Cracking the Code: The Genetic Basis of Disease

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SITN DayCon 2015

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What we will discuss today

Part I: Basics of Genetics

Part II: Genetic Variation

Part III: Genetic Basis of Disease

Part IV: Mutations to Therapeutics

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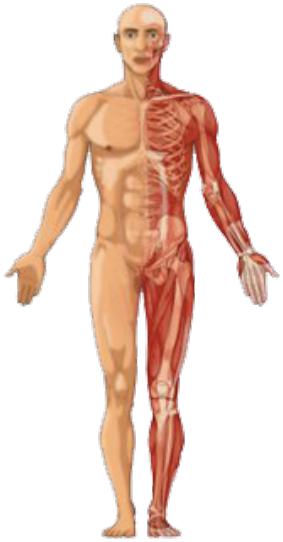
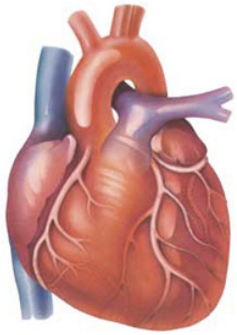
Nature vs. Nurture

Image by hepingting via Wikimedia Commons

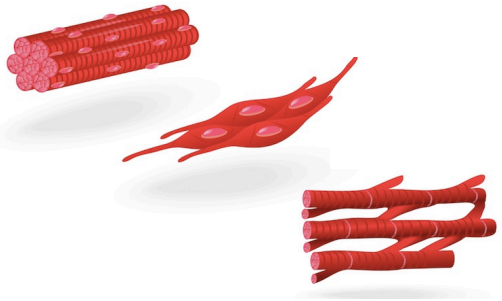
The cell is the unit of life



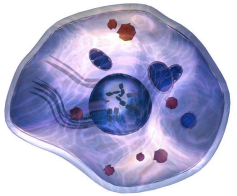
Organism



Organ

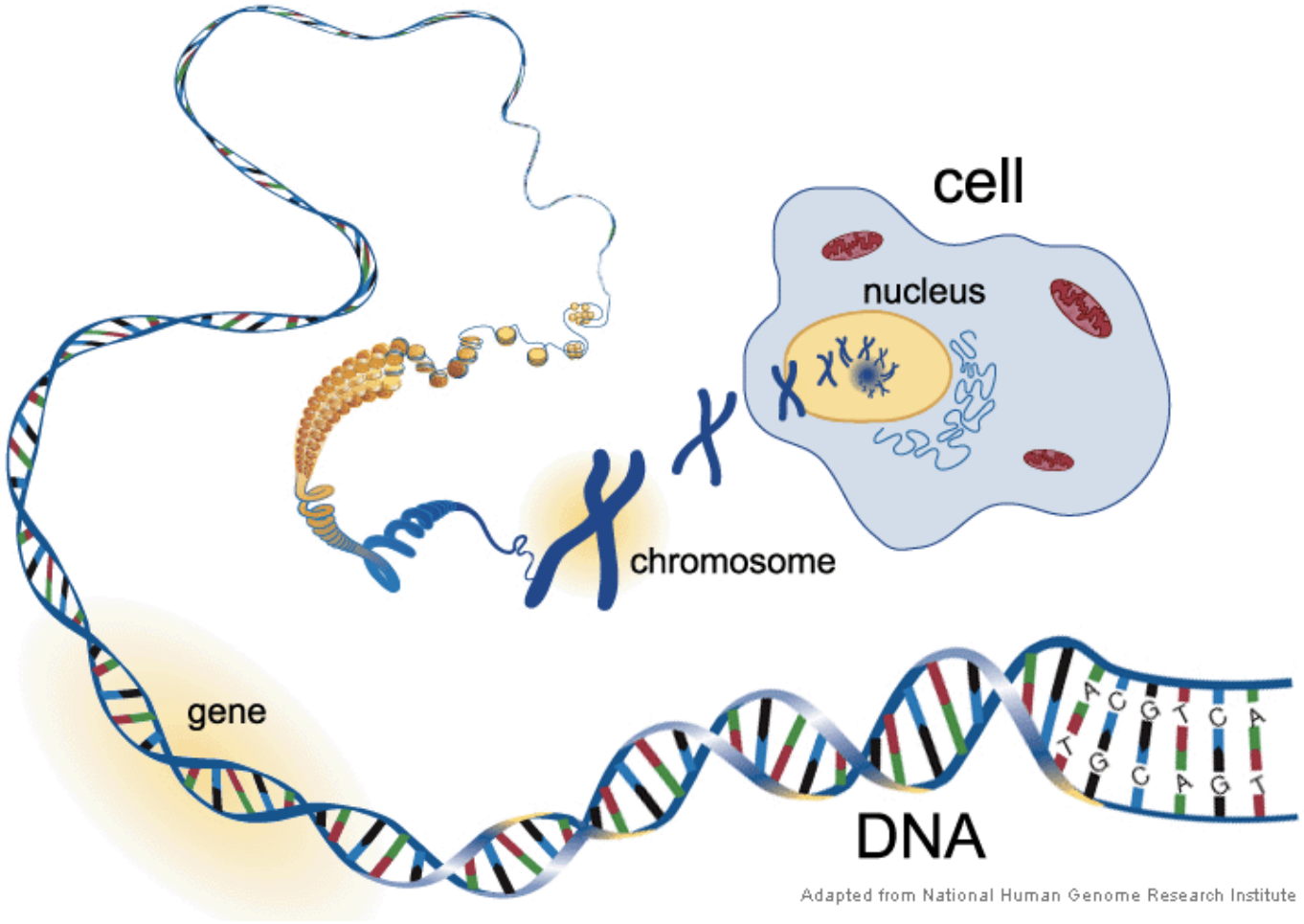


Tissue



Cell

All cells contain DNA



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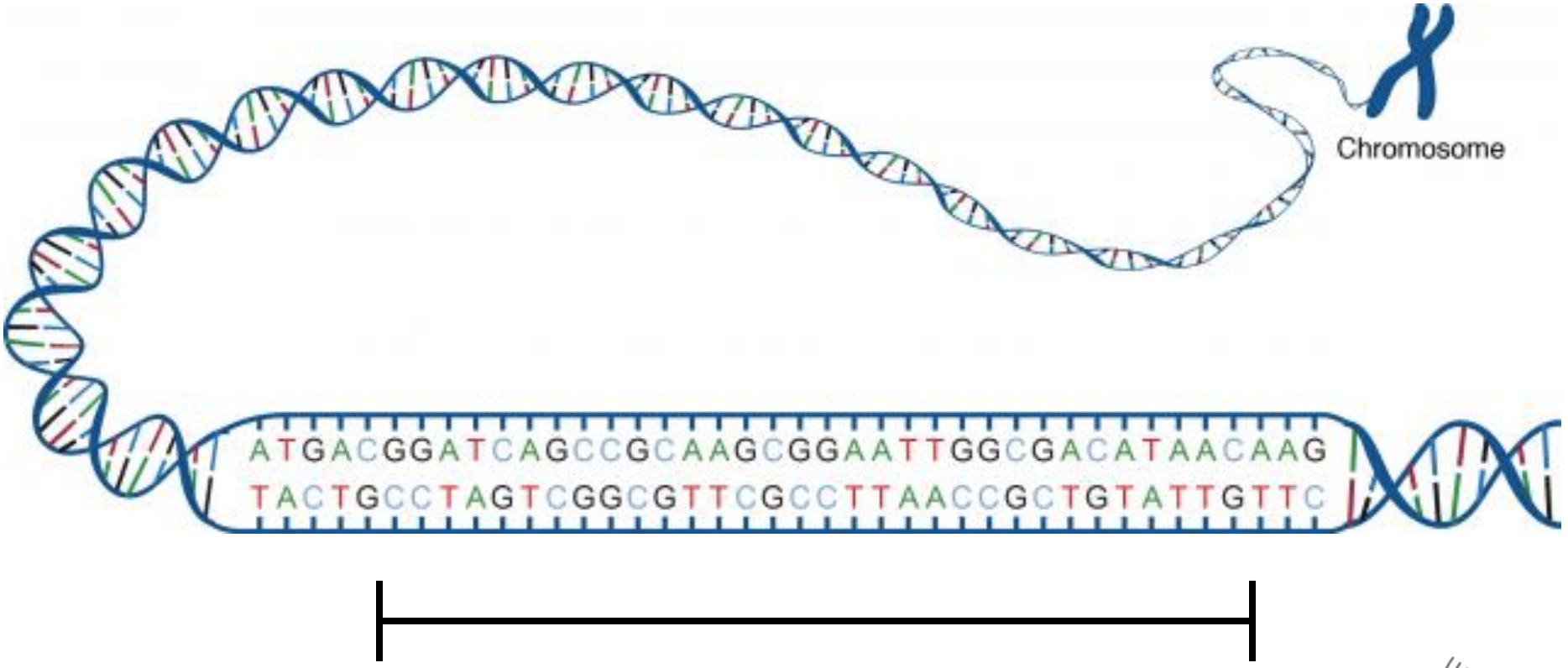
DNA contains genes



Gene:
portion of DNA that encodes one protein

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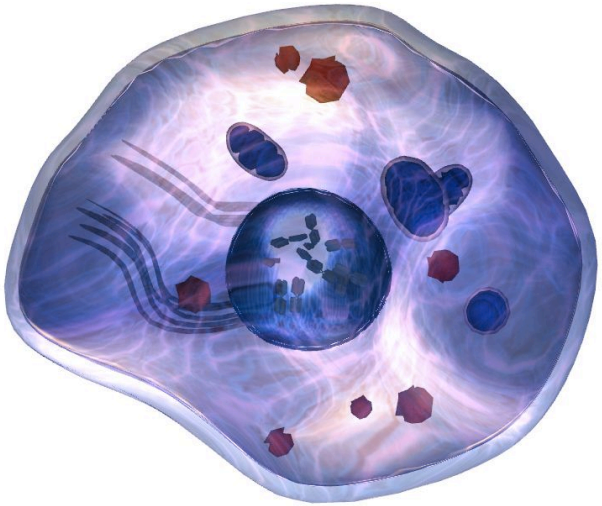
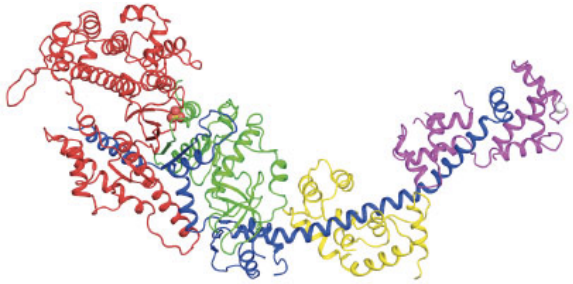
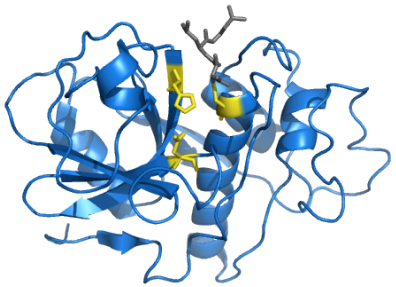
Proteins are the molecular machines of the cells







