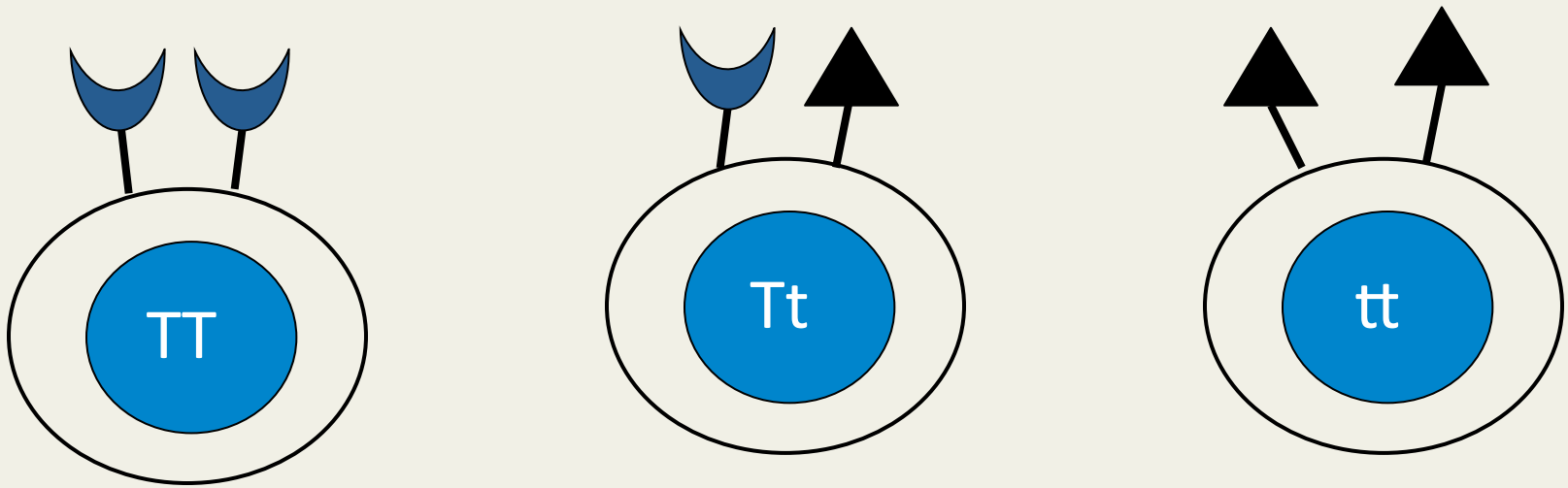
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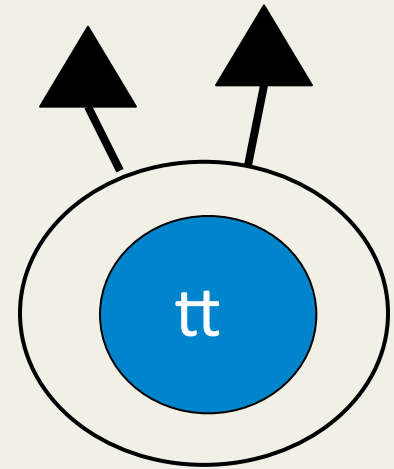
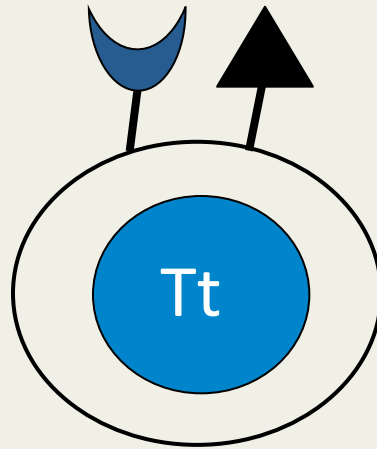
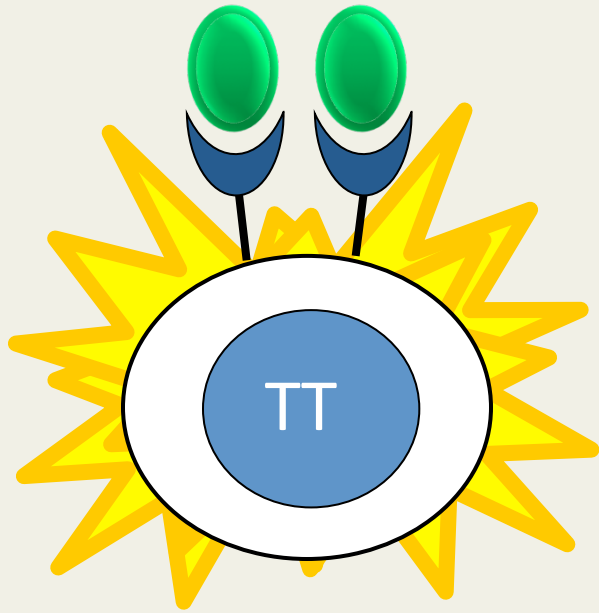


Tasting PTC is **dominant** (T) over inability taste PTC which is **recessive** (t)



For individuals with these **genotypes**,
what would their **phenotypes** be?

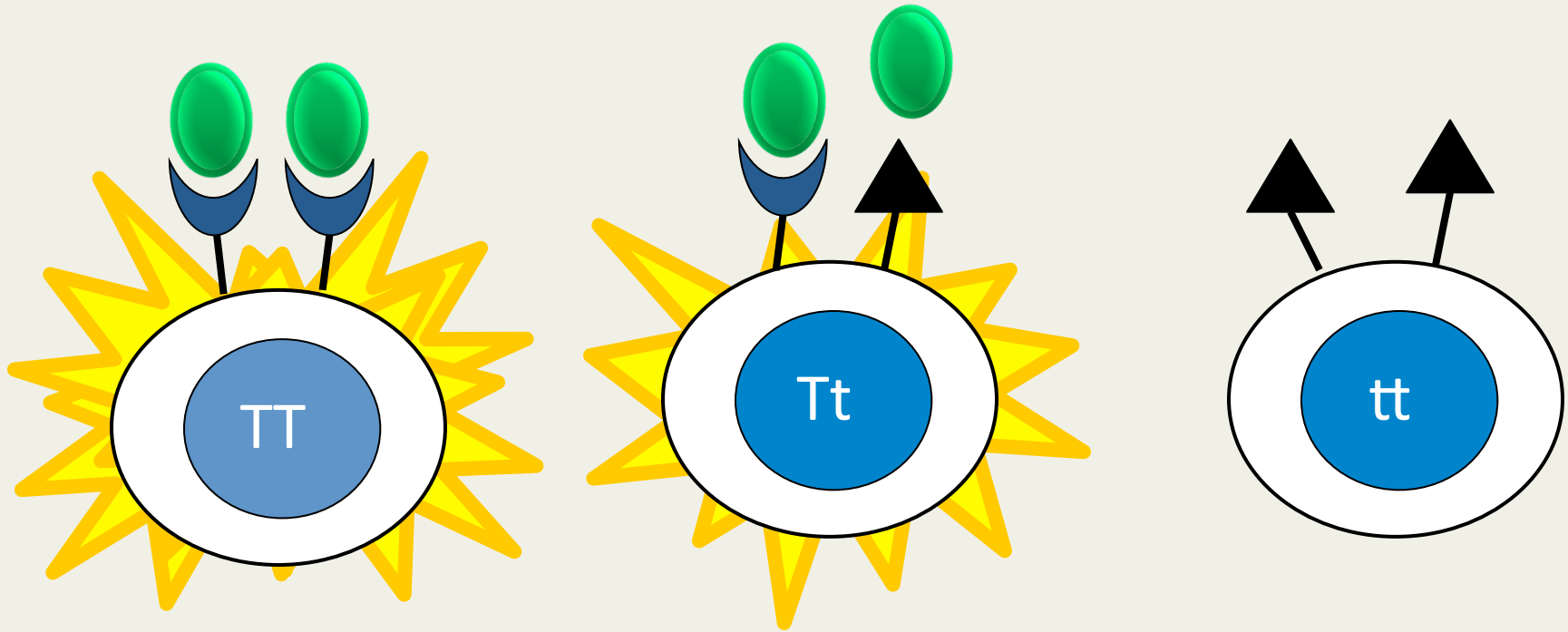
Tasting PTC is **dominant** (T) over inability taste PTC which is **recessive** (t)



“This tastes REALLY bitter!”

SUPERTASTER

Tasting PTC is **dominant** (T) over inability taste PTC which is **recessive** (t)

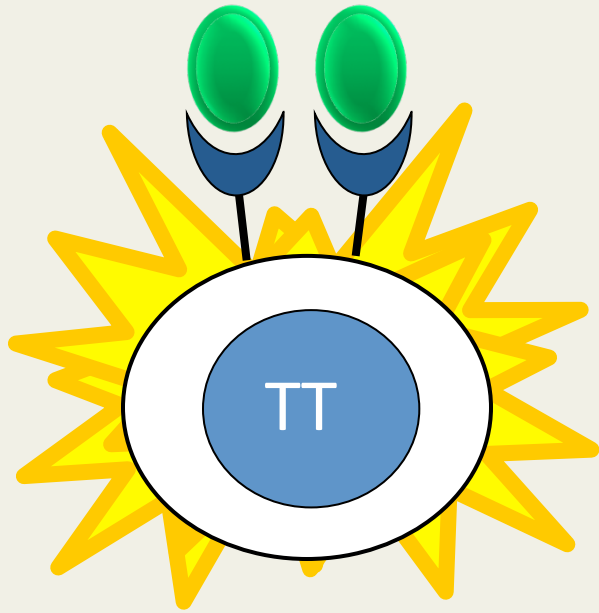


“This tastes REALLY bitter!” “This tastes bitter!”

SUPERTASTER

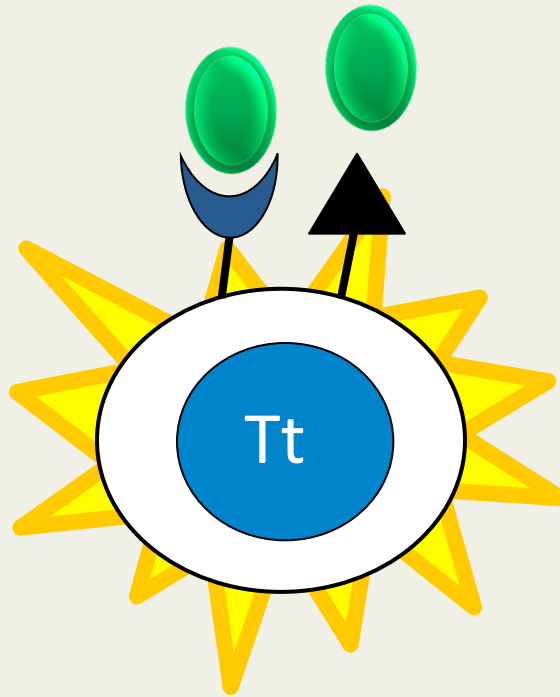
TASTER

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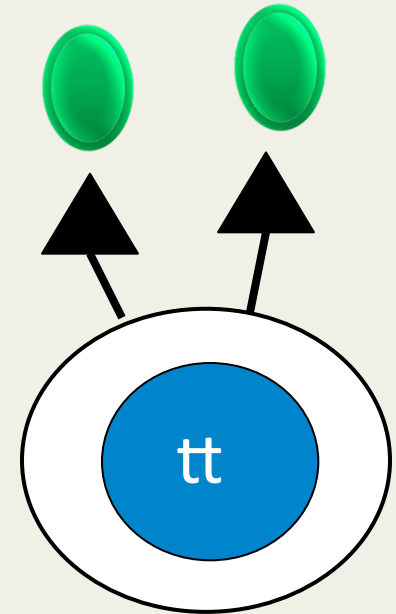
“This tastes REALLY bitter!” “This tastes bitter!”

SUPERTASTER



“This tastes bitter!”

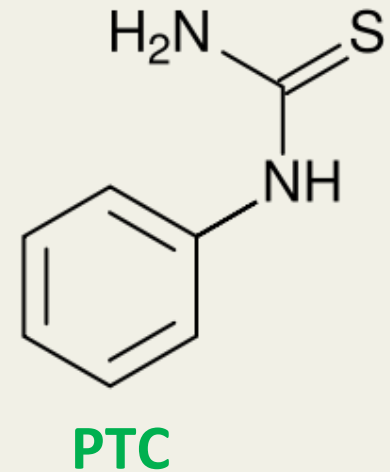
TASTER



“I don’t taste anything!”