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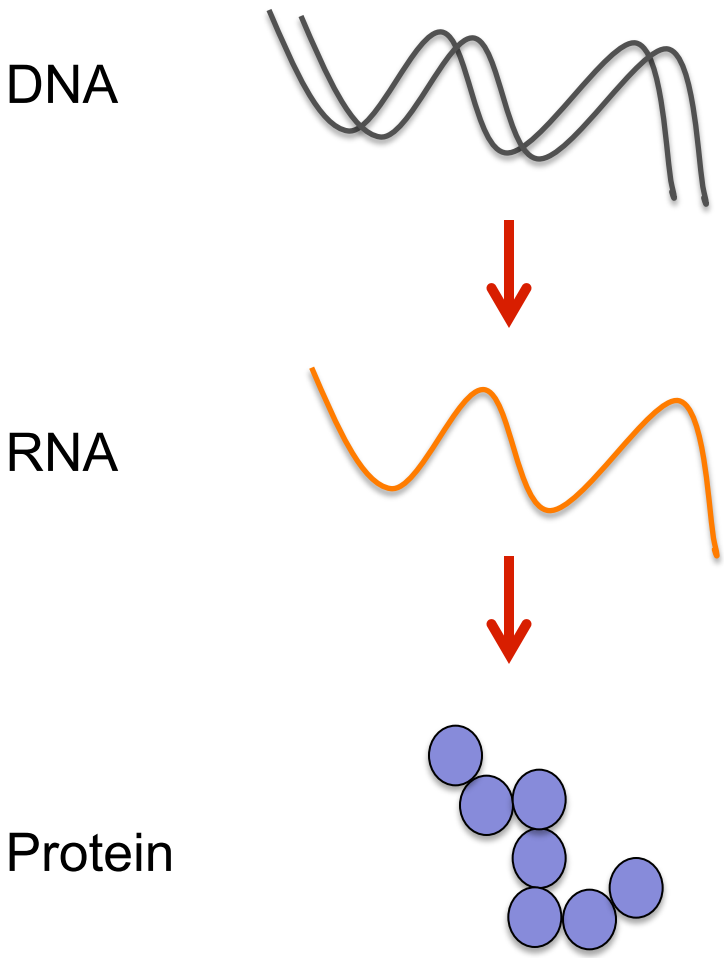
Central Dogma of Molecular Biology



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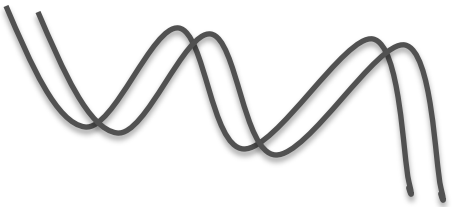
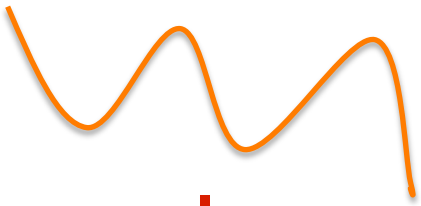
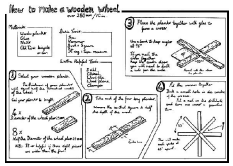
Central Dogma – car analogy

DNA

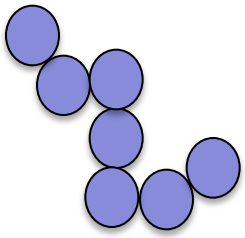


RNA





Protein



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Human Genome

Full sequence of DNA – 3 billion letters (ATCG)

QUESTIONS?

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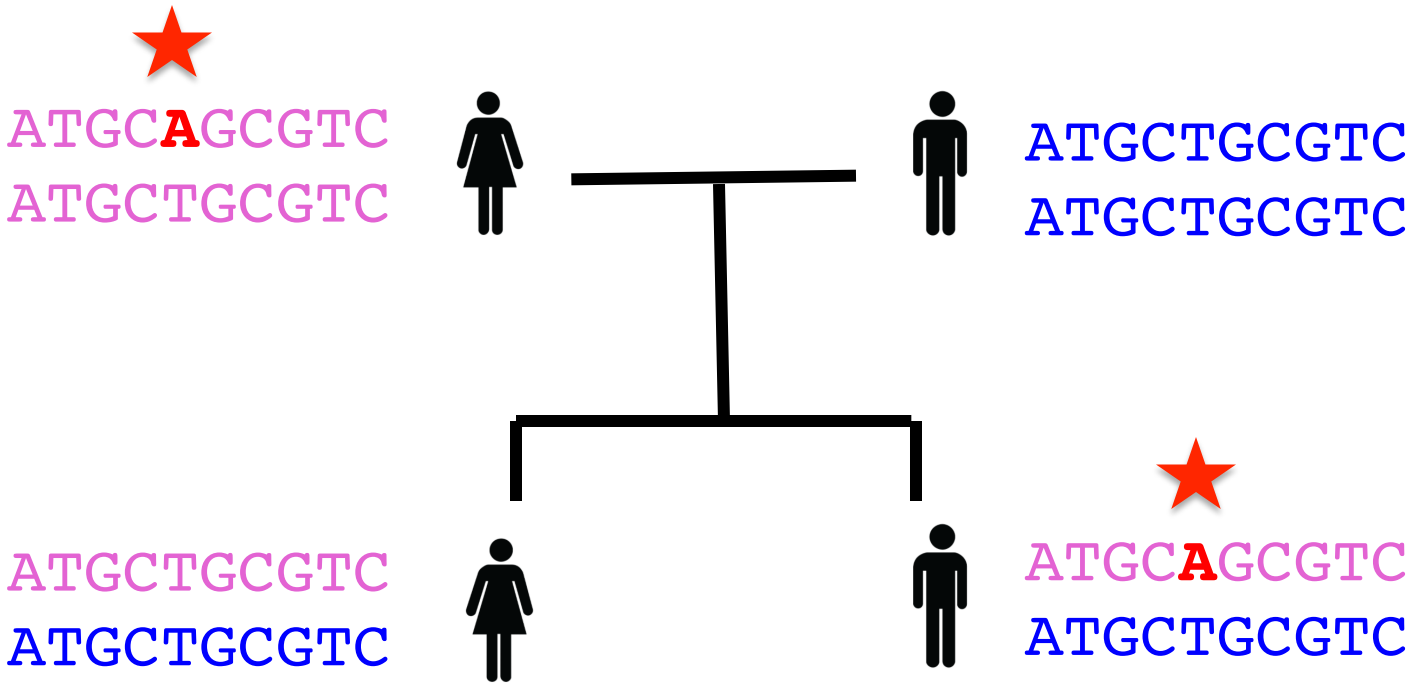
Genetic mutations

ATGCAGCGTC
ATGCTGCGTC

ATGCTGCGTC
ATGCTGCGTC

Genetic mutations

Genetic mutations can get passed on to offspring



Genetic variant: Any DNA change that is present in the population

Mutation: A genetic variant with an effect

We'll use them interchangeably…

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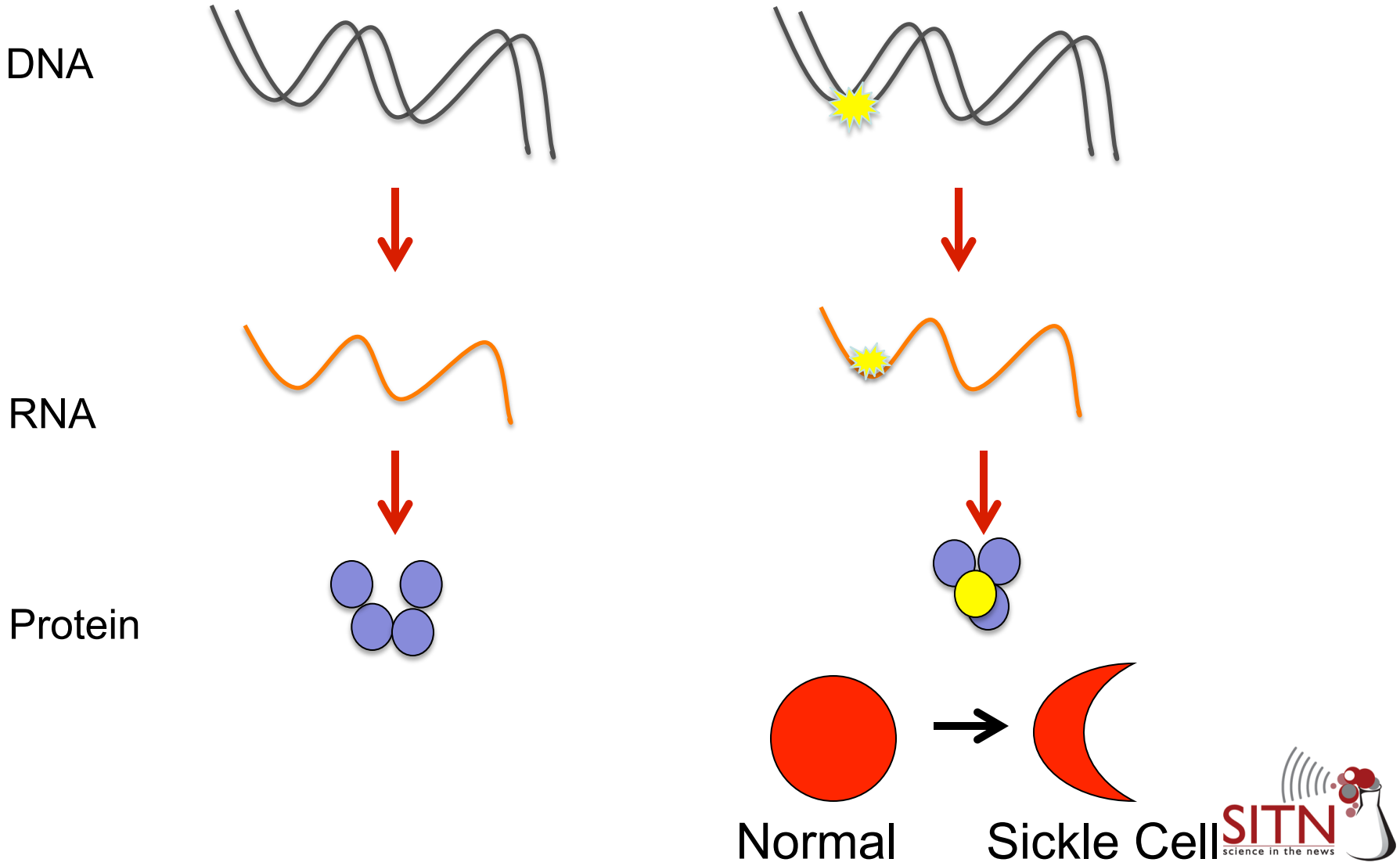
Mutation to Disease: Sickle Cell



Human Genetic Variation

Humans are 99.9% identical: differ on average 1 in 1000 base pairs

Image by hepingting via Wikimedia Commons

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Genetic variants may be common or rare

Reference	ATGTGTCGTGCTGCTC
Person 1	ATGTGTCGTTCTGCTC
Person 2	ATGTGTCGTGCTGCTC
Person 3	ATGAGTCGTGCTGCTC
Person 4	ATGTGTCGTGCTGCTC
Person 5	ATGAGTCGTGCTGCTC
Person 6	ATGAGTCGTGCTGCTC
Person 7	ATGAGTCGTGCTGCTC
Person 8	ATGTGTCGTGCTGCTC
Person 9	ATGTGTCGTGCTGCTC
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Person 7	ATGAGTCGTGCTGCTC
Person 8	ATGTGTCGTGCTGCTC
Person 9	ATGTGTCGTGCTGCTC
Person 10	ATGAGTCGTGCTGCTC

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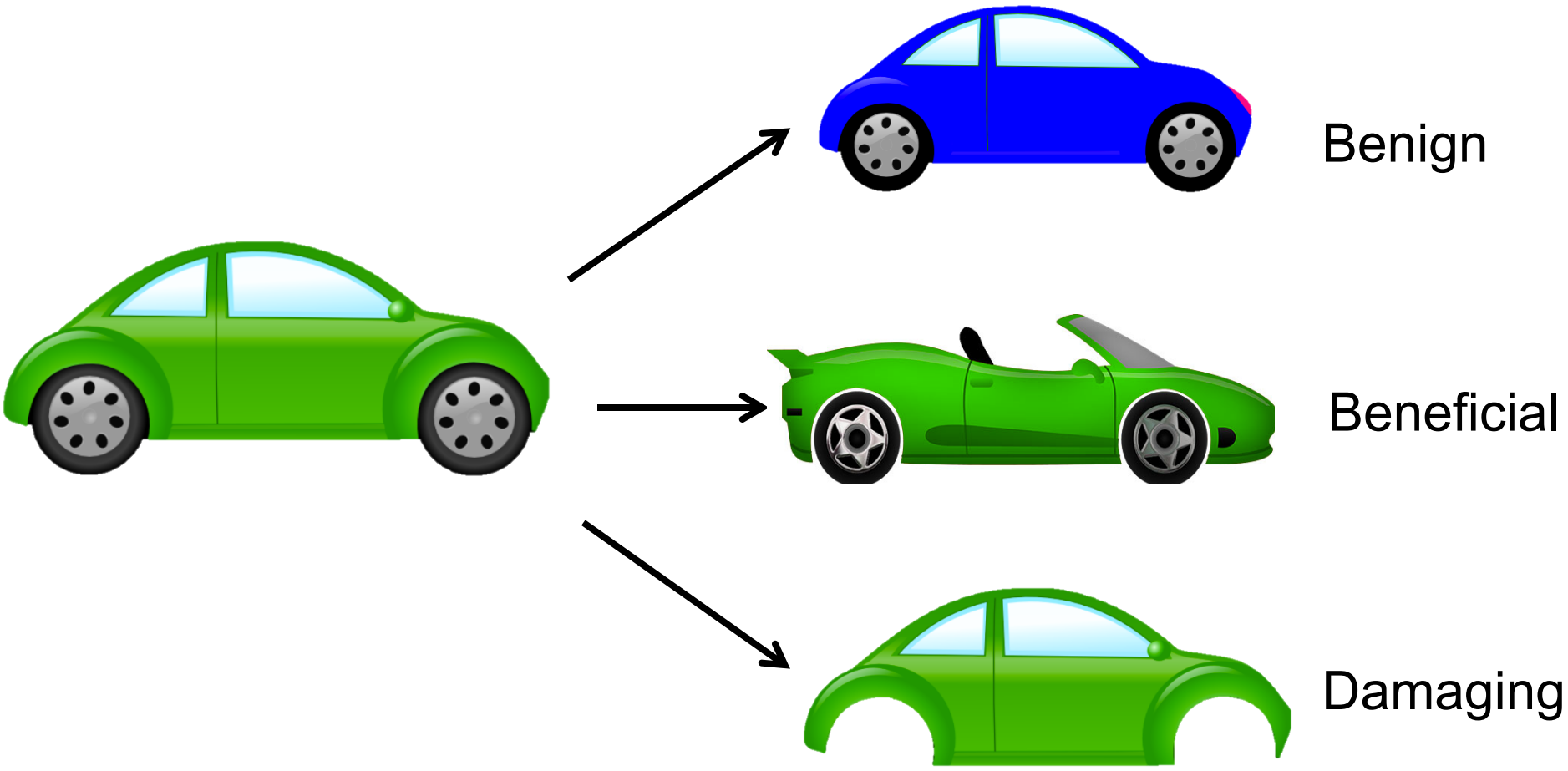
Genetic variants may have a range of effects



Summary

- Genes code for proteins that perform cellular functions
- Individuals differ at some sites in their DNA
- These genetic variants may be common or rare
- Genetic variants are mostly benign, but can be beneficial or damaging

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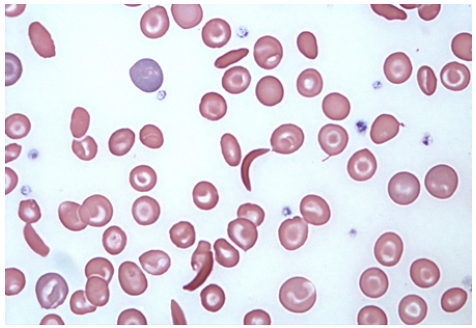
Basis of Disease

- Environmental
  - Snake bite
  - Car accident



- Genetic
  - Sickle cell anemia
  - Cystic Fibrosis

- Genetics and Environment
  - Cholesterol levels
  - Obesity

Images courtesy of Geoff Gallice, sicklecellanemia.org and ParentingPatch via Wikimedia Commons

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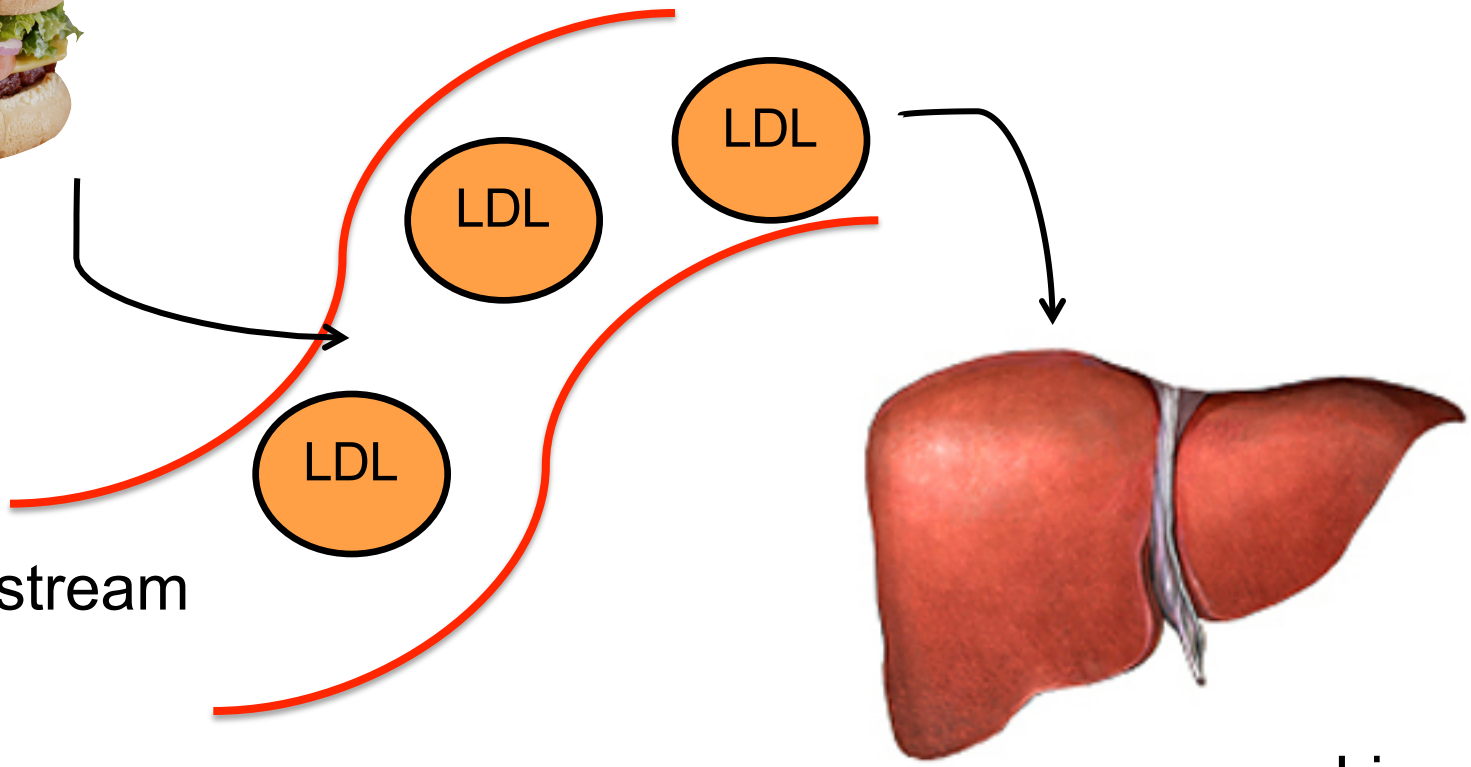
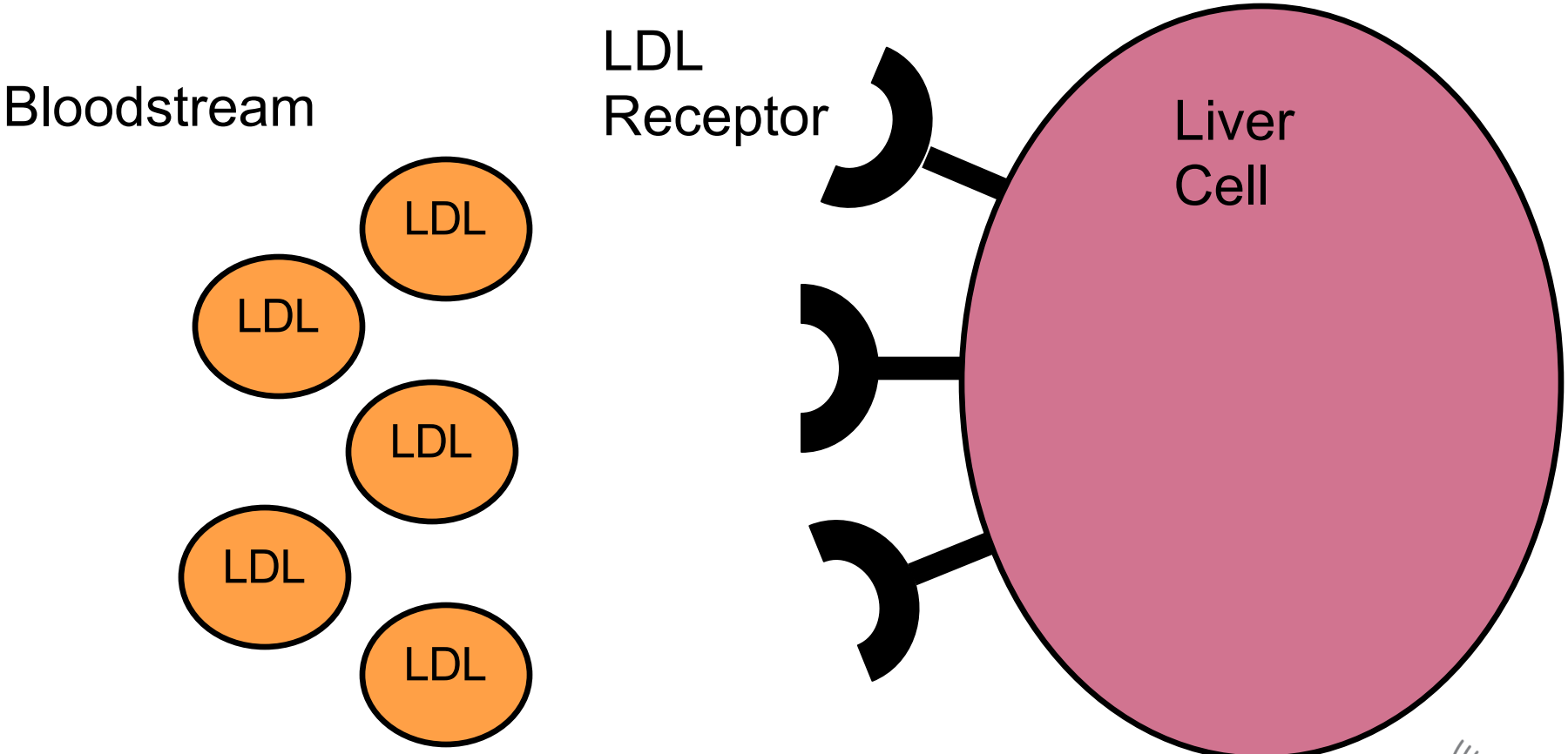
Genetic Diseases

Rare Monogenic	Common Polygenic
• Single mutations of large effect • Environment less important • Cystic fibrosis, sickle cell anemia, Duchenne muscular dystrophy	• Many common genetic variants of small effect • Often strong role of environment • Type 2 diabetes, obesity