NON-TASTER

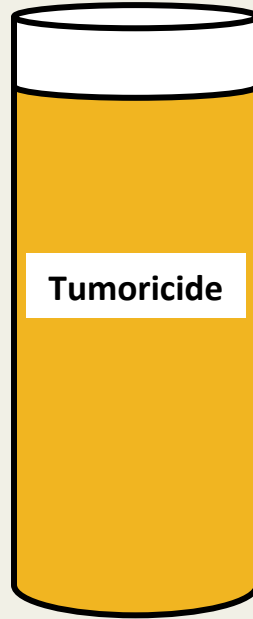
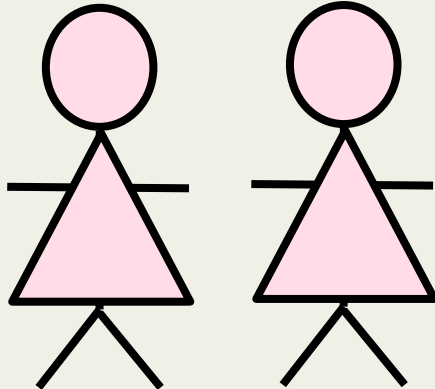
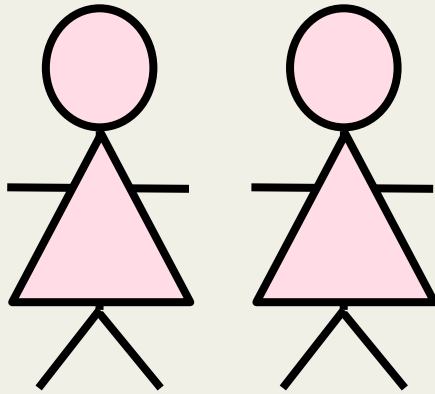
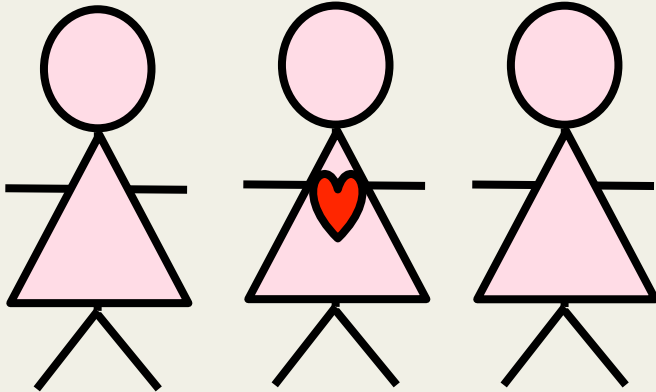
Drug receptor summary



Ability to taste PTC has a very strong **genetic component**
PTC = chemical and Drugs = chemical

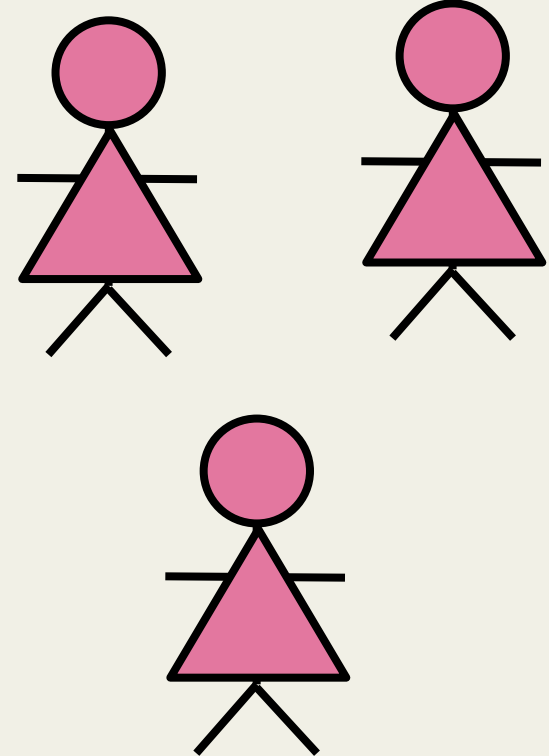
Differences in ability to taste PTC is similar to
differences in reactions to drugs

No Effect/Hurt

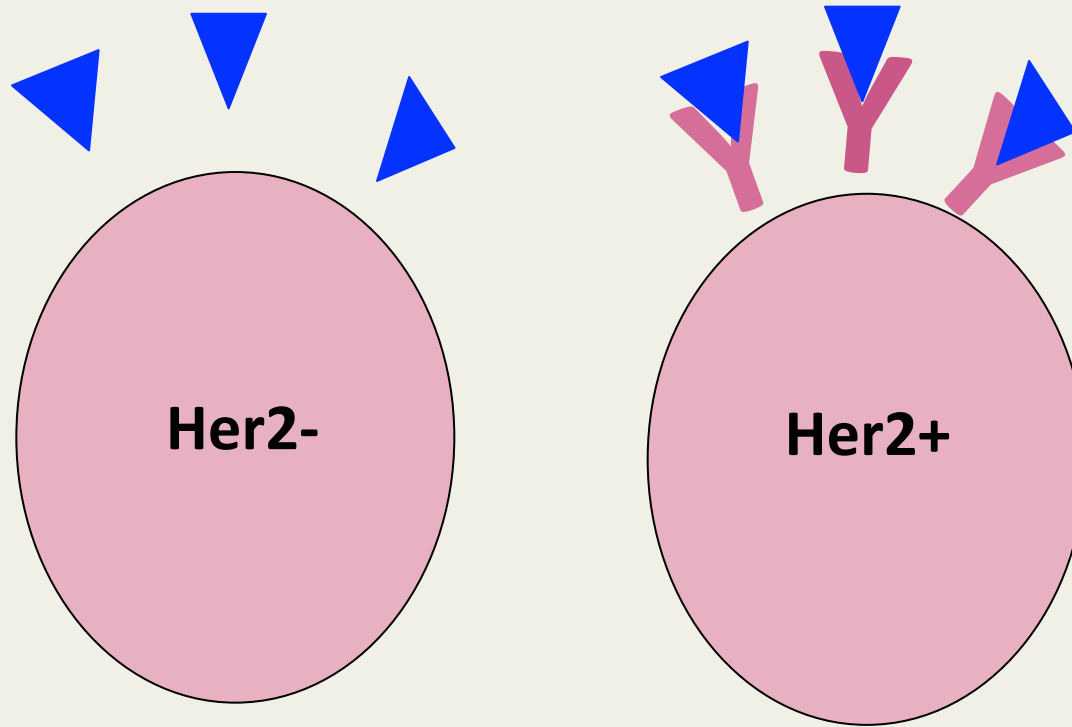


Why?

Helped

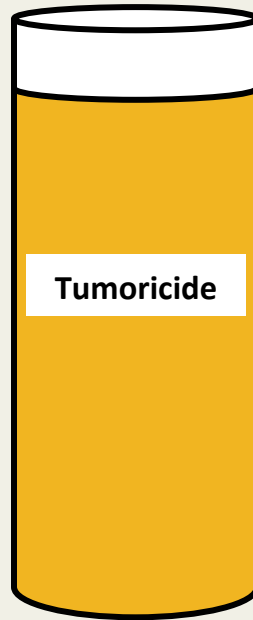
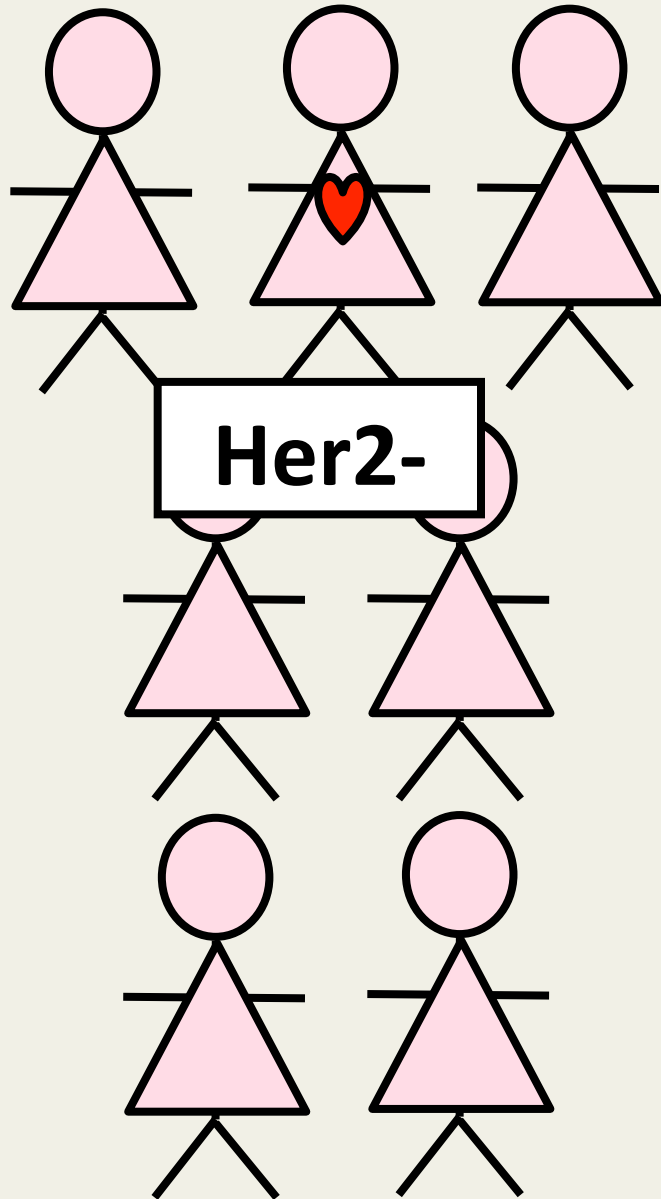


Two Types of Breast Cancer

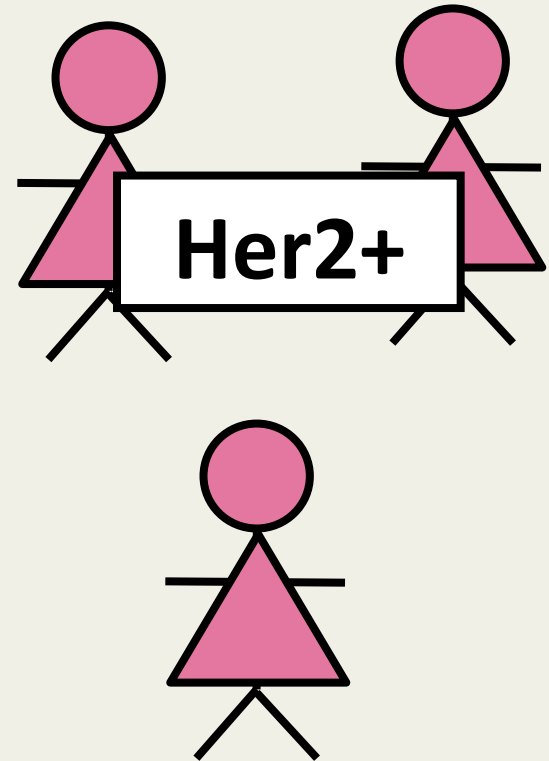


- Tumoricide is a personalized medication
- Tumoricide *only* works for **Her2+** breast tumors

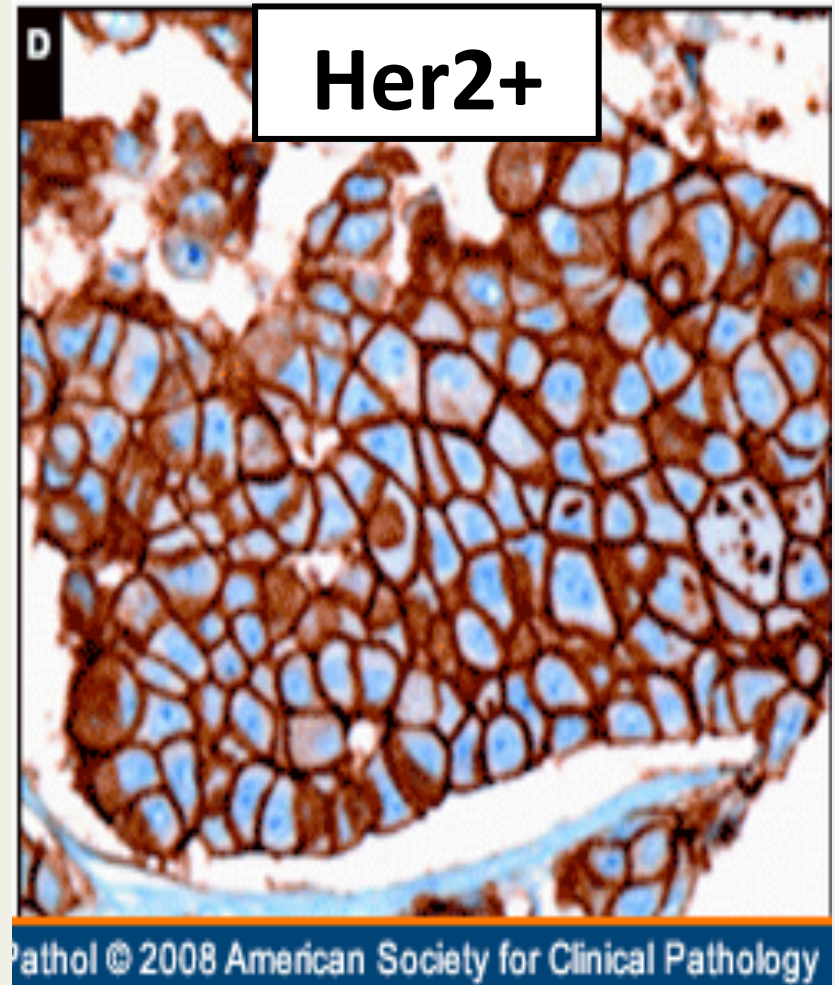
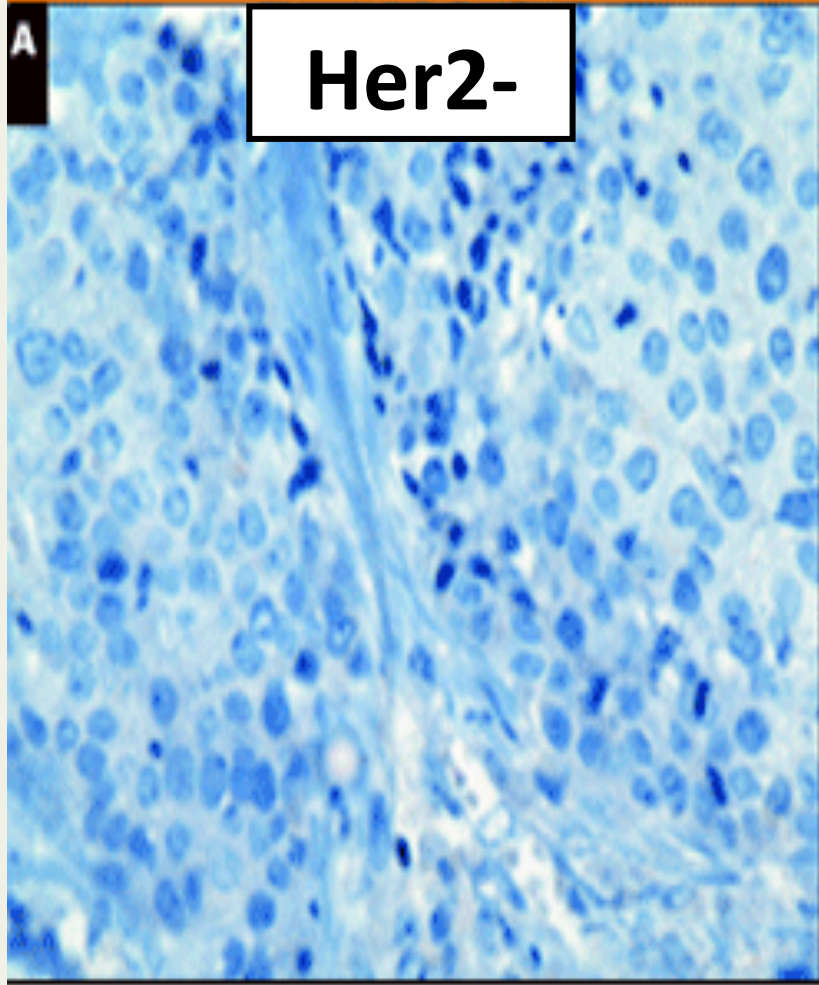
No Effect/Hurt