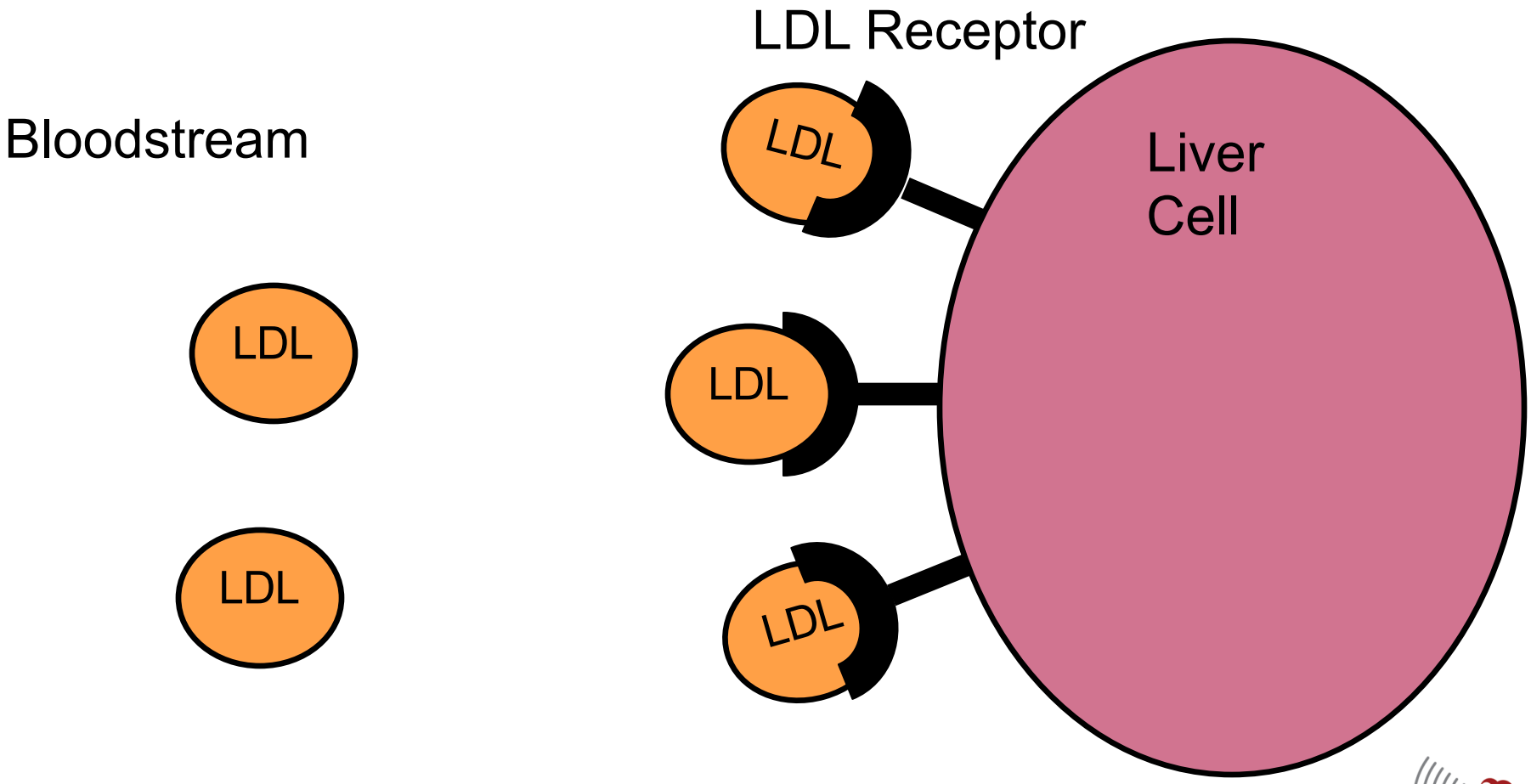
Cholesterol/LDL



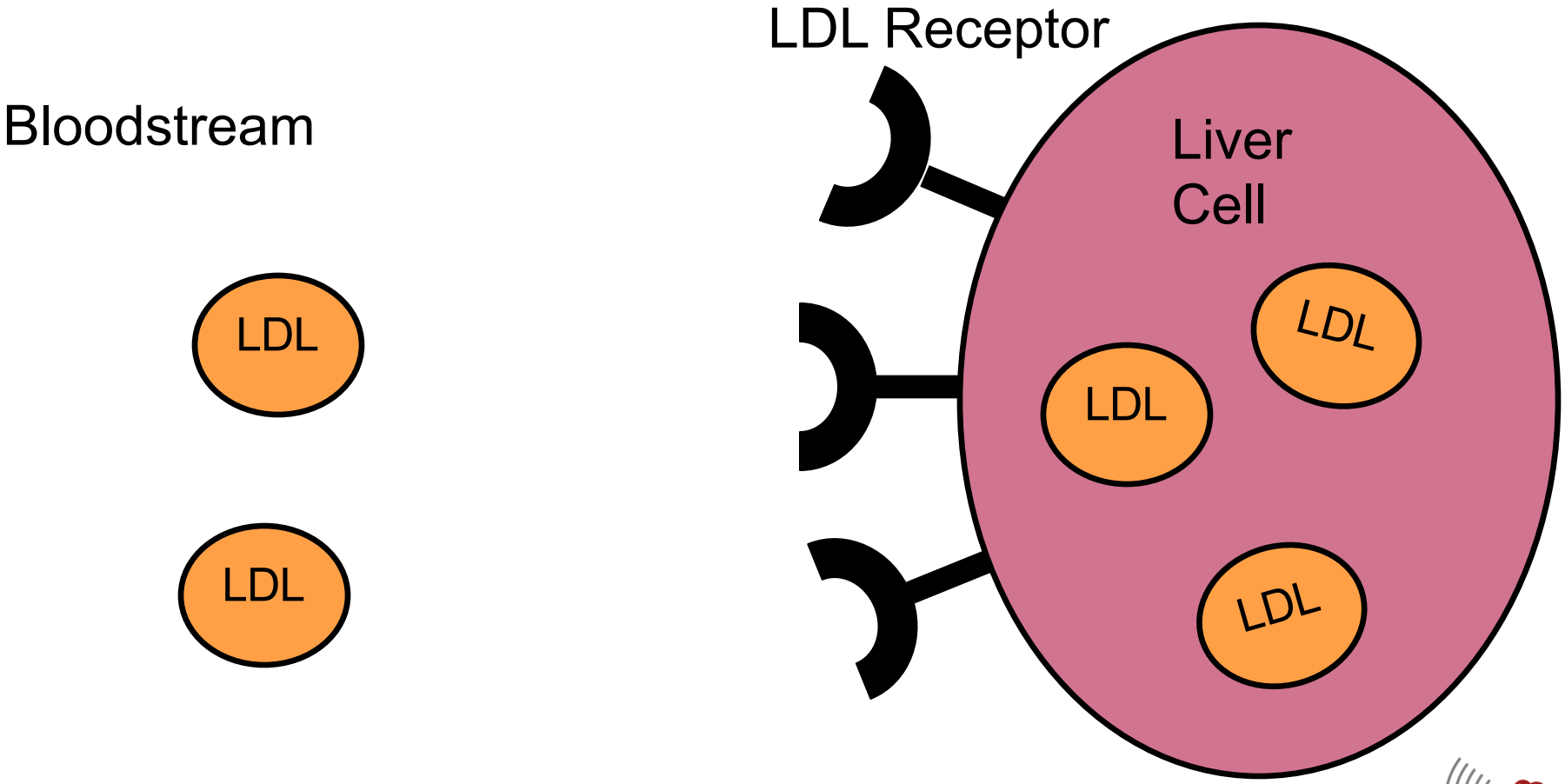
Cholesterol in the blood is in LDL



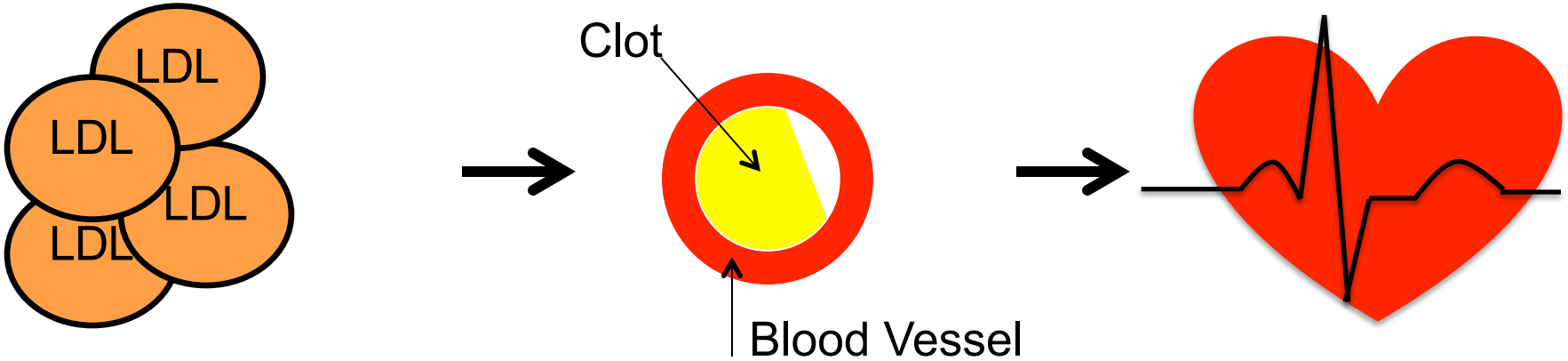
LDL Binds to LDL Receptor

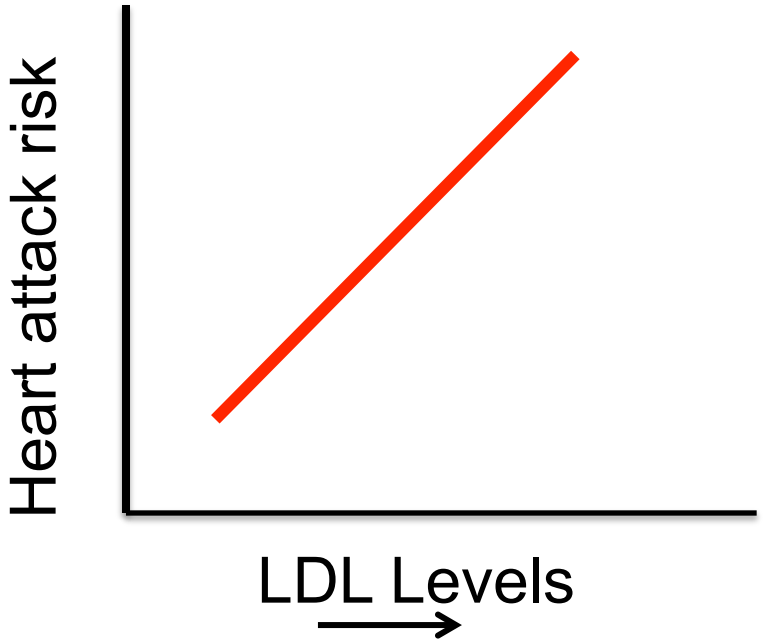


Liver cells take LDL out of blood



Increased LDL leads to heart attack





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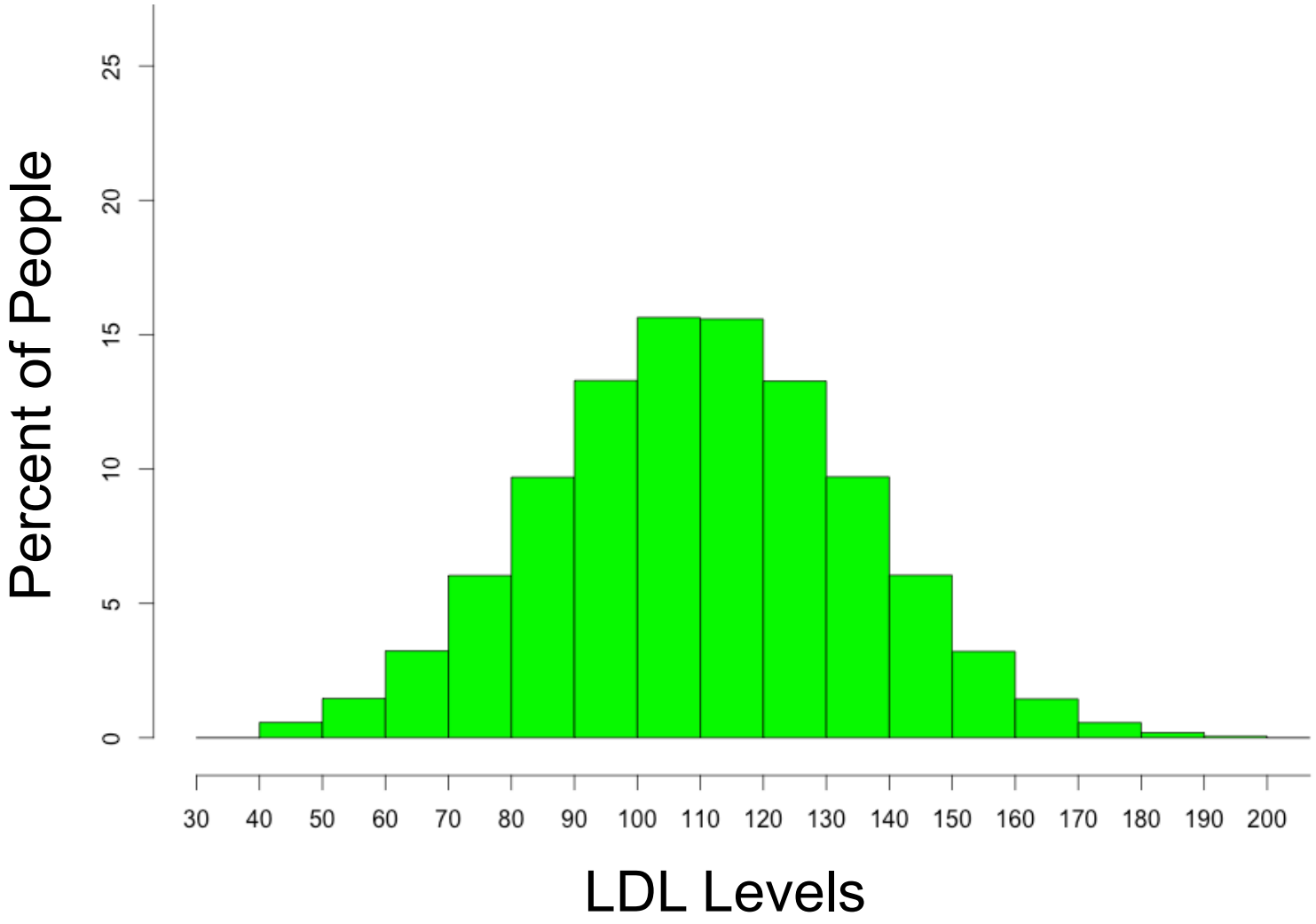
Variation in LDL



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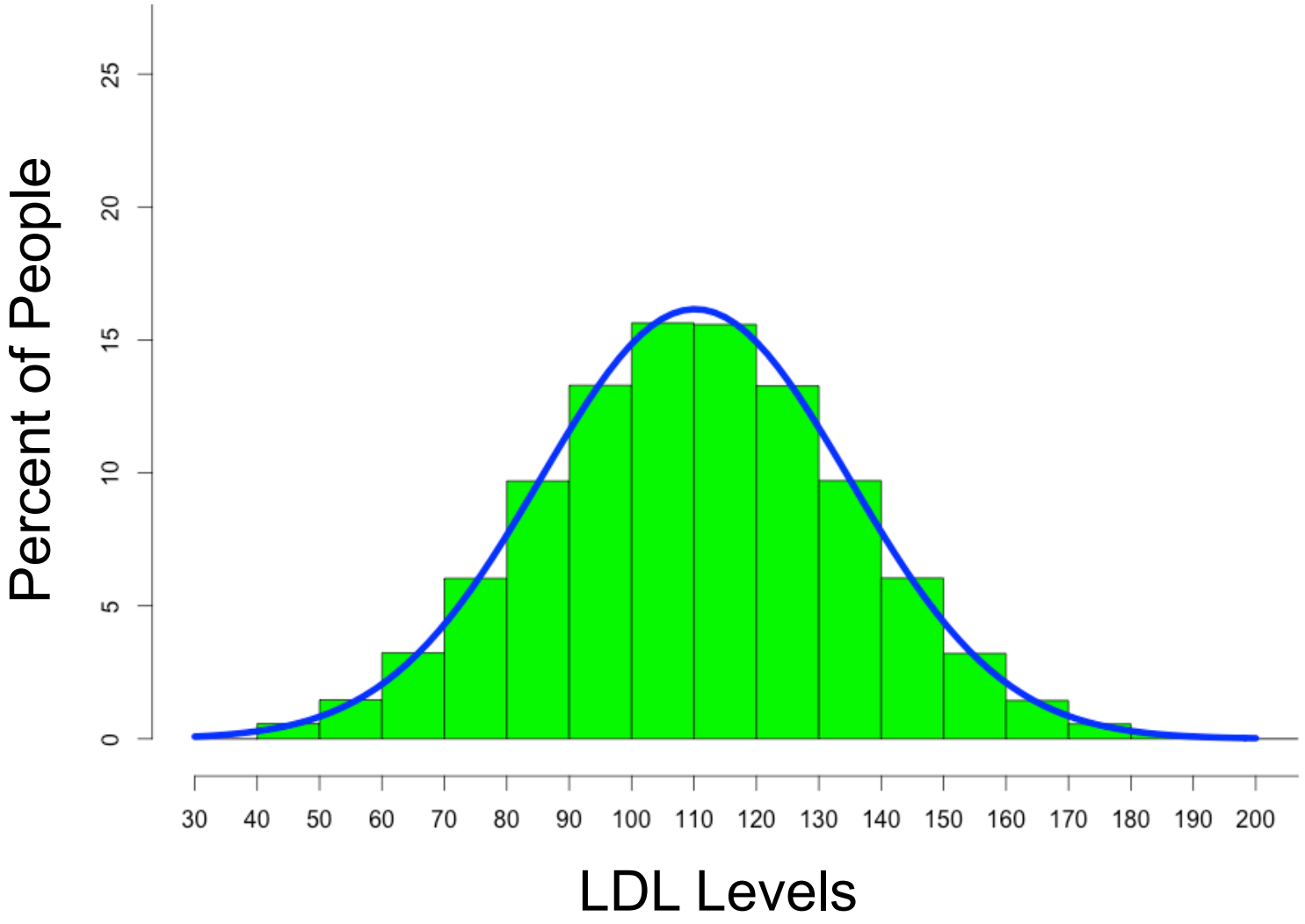
Percent of People
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5
10
15
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130
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170
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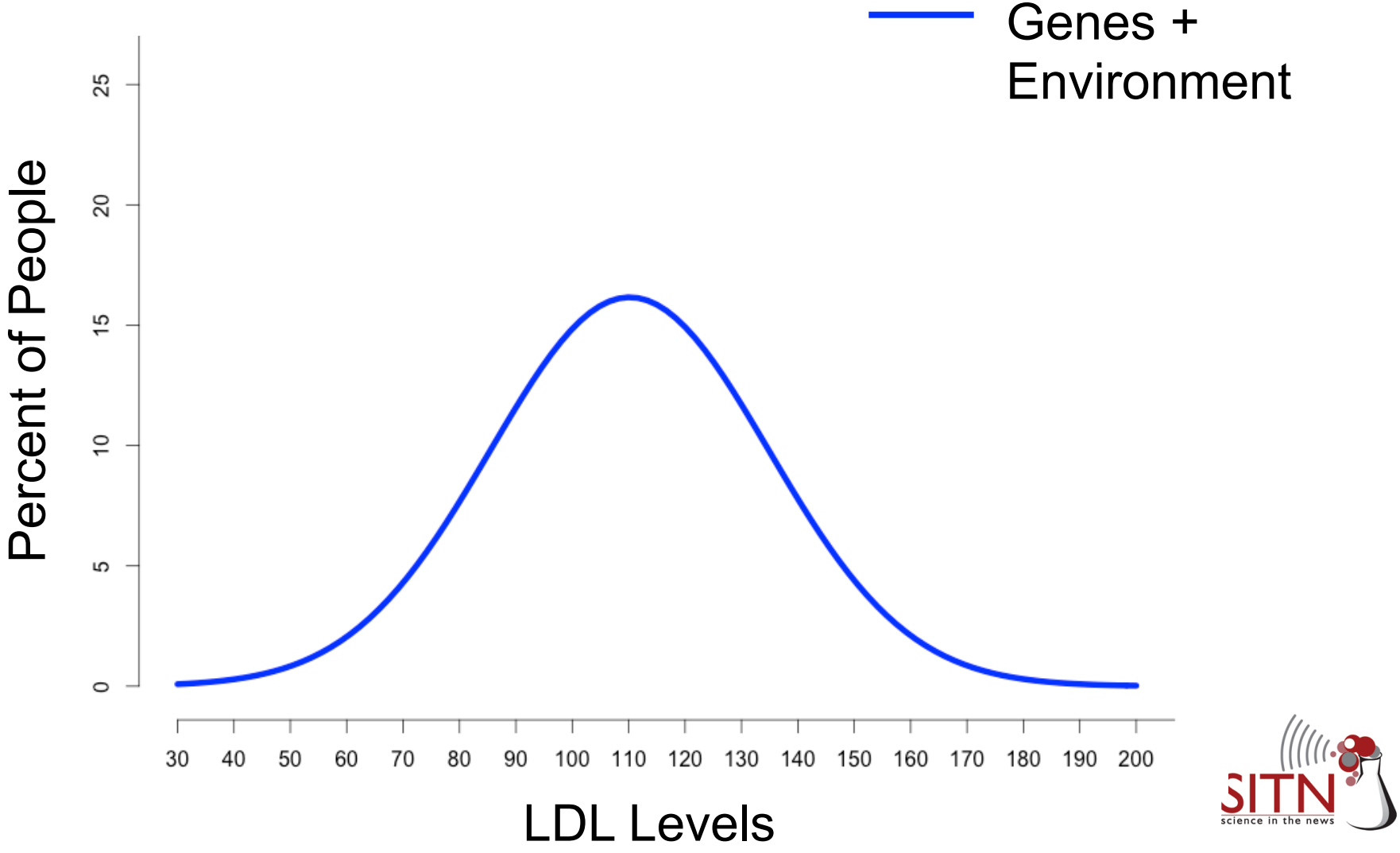
190
200
LDL Levels


Genes +
Environment
Percent of People
0
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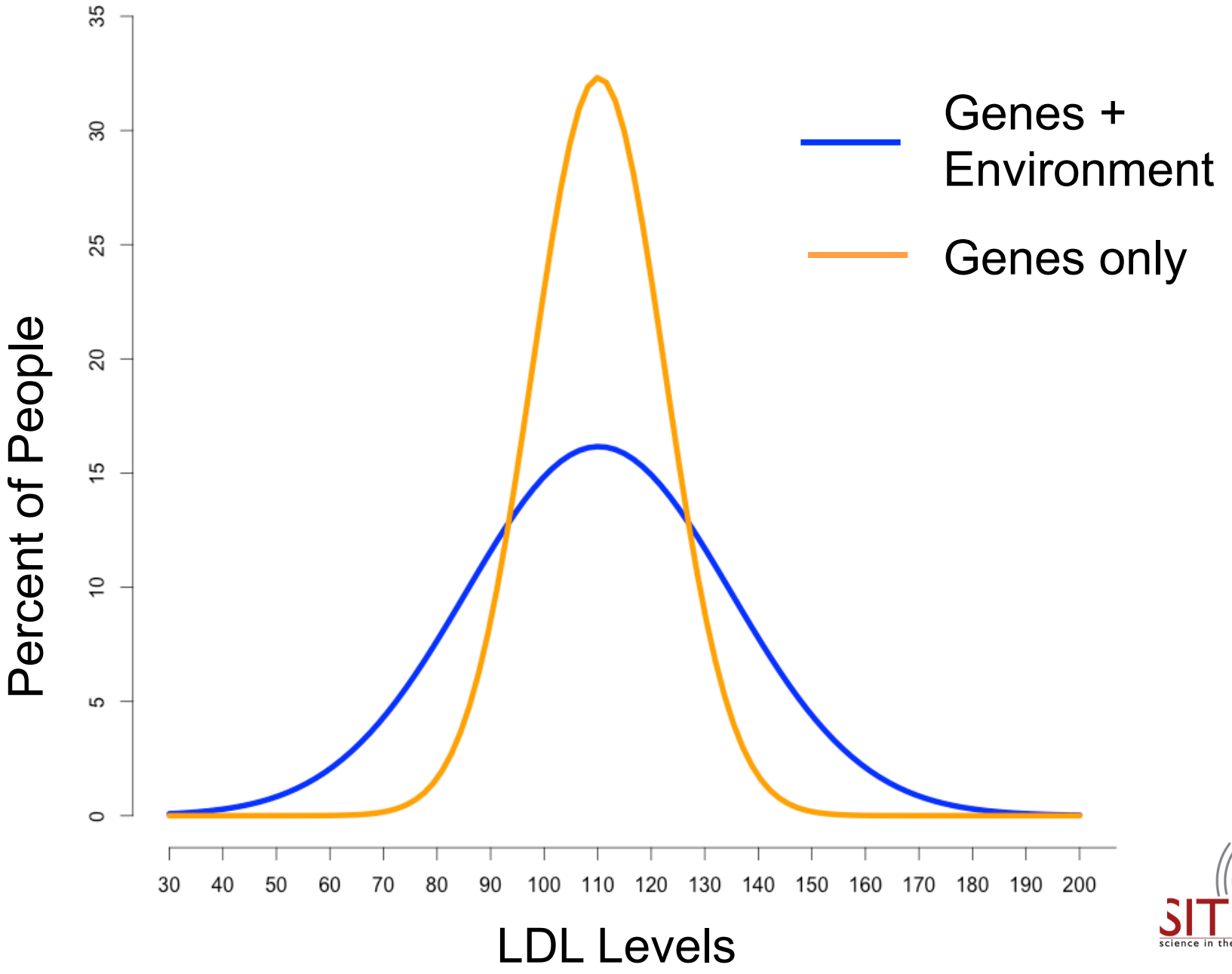
LDL Levels