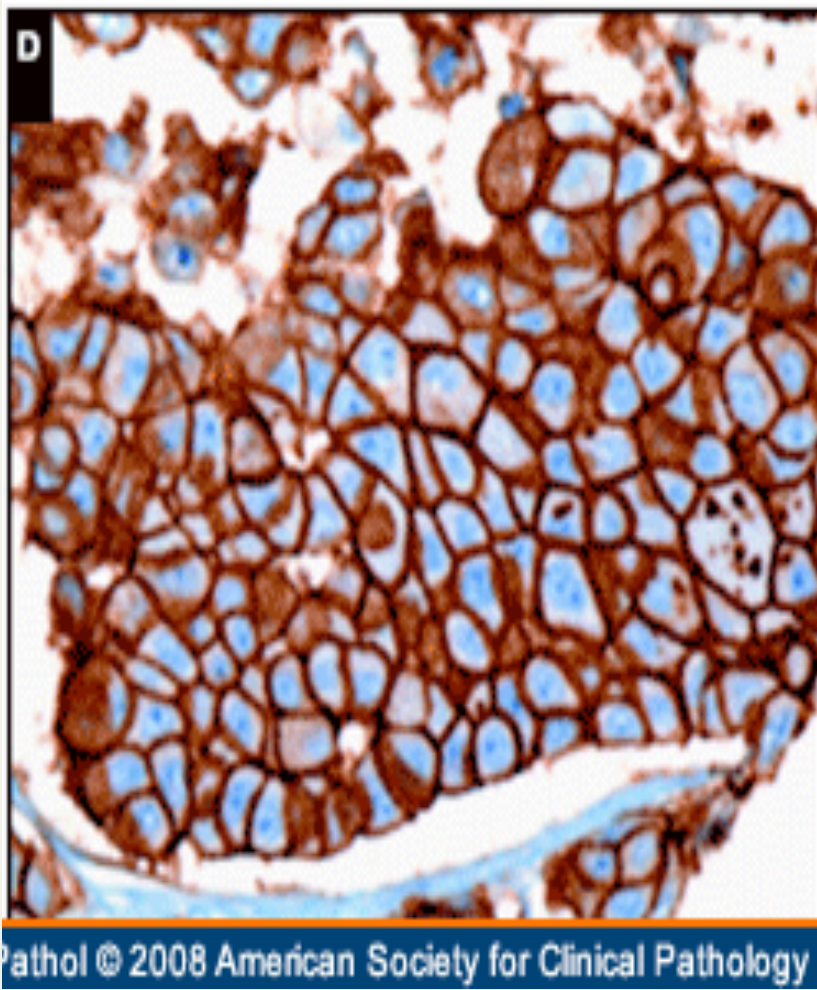
Helped



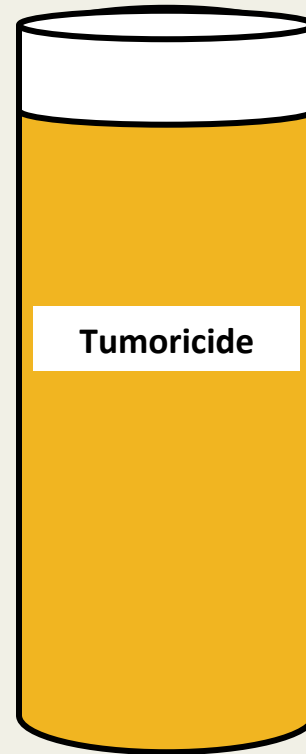
Screening for Her2+ Cells



Screening for Her2+ Cells



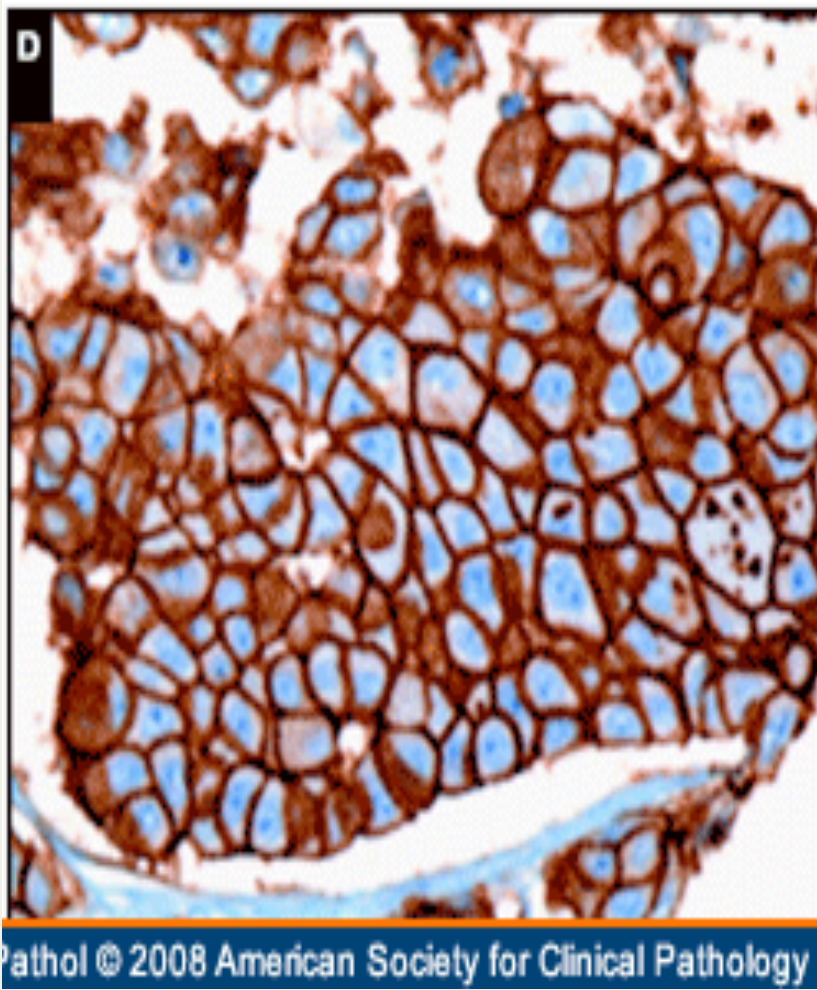
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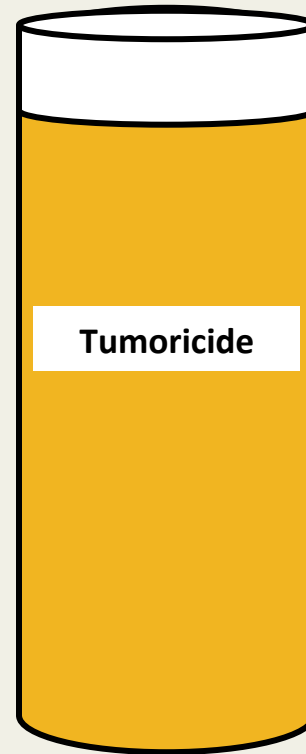
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Screening for Her2+ Cells



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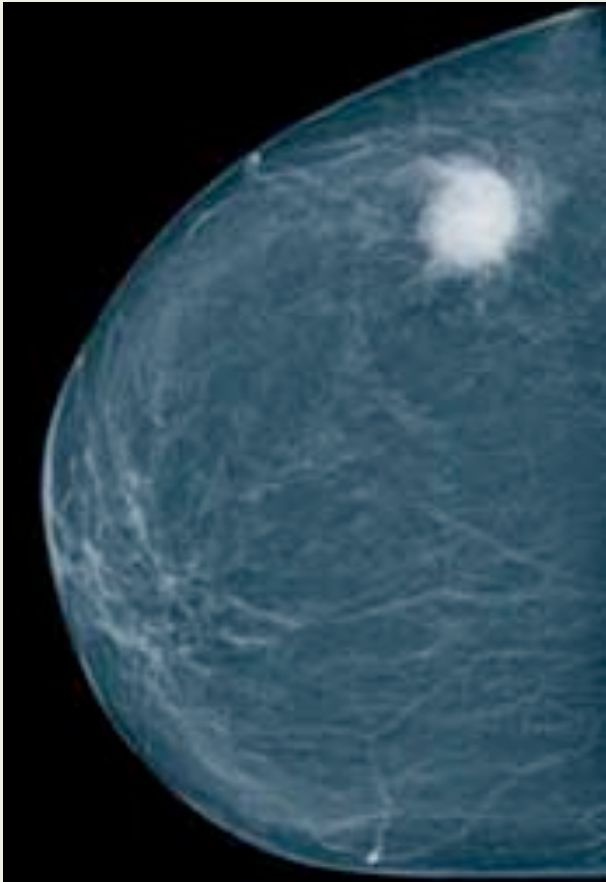
Breast Cancer

1990

- Surgery
- Radiation
- Chemotherapy (drugs)

2012

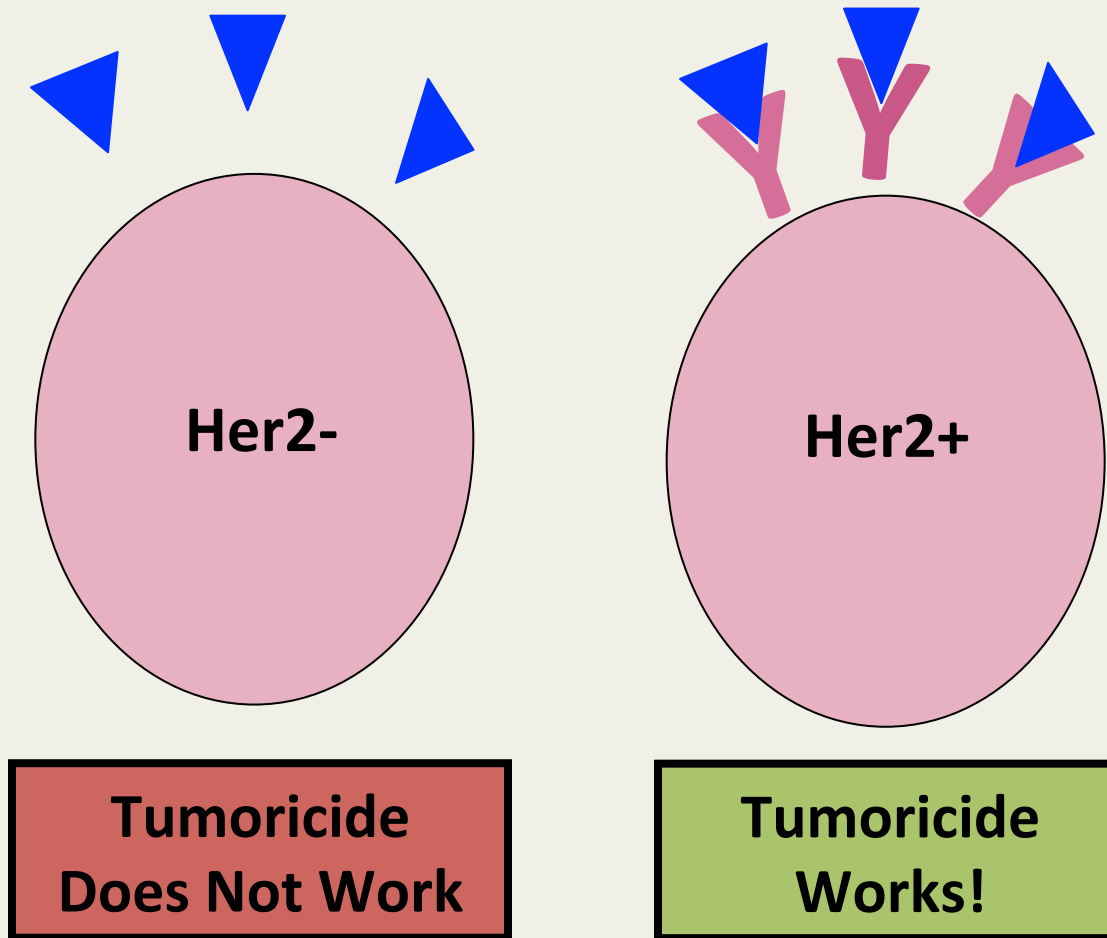
- Surgery
- Radiation
- Chemotherapy
 - Specialized treatments (for certain types of breast cancer)