Percent of People
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190
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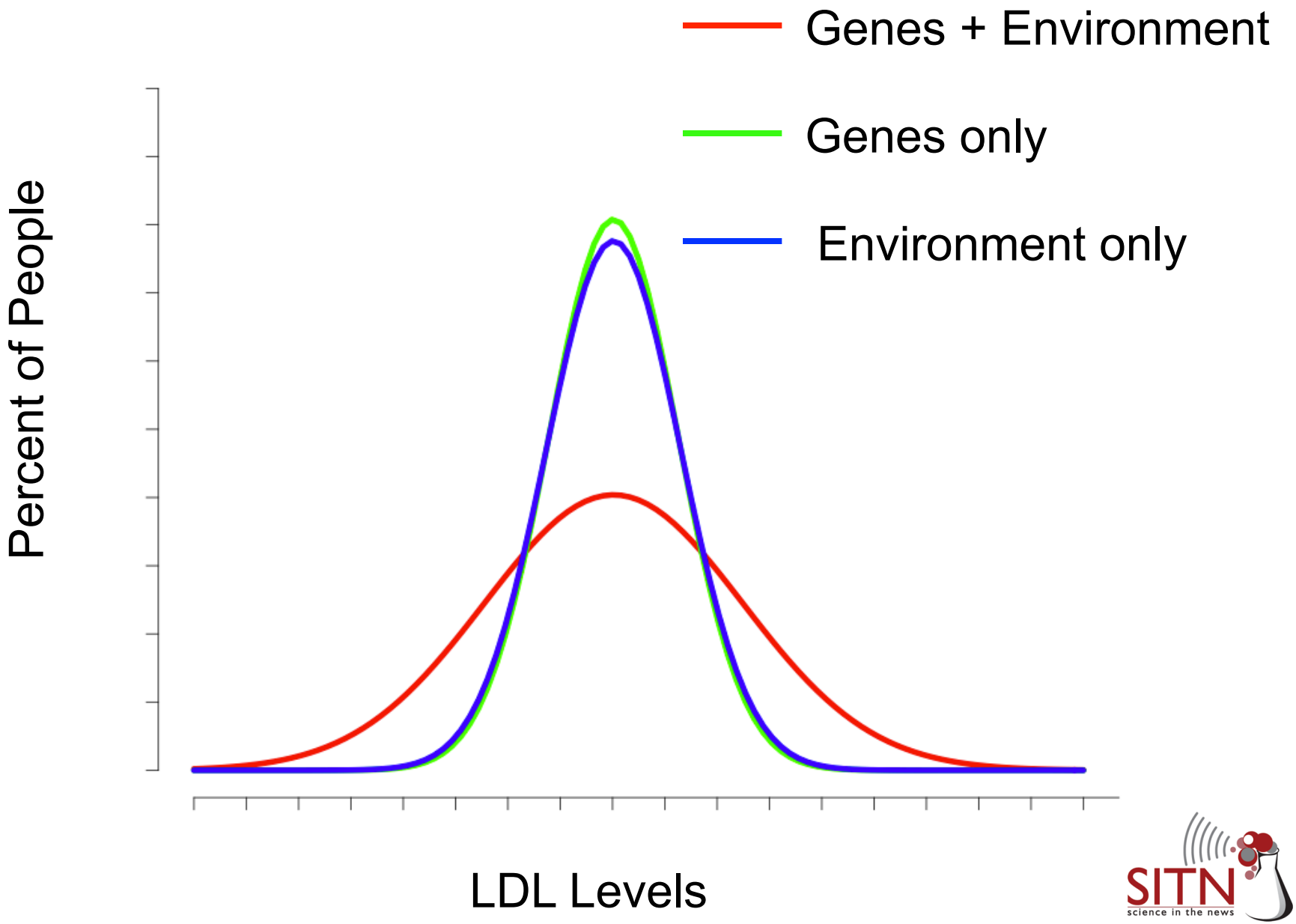
LDL Levels
Genes + Environment
Genes only


Genes + Environment
Genes only
Environment only
Percent of People
LDL Levels

- Previously, a few dozen genes for cholesterol (cell models, model organisms)
- Need to find genes relevant for cholesterol in humans
- Find mutations in genes that alter cholesterol levels in humans
  - Genome wide association study (GWAS)
  - Family-based linkage studies

GWAS

- GWAS: Genome Wide Association Study
- Perform in large numbers of people
- Find variants in genes associated with cholesterol levels
- For each common genetic variant:
  - Test whether variant is associated with differences in cholesterol levels

Reference	ATGTGTCGTGCTGCTC
Person 1	ATGTGTCGTTCTGCTC
Person 2	ATGTGTCGTGCTGCTC
Person 3	ATGTGTCGTGCTGCTC
Person 4	ATGTGTCGTGCTGCTC
Person 5	ATGTGTCGTGCTGCTC
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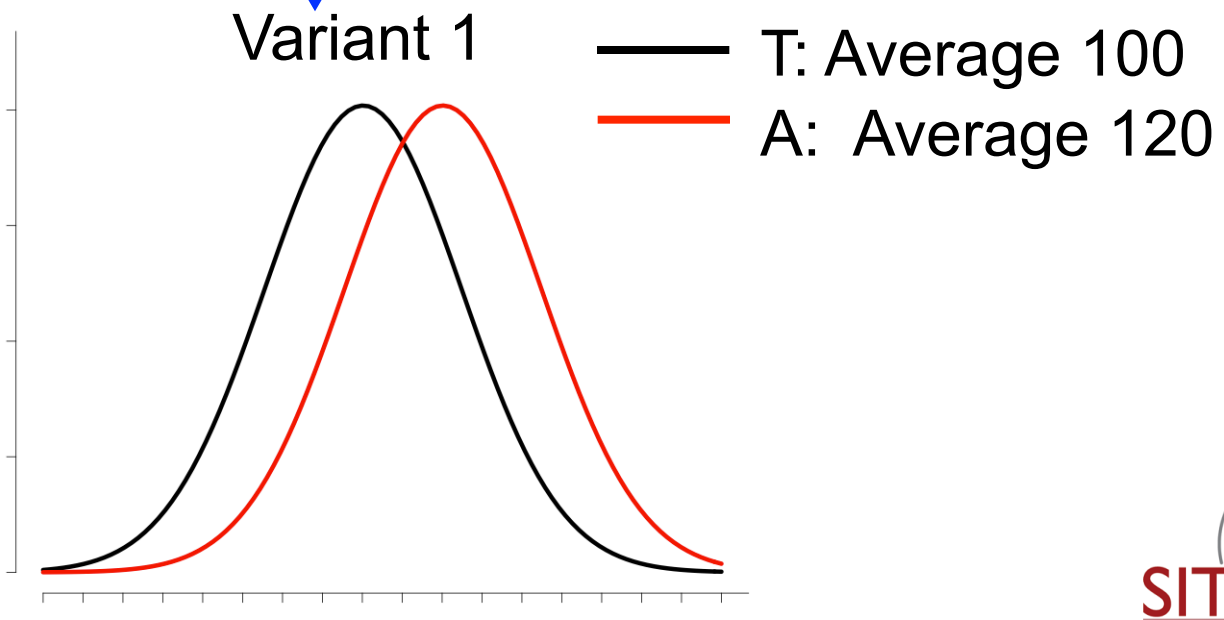

Reference	CTCGTGCAGTGCGATC
Person 1	CTCGTGCAGTGCGATC
Person 2	CTCGTGCAGTACGATC
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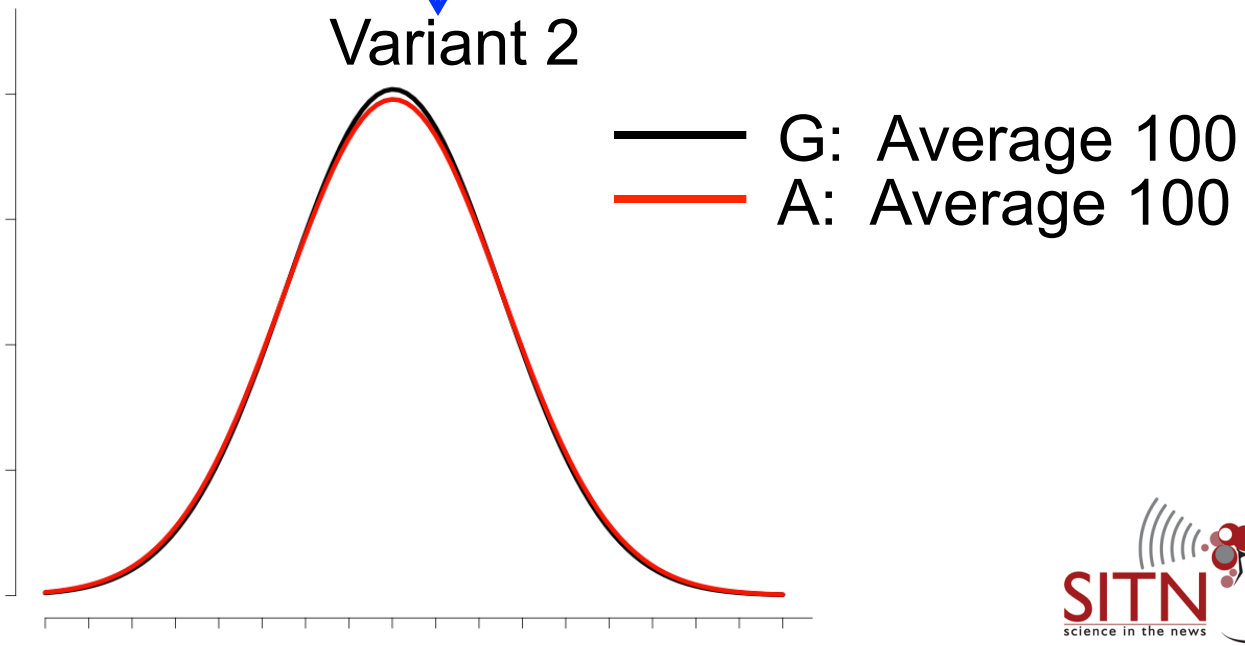
Person 4	CTCGTGCAGTGCGATC
Person 5	CTCGTGCAGTGCGATC
Person 6	CTCGTGCAGTGCGATC
Person 7	CTCGTGCAGTACGATC
Person 8	CTCGTGCAGTACGATC
Person 9	CTCGTGCAGTGCGATC
Person 10	CTCGTGCAGTACGATC



Cholesterol: Findings from GWAS

- Performed in ~200,000 people
- Identified 157 genes associated with cholesterol levels
  - Many genes known to play role in cholesterol
  - Some genes are known drug targets
  - Many new genes
    - New biology
    - New drug targets

Global Lipids Genetics Consortium. *Nature Genetics.* 2013.