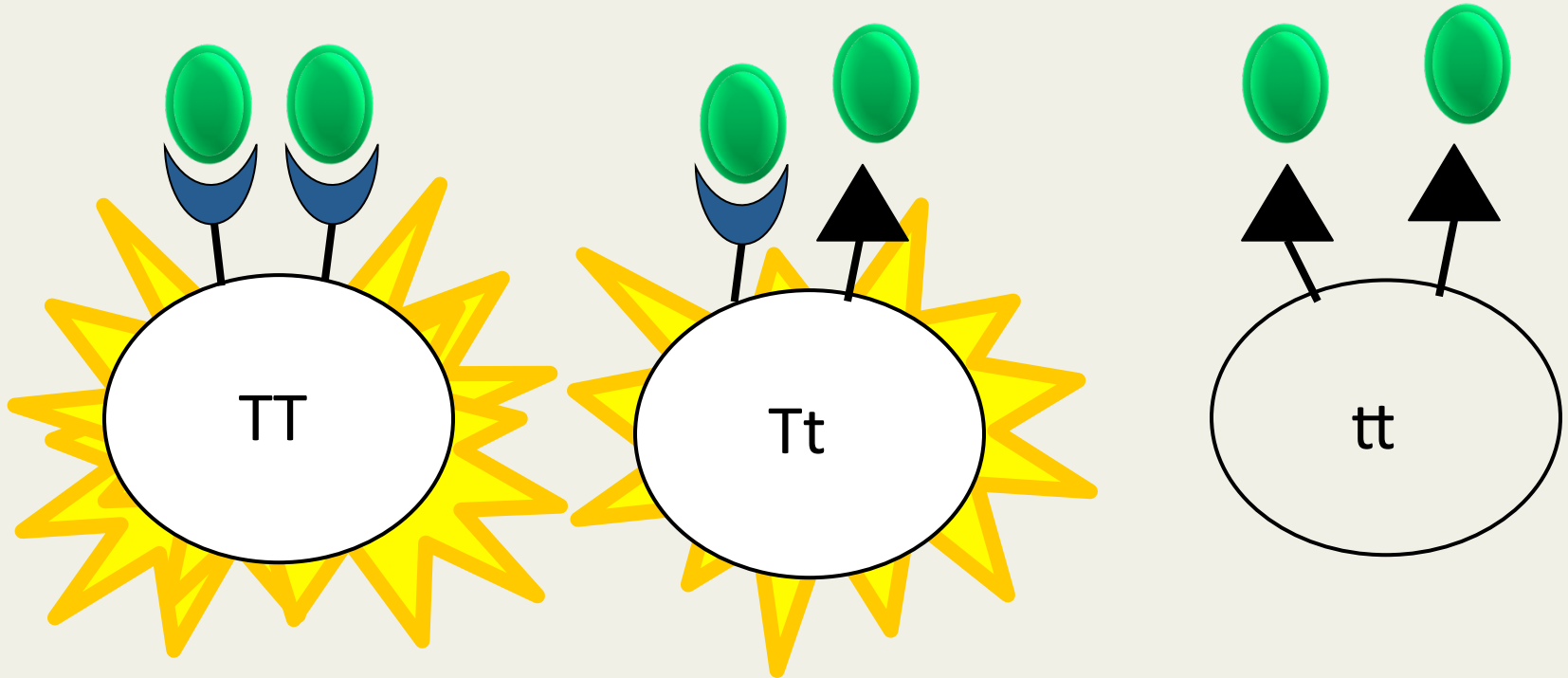
What are the reasons a person would react differently to drugs?

1. Having the receptor (protein) to recognize the drug
2. Other physiological traits that enable you to respond to a drug
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The presence of receptors influence how we react to drugs like Tumoricide or chemicals like PTC



The presence of receptors influence how we react to drugs like Tumoricide or chemicals like PTC



“This tastes REALLY bitter!” “This tastes bitter!”

“I don’ t taste anything!”

SUPERTASTER

TASTER

NON-TASTER

Where are the PTC receptors?

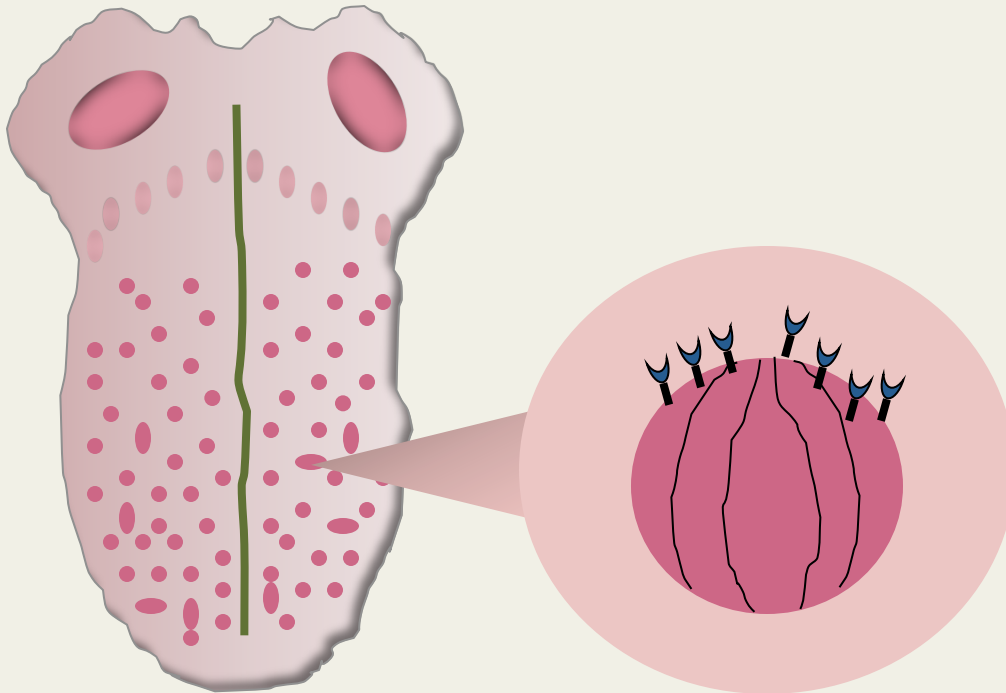
Where are the PTC receptors?



They are on your taste buds!

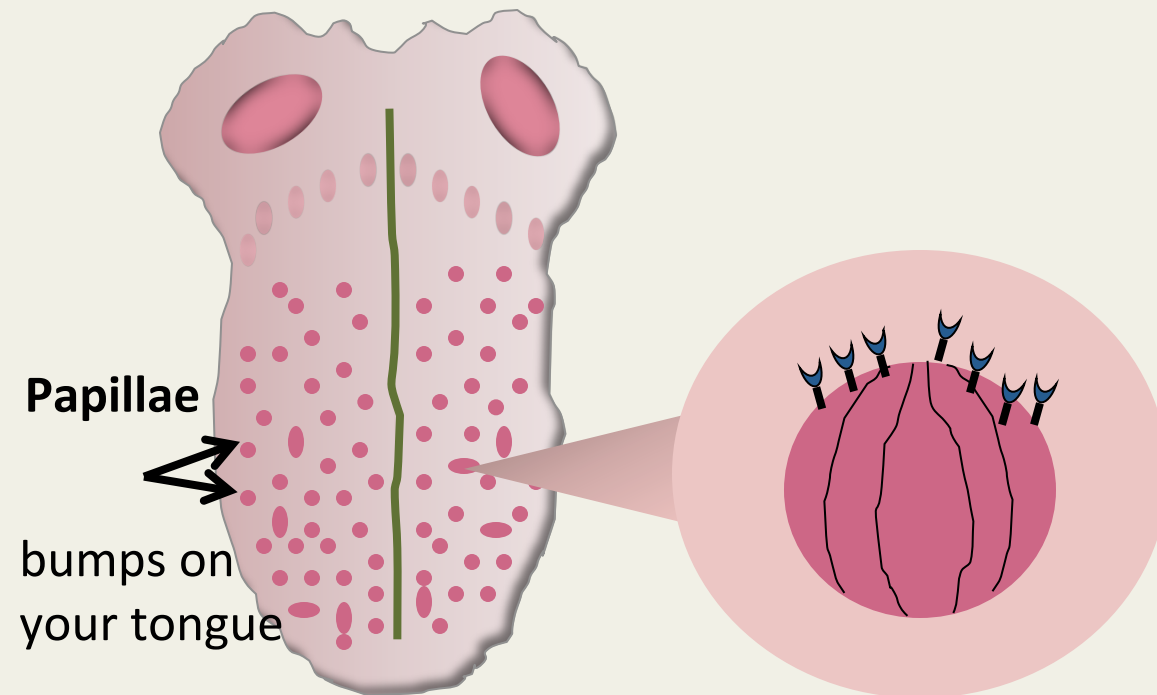
What are taste buds?

Taste buds are found on papillae on your tongue



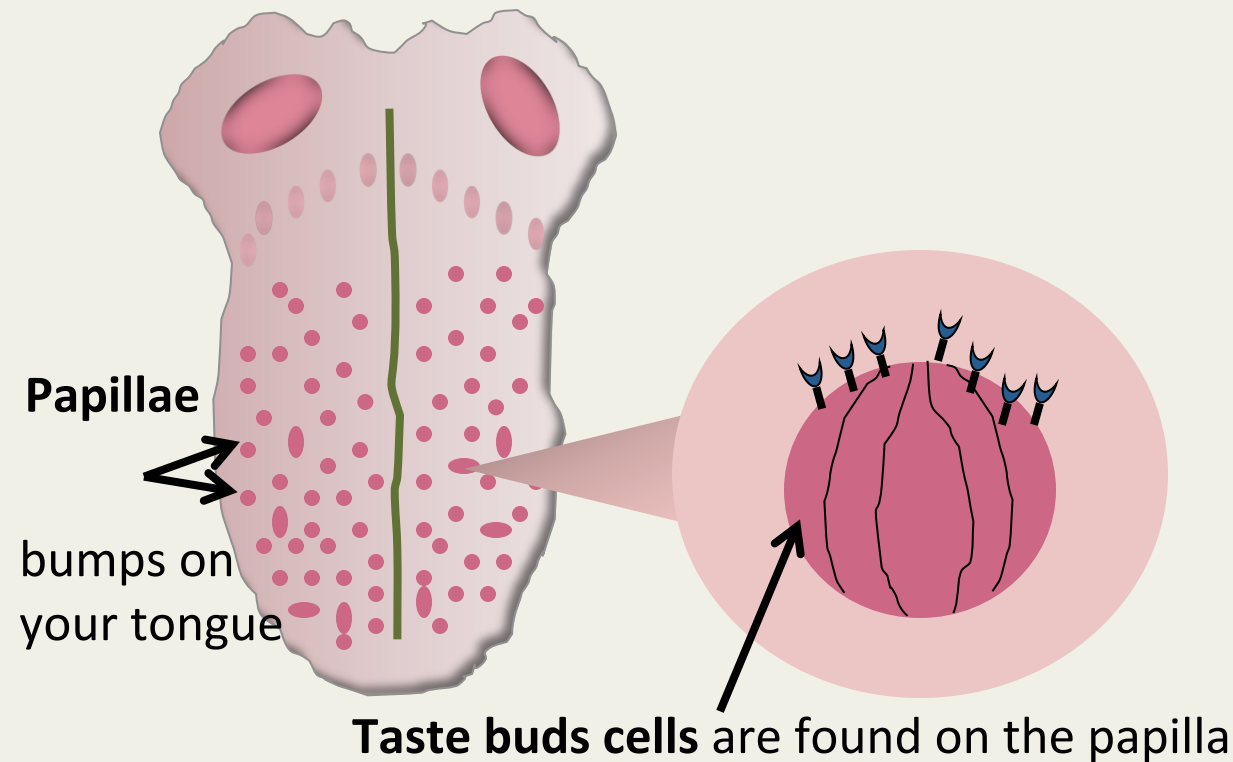
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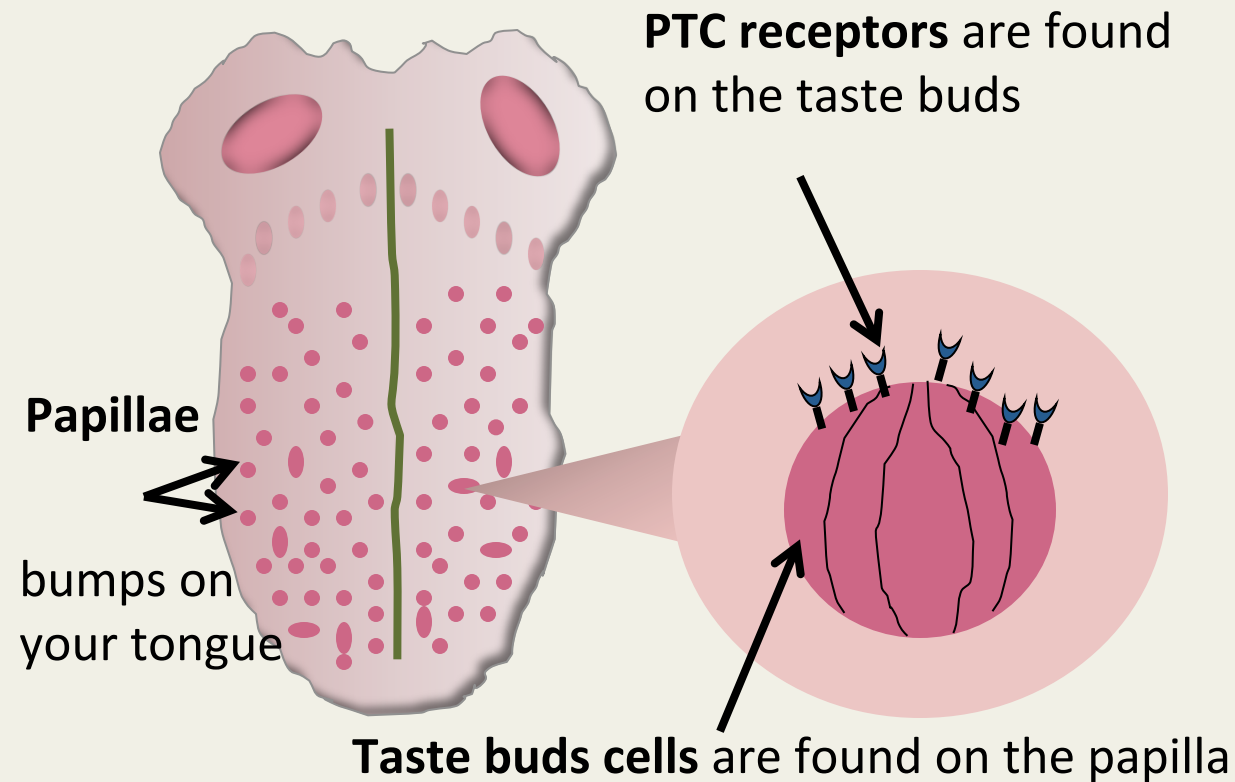
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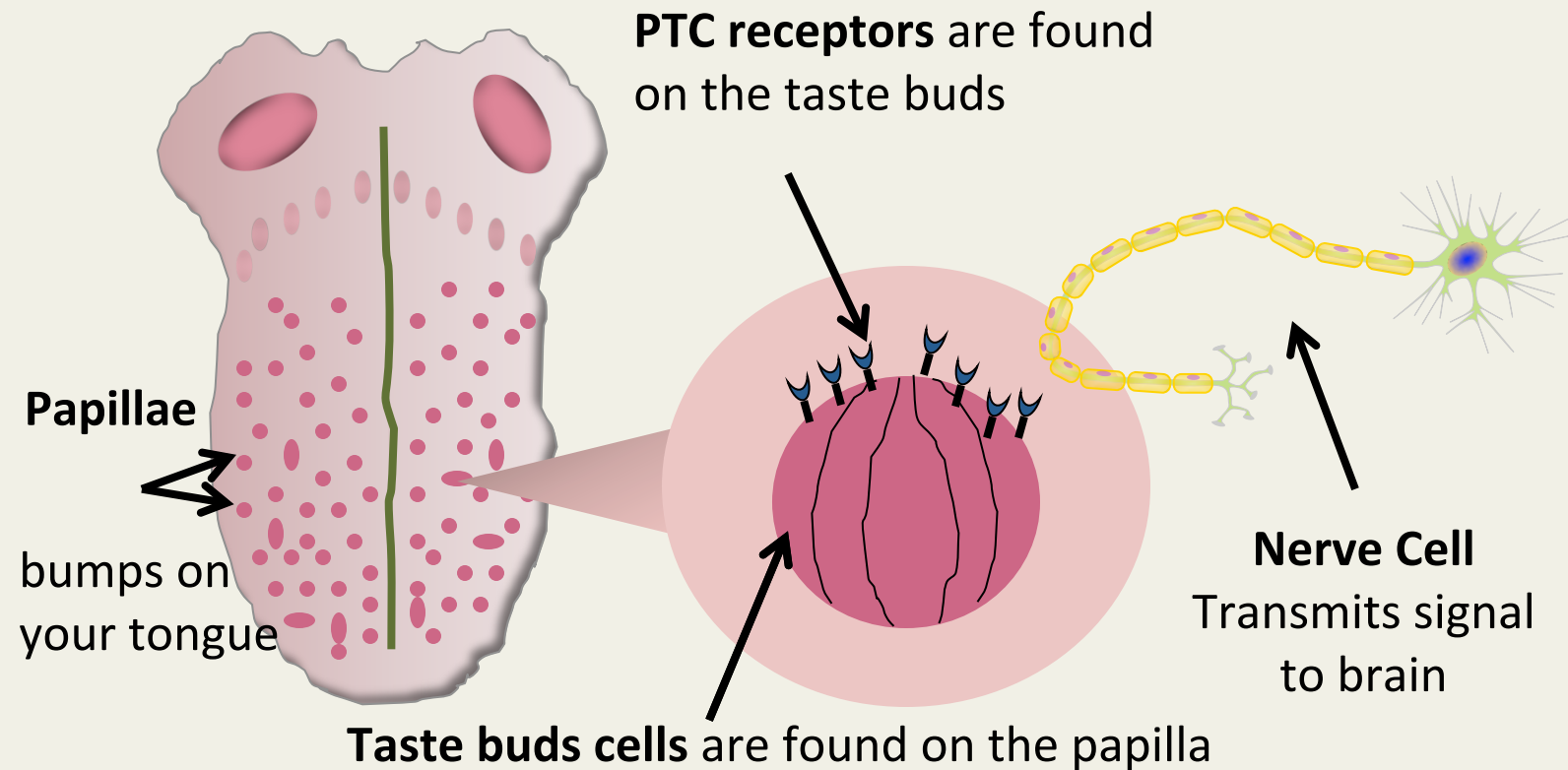
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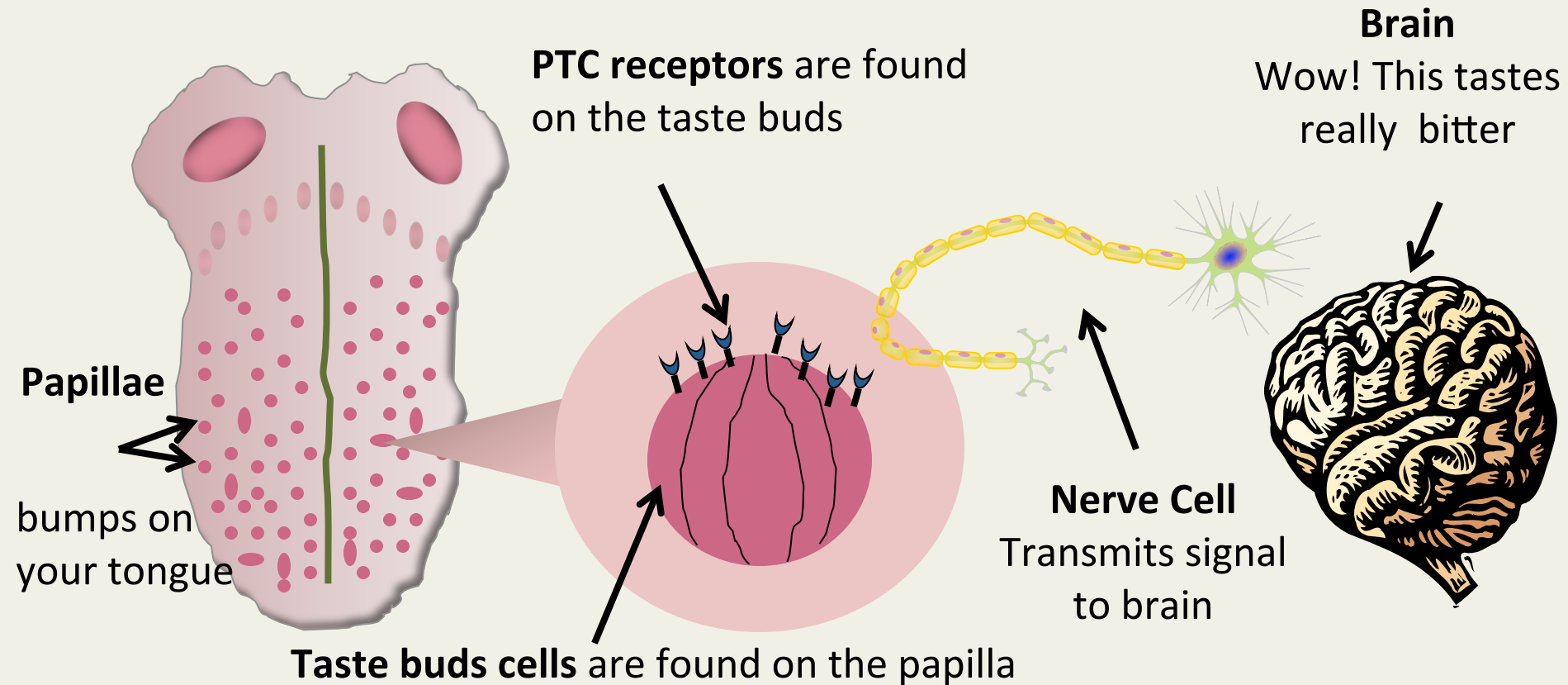
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Question:

Are there other traits that can allow a person to more strongly taste PTC?

Hypothesis:

Question:

Are there other traits that can allow a person to more strongly taste PTC?

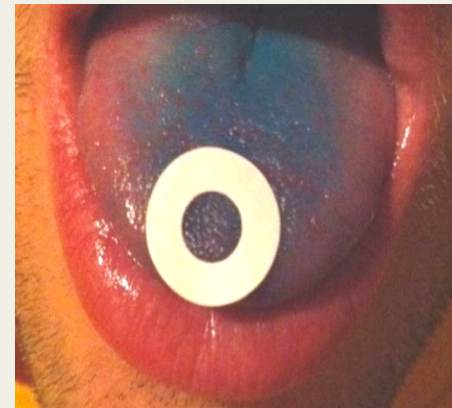
Hypothesis:

If a person has more taste buds, then he/she may be able to taste the PTC more strongly.

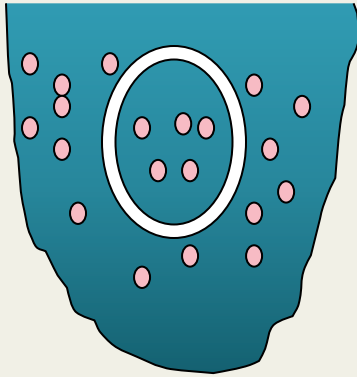
Let's test our hypothesis and count our taste buds!

- 1) Lollipop time! Lick your lollipop such that the blue gets all over your tongue...especially the tip of your tongue.
- 2) Once your tongue is really blue, place one hole reinforcer on the tip of your tongue—so it looks like the picture on the bottom on this slide.
- 3) Have your partner count the bumps or papillae on your tongue...these will not stain blue.

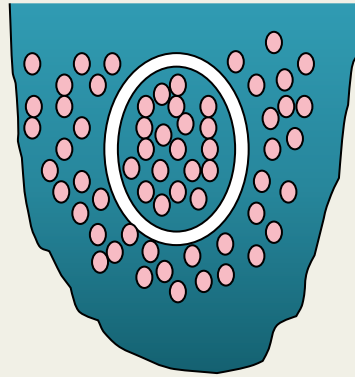
* Remember that your taste buds are on your papillae.
Therefore the number of papillae correlates to the
amount of taste buds on your tongue. *



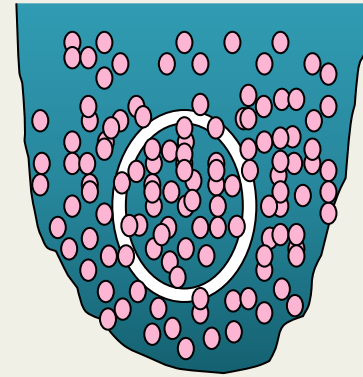
Counting the number of tongue papillae



5 papillae

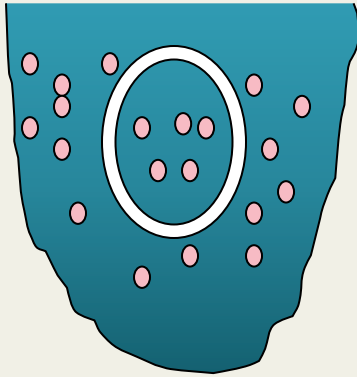


20 papillae

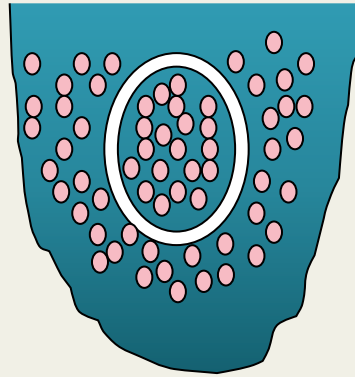


35 papillae

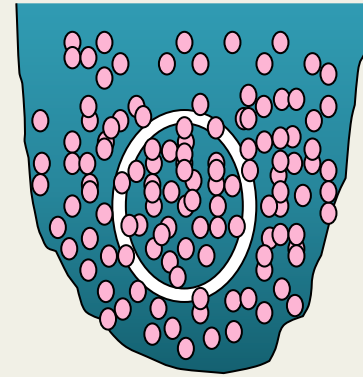
Counting the number of tongue papillae



5 papillae

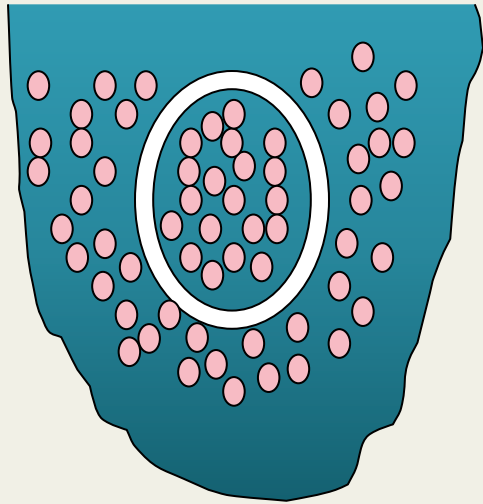


20 papillae



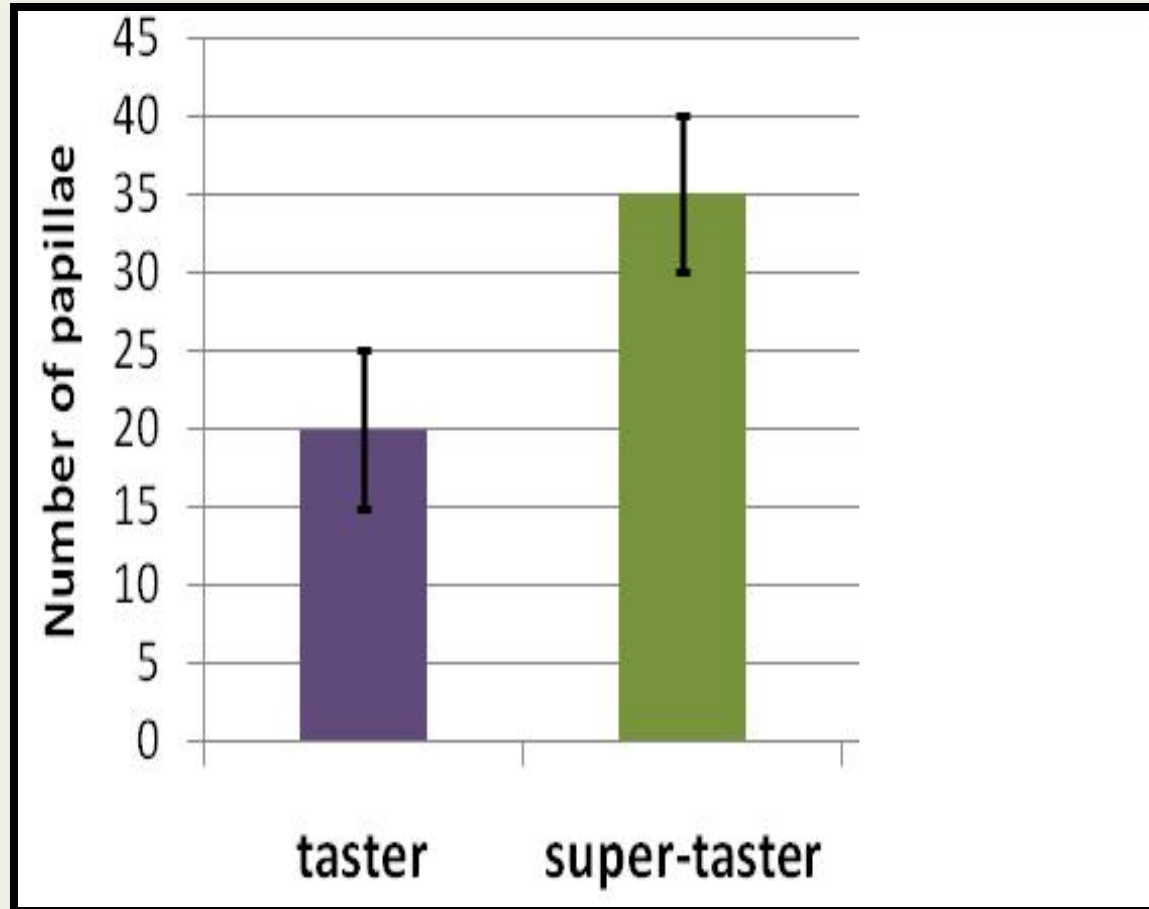
35 papillae

Come to the front of the class to report your PTC phenotype (taster, super-taster and non-taster) and the number of papillae on your tongue