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Monogenic Disorders

Familial Hypercholesterolemia (FH)

- Rare disease (1 in 500)
- Very high cholesterol levels
- Cholesterol deposits
- Heart disease by age 60

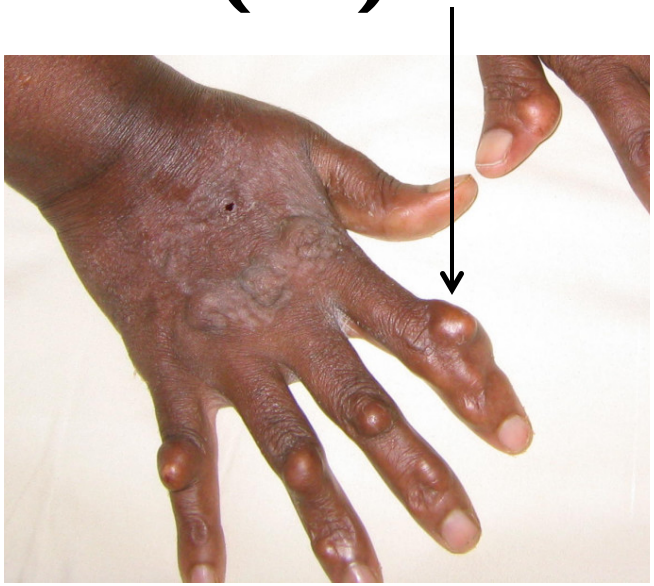

Image by A. Kumar via Wikimedia Commons

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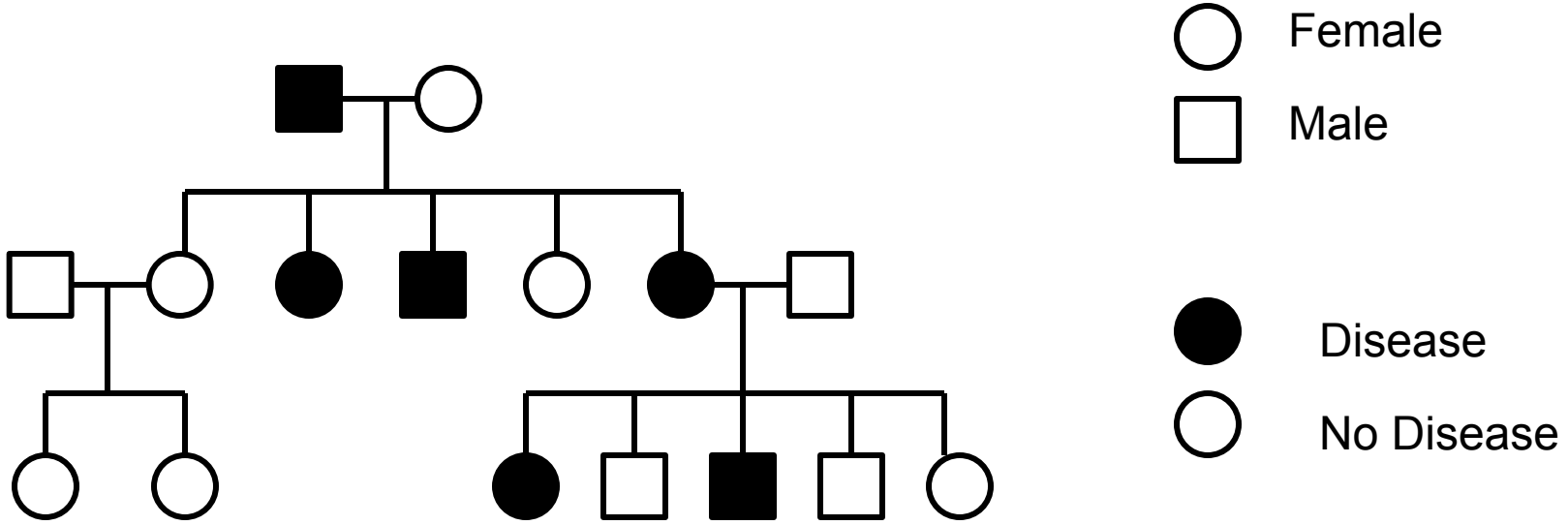
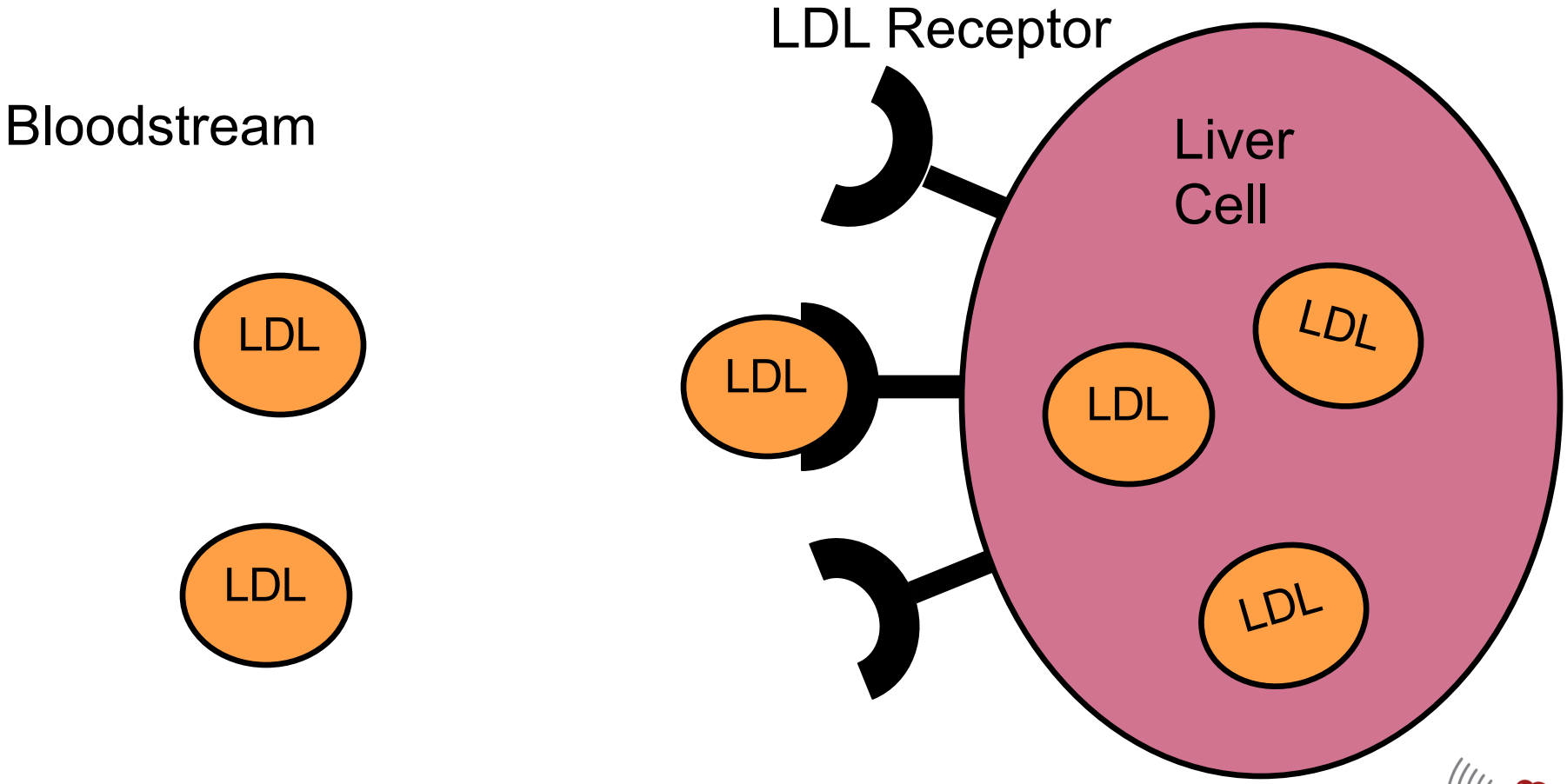
Linkage Study

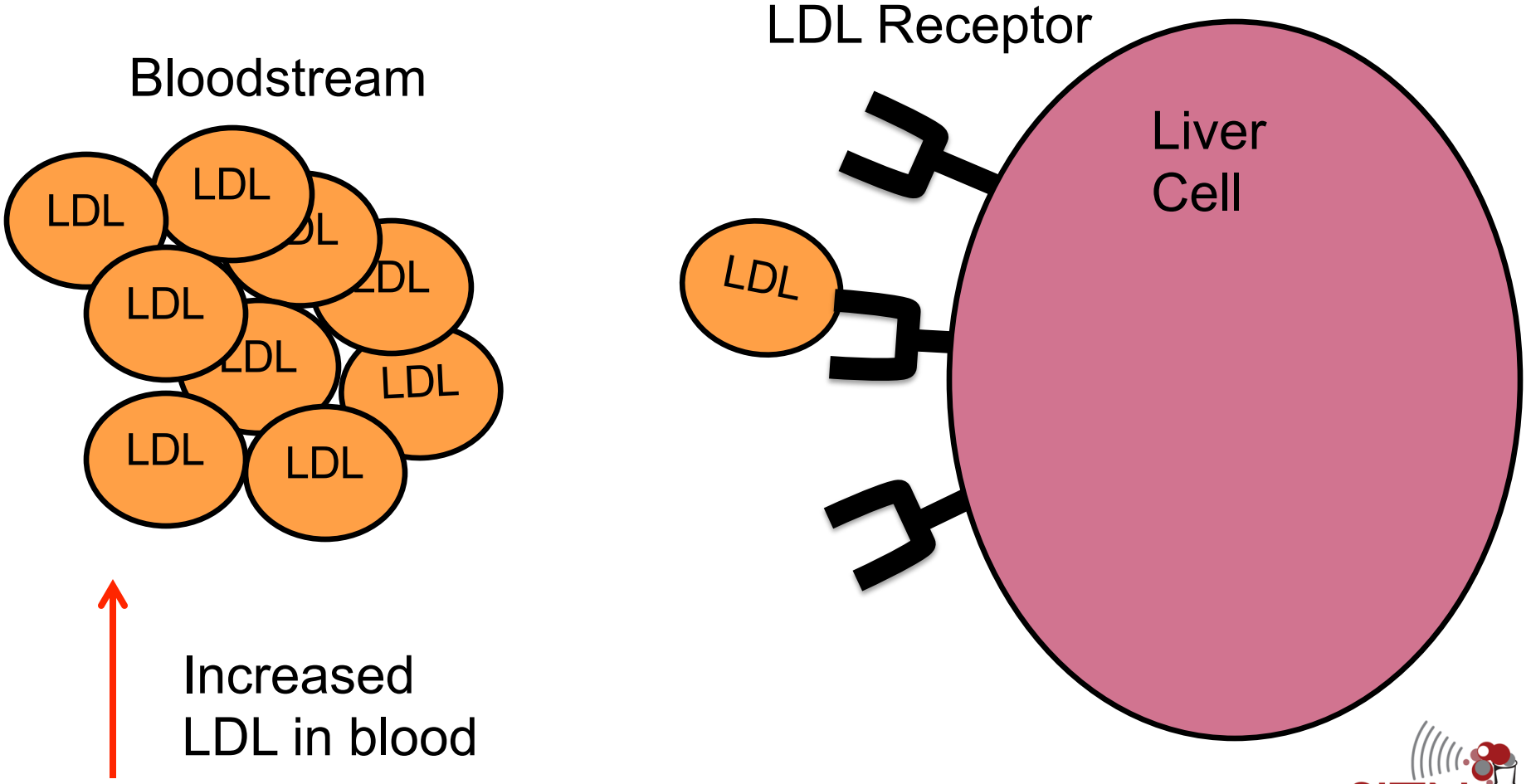


- Which mutations are "linked" with disease?
- Search for rare mutations of large effect
- Mutations in gene for LDL receptor (*LDLR*)

Normal LDL Receptor



LDL receptor mutation leads to increased LDL



Summary

- For rare monogenic diseases, genetics plays a primary role
- For common polygenic diseases, genetics and environment are both important
- Genes for disease can be found through genetic association studies
- Genetic studies have unveiled new biology and drug targets

QUESTIONS?