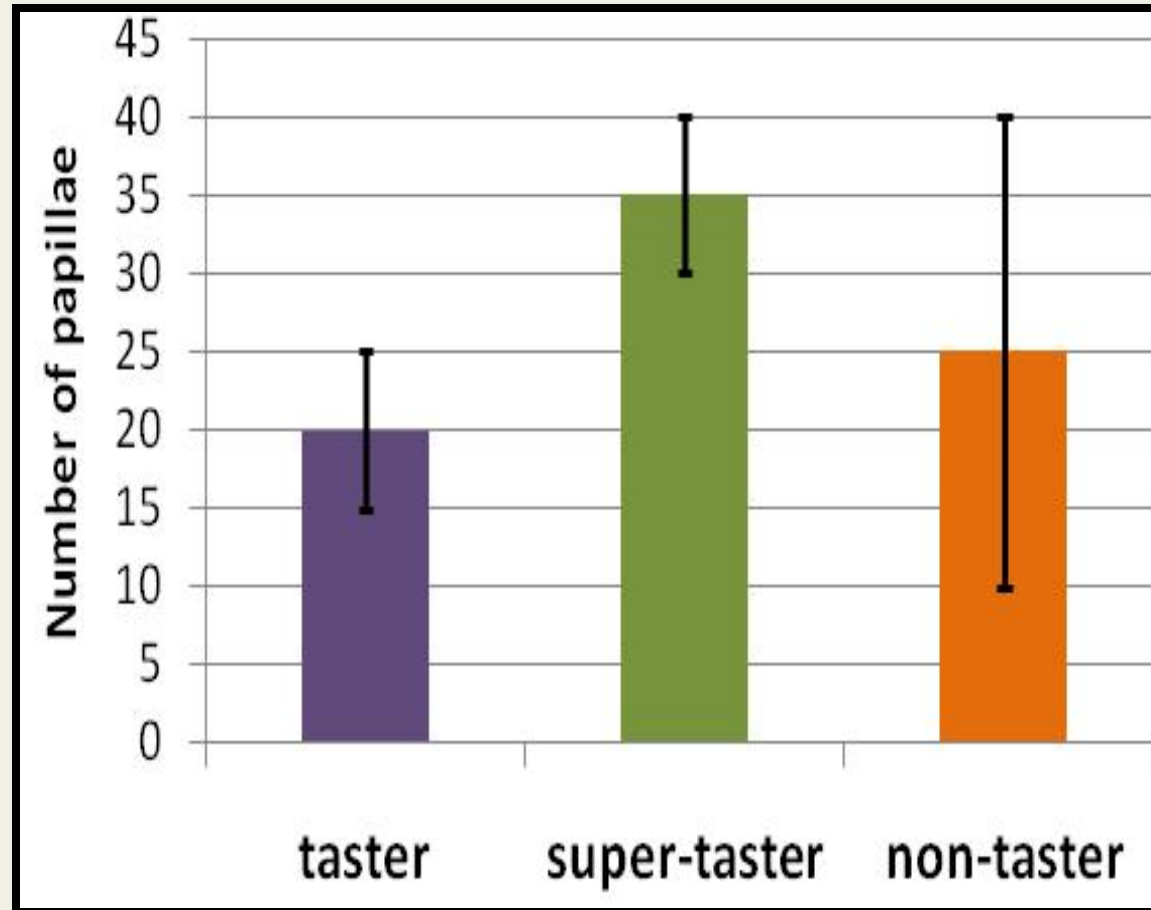
Please **PAUSE** and take a moment to count your taste buds and report your results on the spreadsheet at the front of the classroom

Ideal graph representing the number of tongue papillae related to the phenotype of PTC taste

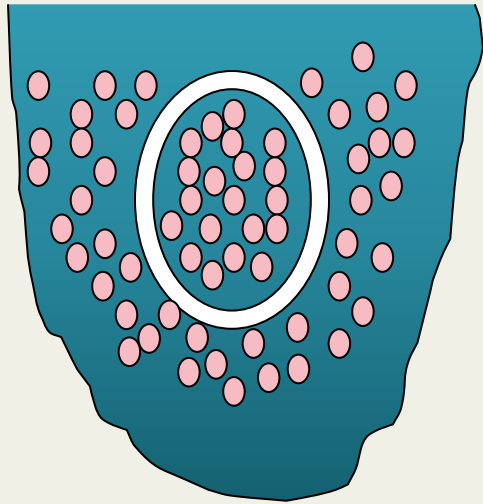


These results support our hypothesis that the super-taster has more papillae!

Ideal graph representing the number of tongue papillae related to the phenotype of PTC taste



The number of papillae in the non-taster is variable.
Why would the number of papillae be variable in a non-taster?

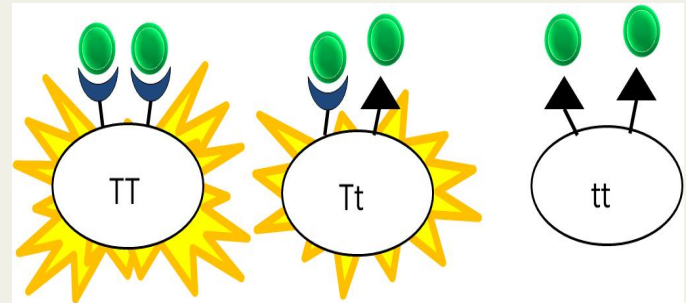


Please **PAUSE** and discuss why you think being a PTC non-taster does not correlate with number of taste buds.

What does it take to be a PTC Taster?

Two traits are important for determining PTC taste sensitivity

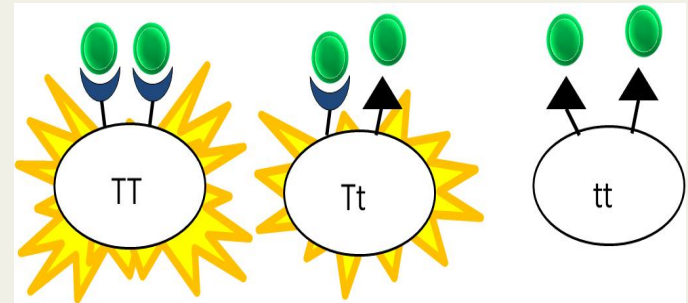
1) PTC receptor genotype—Do you have the receptors that enable you to taste PTC



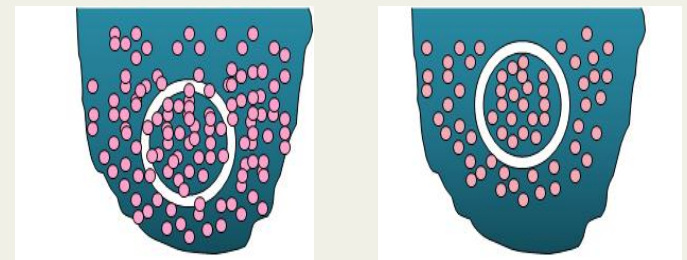
What does it take to be a PTC Taster?

Two traits are important for determining PTC taste sensitivity

1) PTC receptor genotype—Do you have the receptors that enable you to taste PTC



2) The density of papillae on your tongue correlates to the sensitivity of tasting PTC



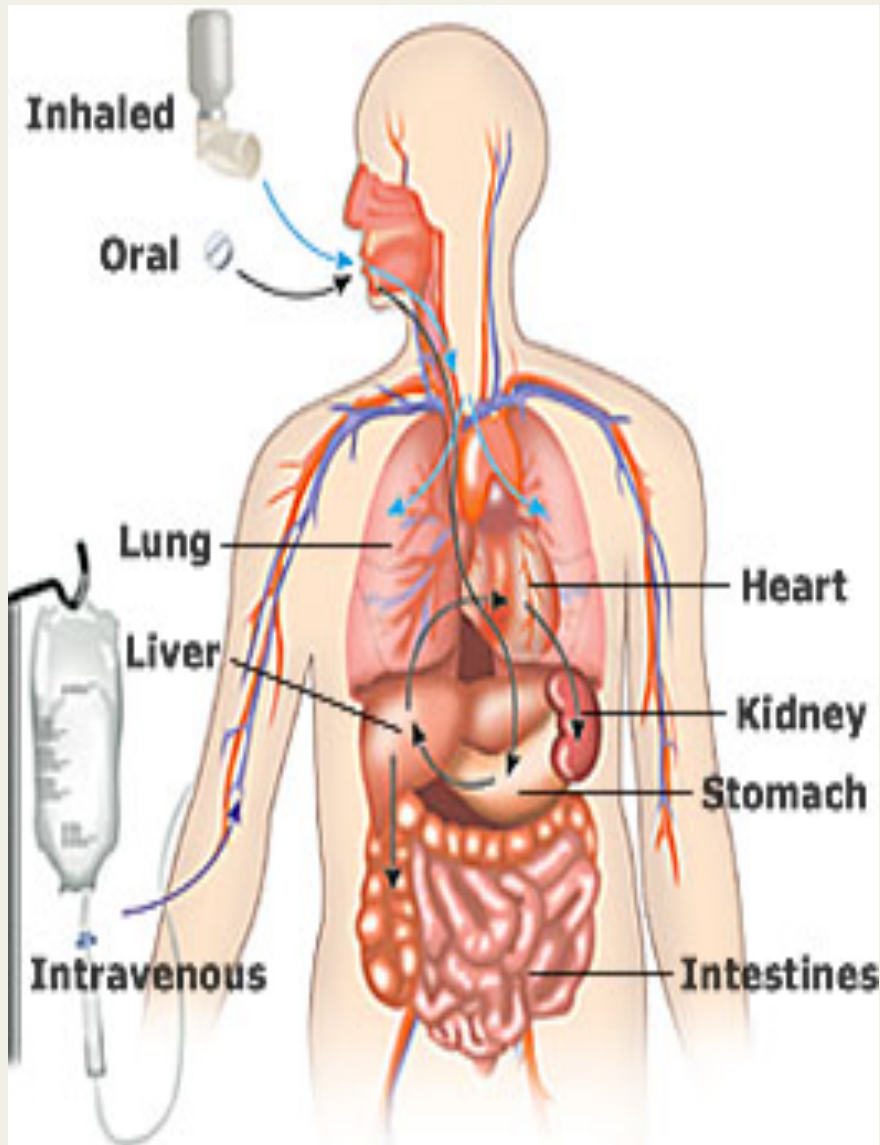
super-taster

taster

What are the reasons a person would react differently to drugs?

1. Having the receptor (protein) to recognize the drug
2. Other physiological traits that enable you to respond to a drug
3. How your body processes the drugs after receiving it

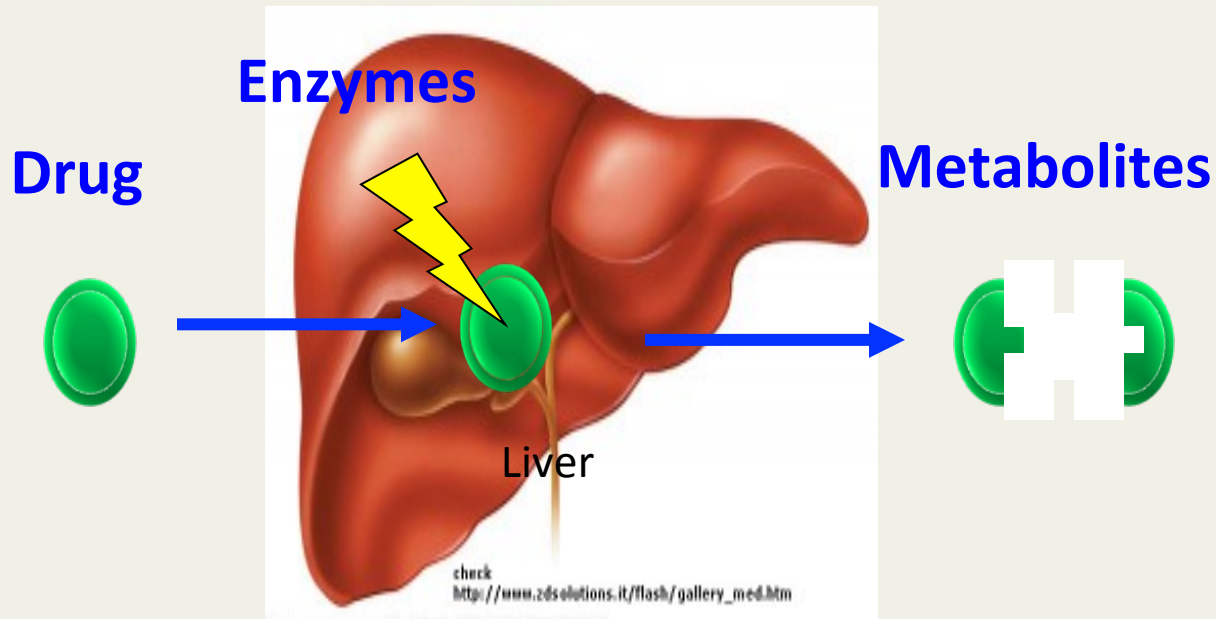
A Drug's Life



ADME

- Absorption
- Distribution
- Metabolism
- Excretion

Metabolic enzymes



DNA variations in special proteins in the liver called **enzymes** can influence a person's ability to metabolize certain drugs

Adverse Drug Reactions (ADR)

- **Definition-** unwanted, negative response to a prescribed drug at normal doses and during normal use
 - Examples?

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 - *environmental* basis
 - *genetic* basis

Adverse Drug Reactions (ADR)

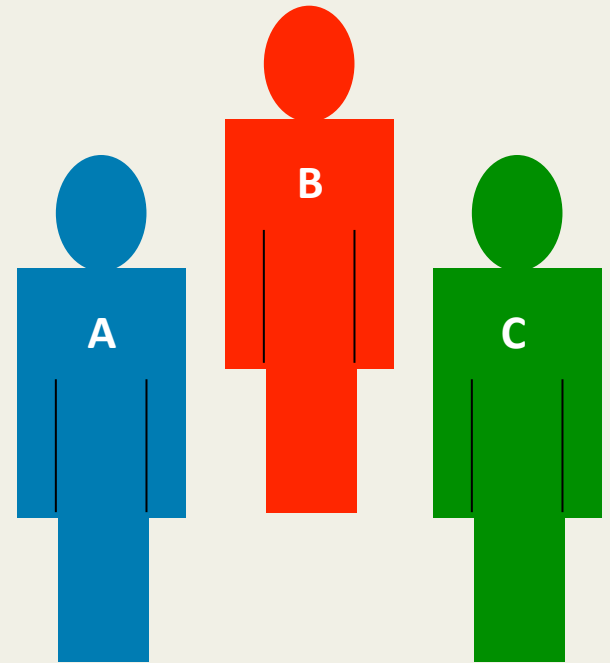
- **Definition**- unwanted, negative response to a prescribed drug at normal doses and during normal use
 - Examples?
- There are multiple causes for ADRs
 - *environmental* basis
 - *genetic* basis
- Poor metabolizers can experience ADRs at normally therapeutic drug doses

Case study: Nortriptyline metabolism

Three women of the same height, weight, age, and racial background are depressed and go to the doctor.

The doctor prescribes an antidepressant, Nortriptyline, at a dose of 100 mg.

- Person **A** has an adverse reaction
- Person **B** nothing happens
- Person **C** gets better...



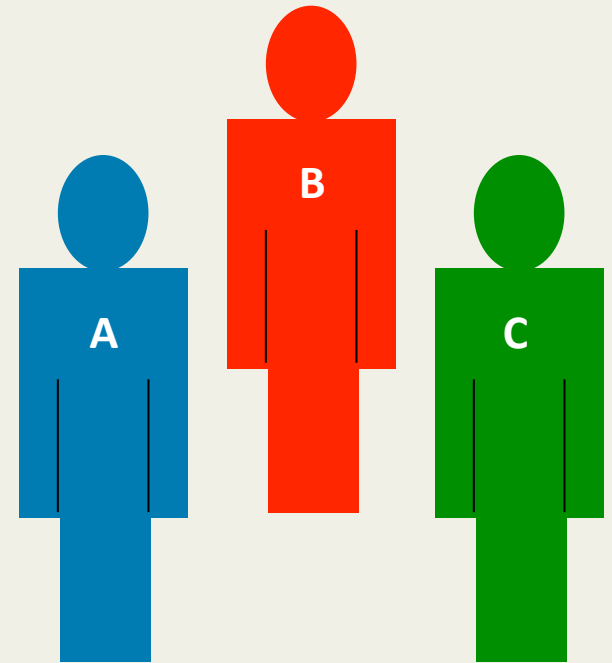
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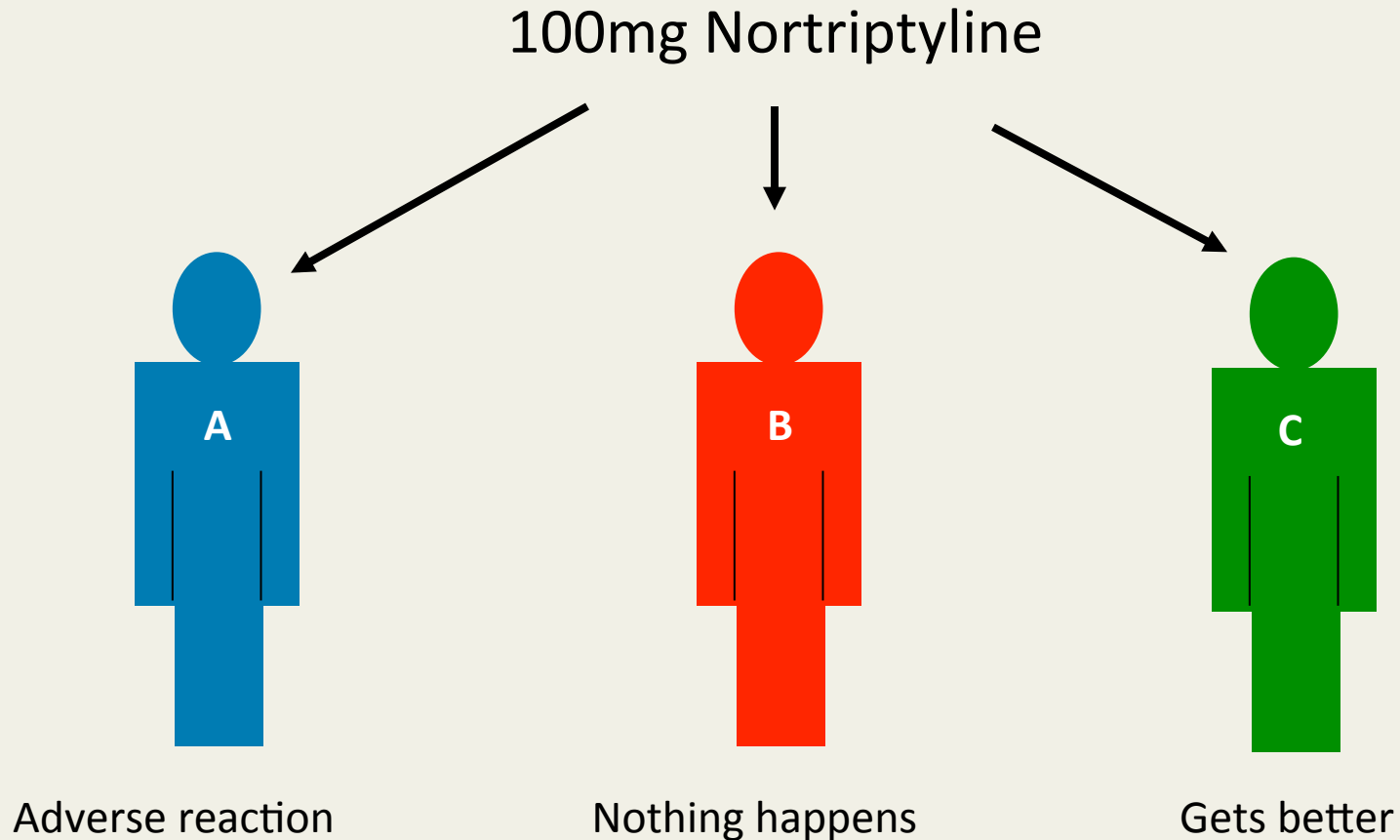
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Why?

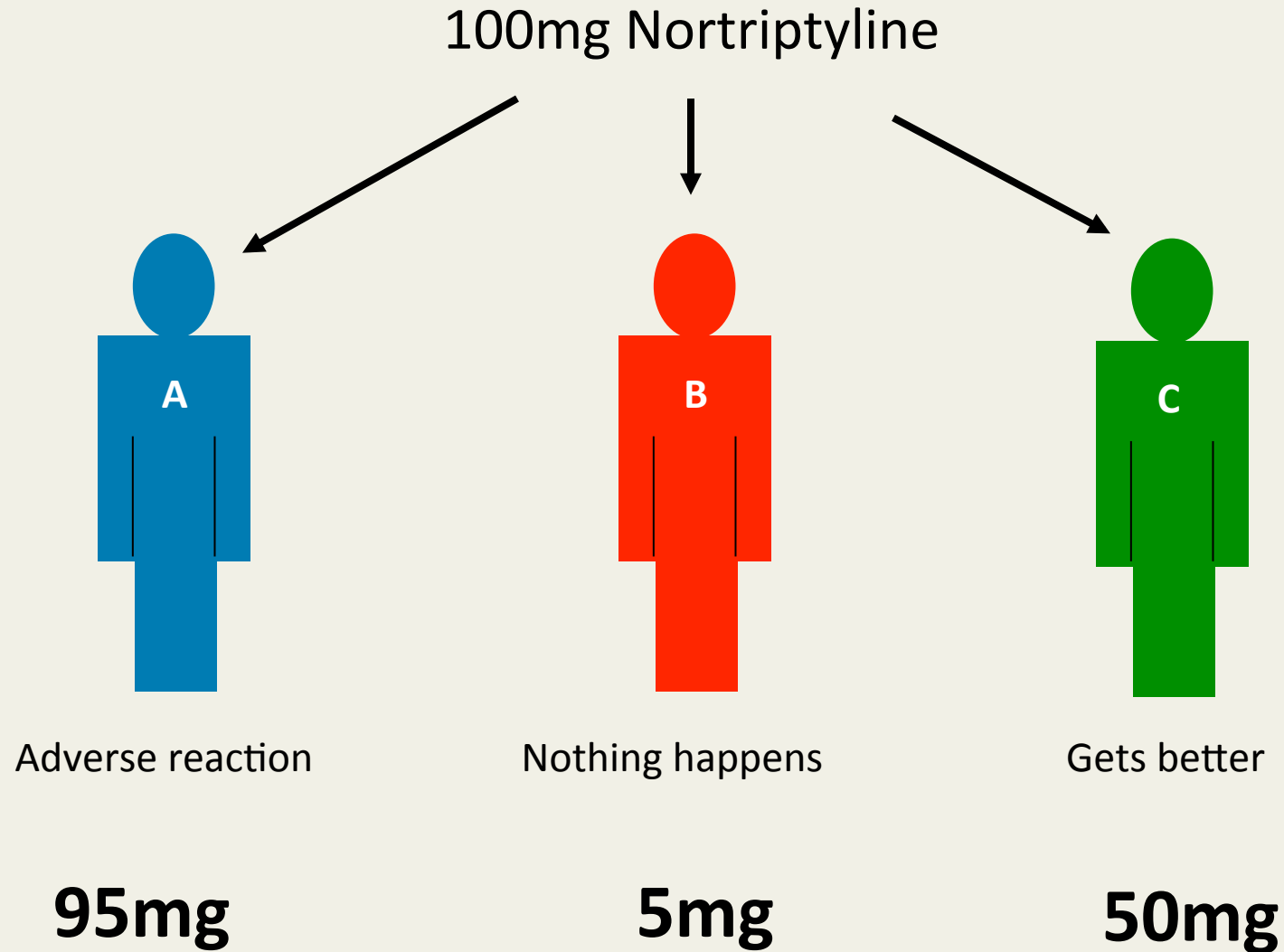


ADME of Nortriptyline

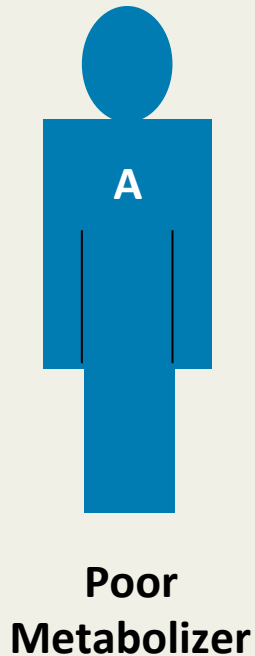


How much active drug in blood?

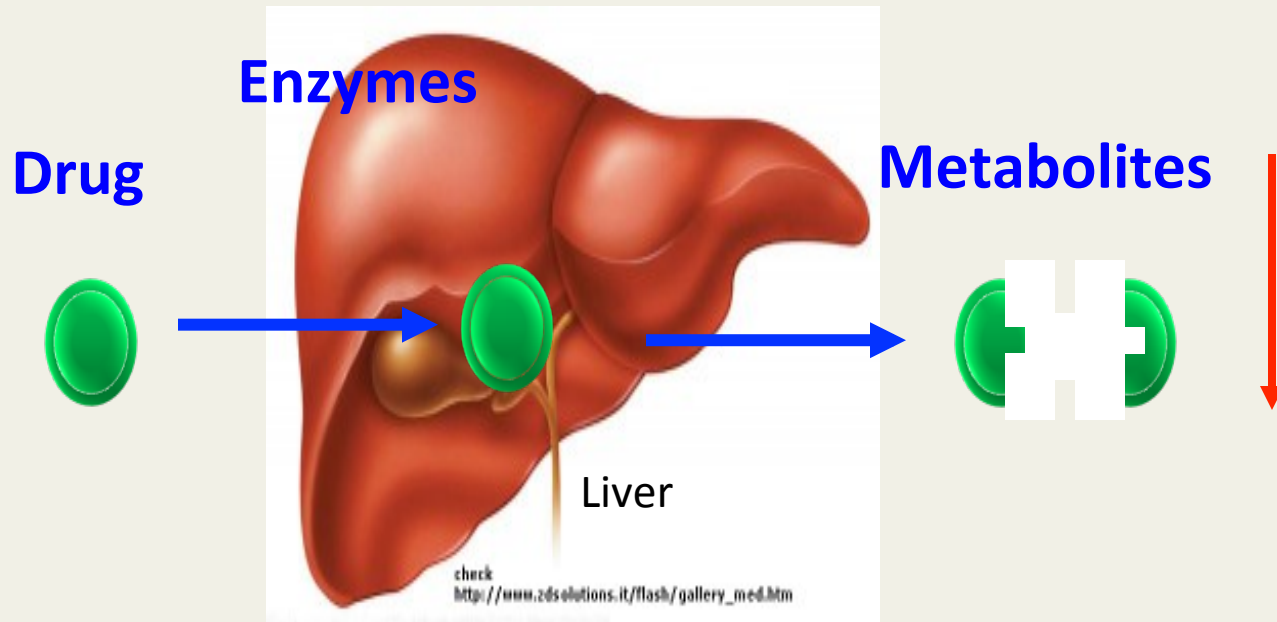
ADME of Nortriptyline



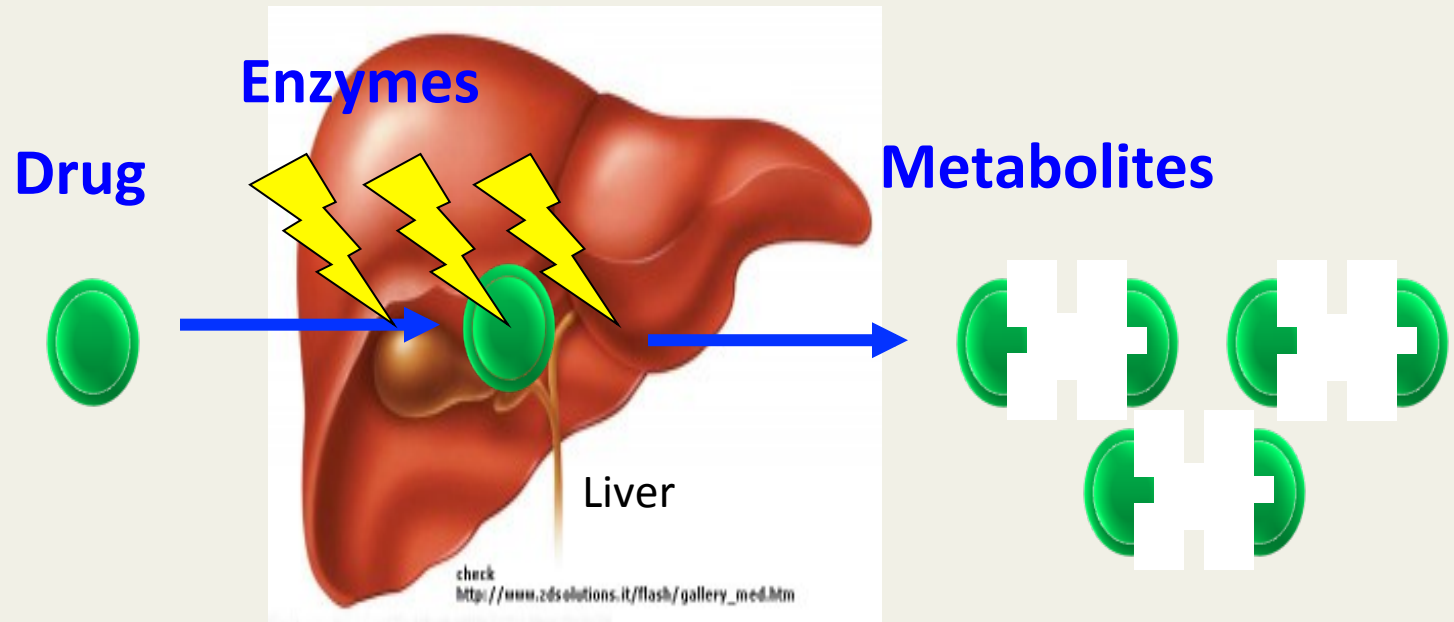
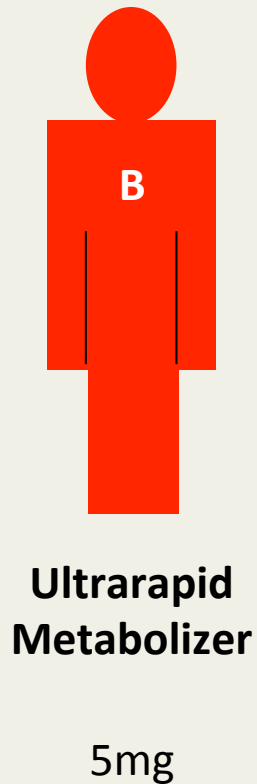
DNA variation influence drug metabolism



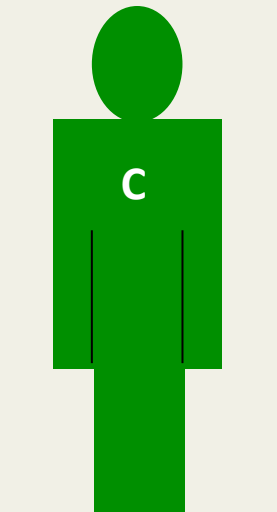
95mg



DNA variation influence drug metabolism

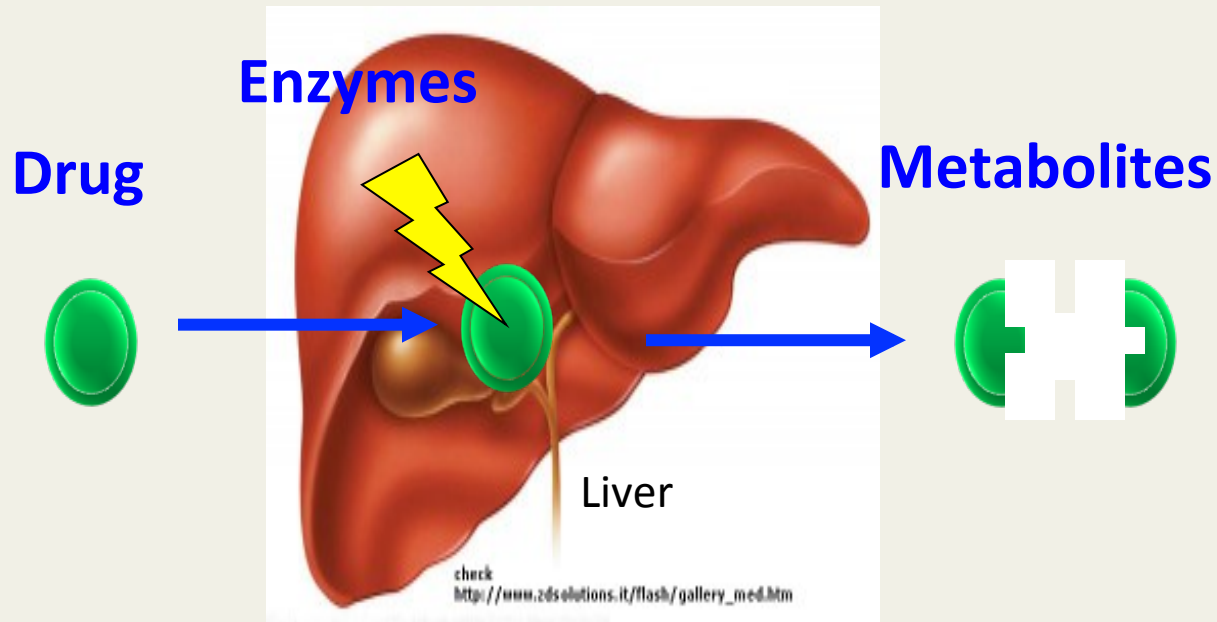


DNA variation influence drug metabolism

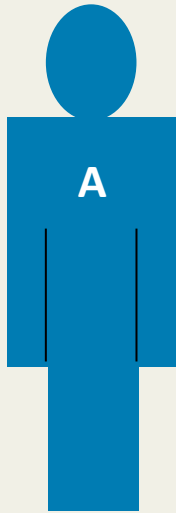


Intermediate
Metabolizer

50mg

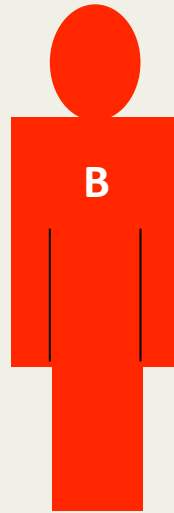


2012 - What do doctors do?



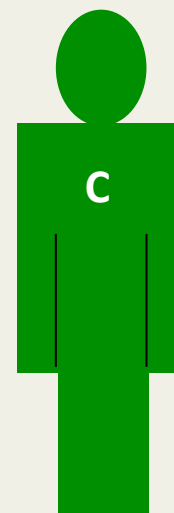
Poor Metabolizer

Decrease Dose



Ultrarapid Metabolizer

Increase Dose



Or change drug

Today

One-size-fits-all drugs

- Current drug development system develops drugs for the average patient
- No simple way to determine who will respond well and who will respond poorly
- One size does NOT fit all!
- **What' s the solution?**

Today

One-size-fits-all drugs

- Current drug development system develops drugs for the average patient
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- **What' s the solution?**

Pharmacogenomics (PGx)
Personalized Medicine

April, 2050

You wake up feeling terrible, and you know it's time to see a doctor. In the office, the physician looks you over, listens to your symptoms, and decides to prescribe you a drug.

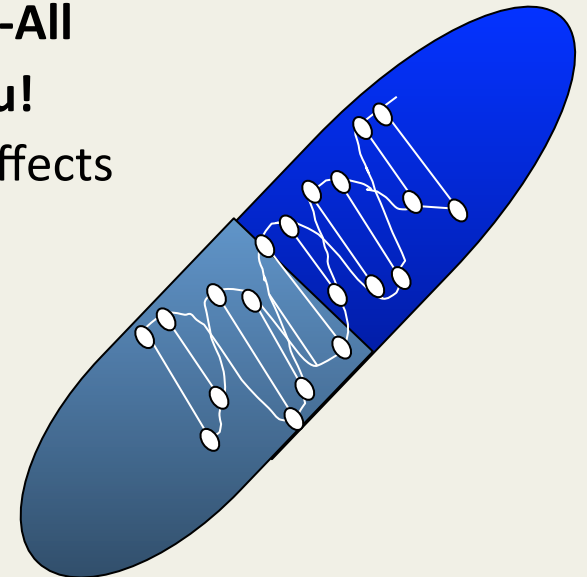
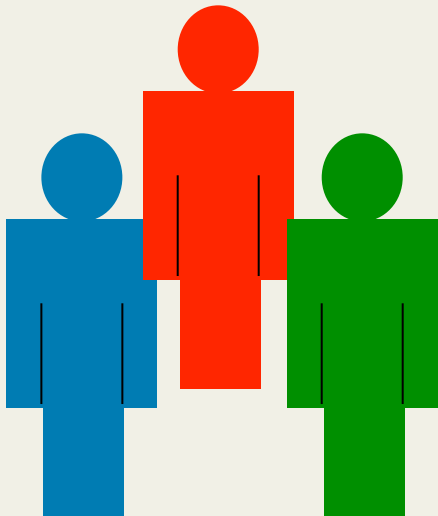
But first, the doctor takes a look at your DNA.

TODAY vs. FUTURE

Today = Drugs are One-Size-Fits-All

Future = Drugs Specific for You!

More effective & minimizes side effects



Summary

Genetic variation leads to phenotypic differences and differences in how we all react to drugs.

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Summary

Genetic variation leads to phenotypic differences and differences in how we all react to drugs.

1. Having the receptor (protein) to recognize the drug
PTC and HER2 receptors
2. Other physiological traits that enable you to respond to a drug
Number of taste buds on tongue

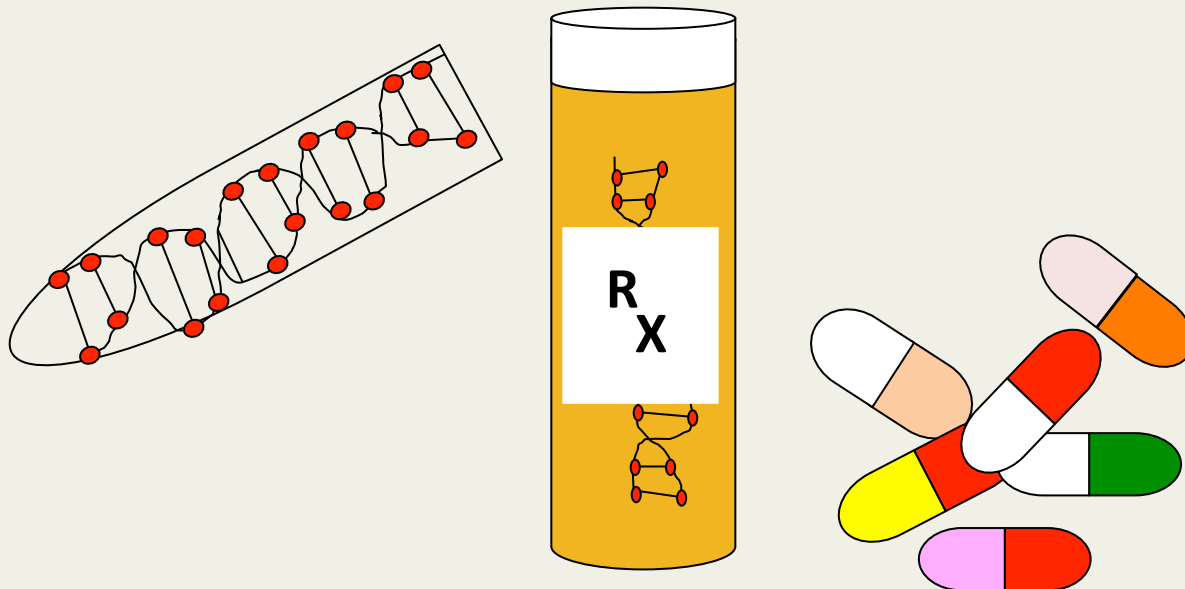
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1. Having the receptor (protein) to recognize the drug
PTC and HER2 receptors
2. Other physiological traits that enable you to respond to a drug
Number of taste buds on tongue
3. How drugs are processed in the body
Enzymes in liver metabolize drugs

Pharamcogenomics

Using people's genetic information for the right drug at the right dose at the right time!



About the Scientist:

- What do I study?
- Why do I love science?
- Questions?