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X-Men Mutants

http://marvel-movies.wikia.com/wiki/X-Men_(team)

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Rare mutations in humans

Gene	Effect
CCR5	resistant to HIV infection
PCSK9	lower blood cholesterol levels and reduced risk of cardiovascular disease
LRP5	extra strong bones
MSTN	abnormally large muscles

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Natural Myostatin (MSTN) Mutants

http://www.whatisgenetic.com
http://discovermagazine.com/sitefiles/resources/image.aspx?item=%7B41CD5607-53C2-42FD-A8C0-7D05CE163CF0%7D

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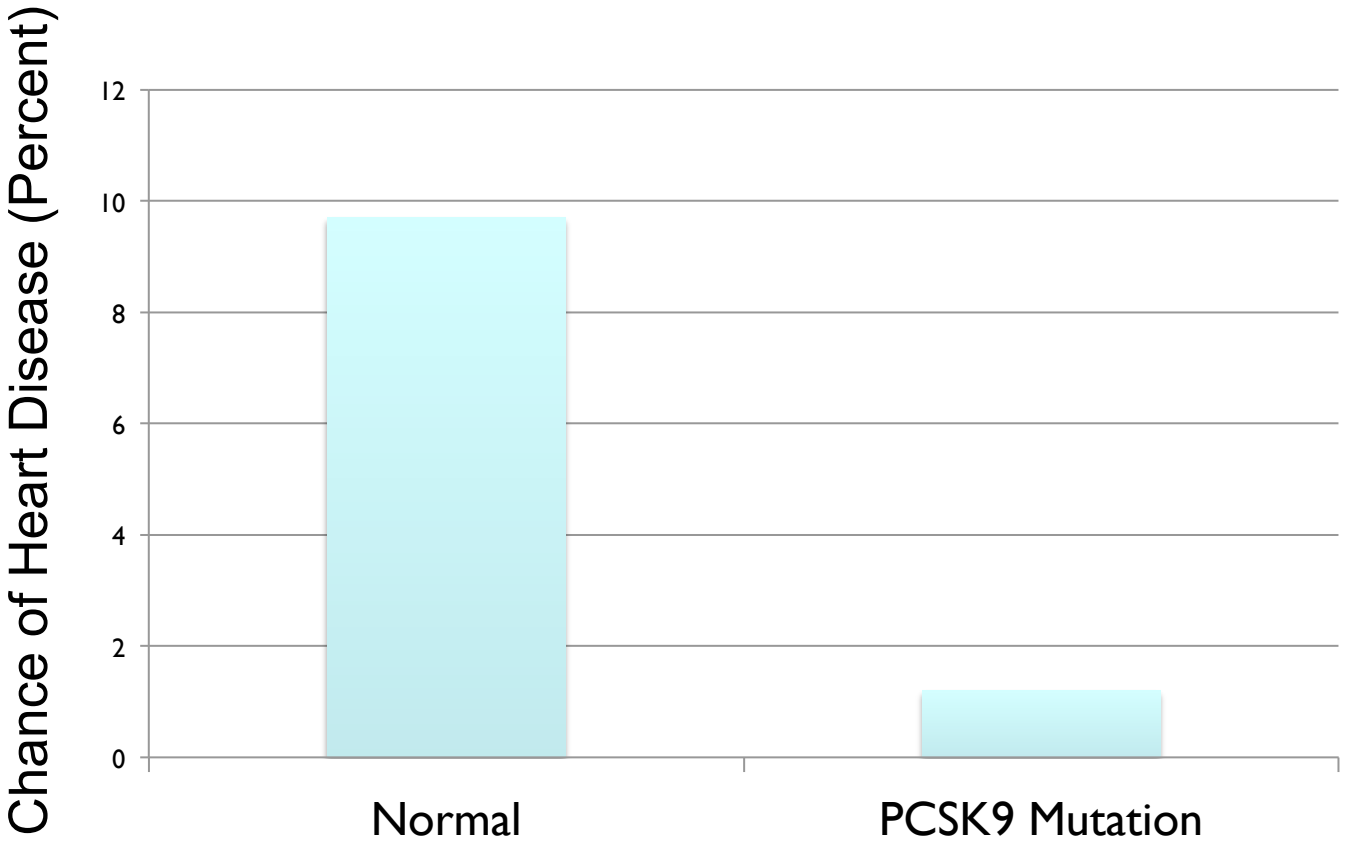
People with PCSK9 Mutations

A very small number of people have an inactivating mutation in the PCSK9 gene:

-lower blood cholesterol/LDL levels
-greatly reduced (up to 90% in some cases) risk of cardiovascular disease (heart attacks, etc)

People with PCSK9 Mutations



Cohen et al, NEHM 2006

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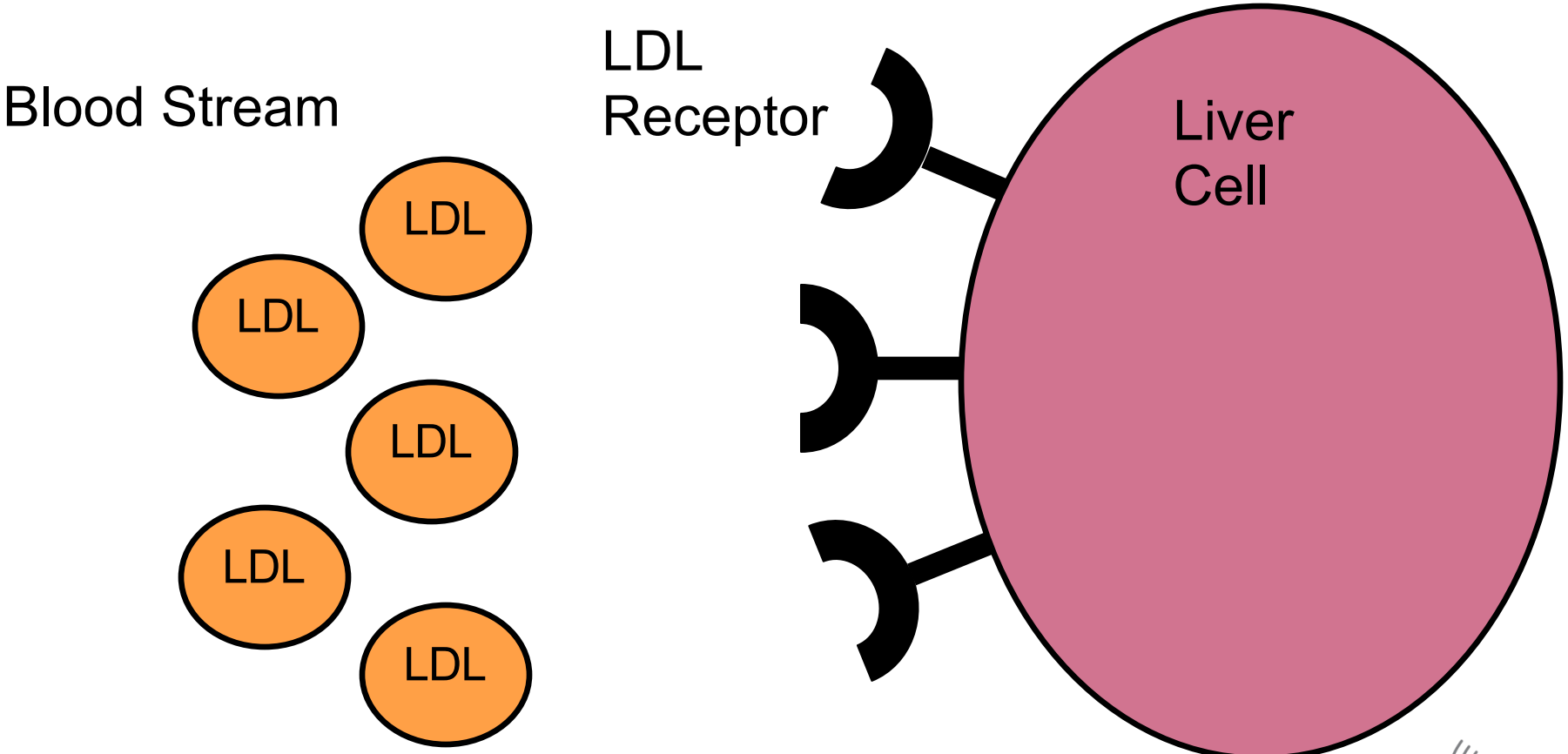
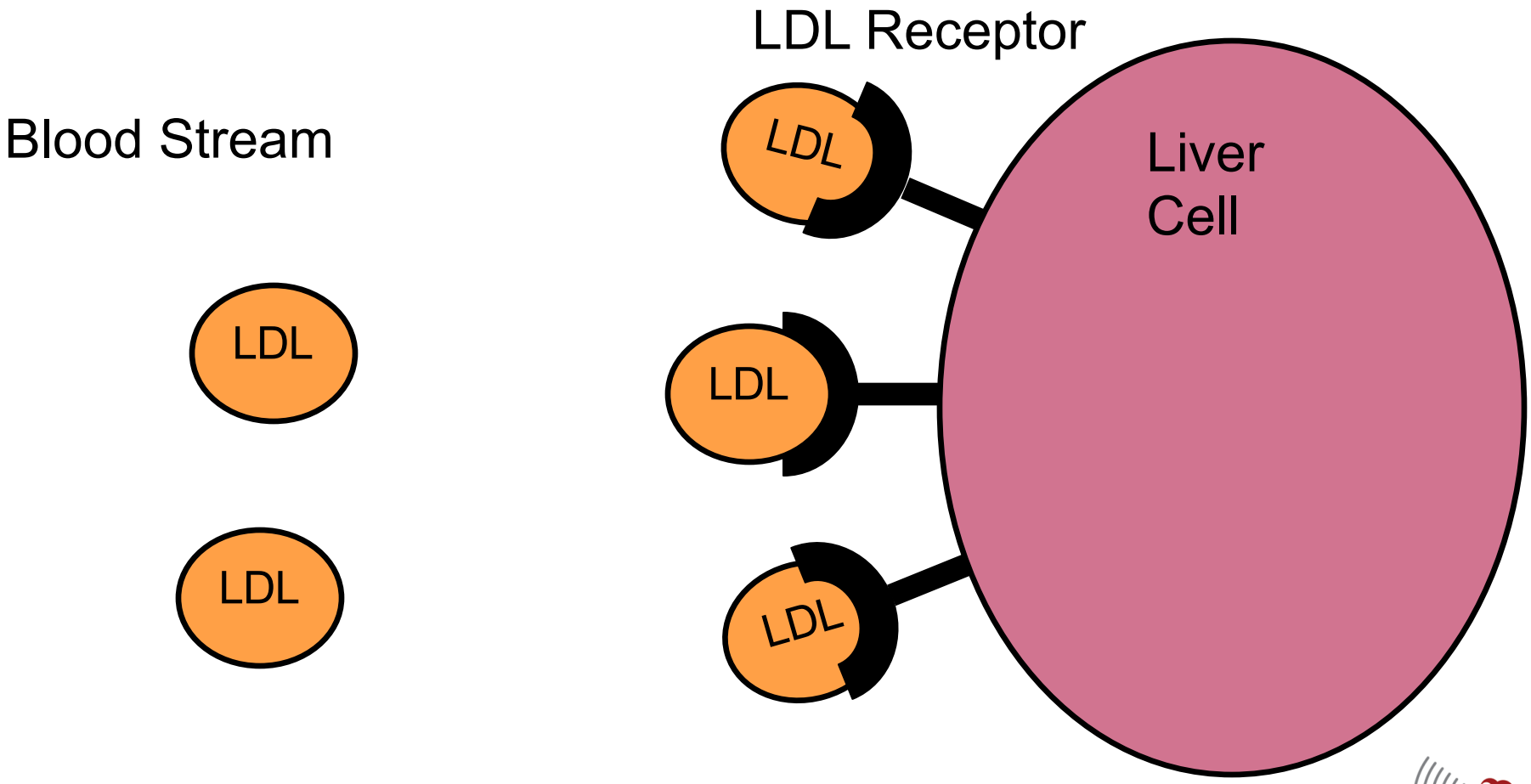
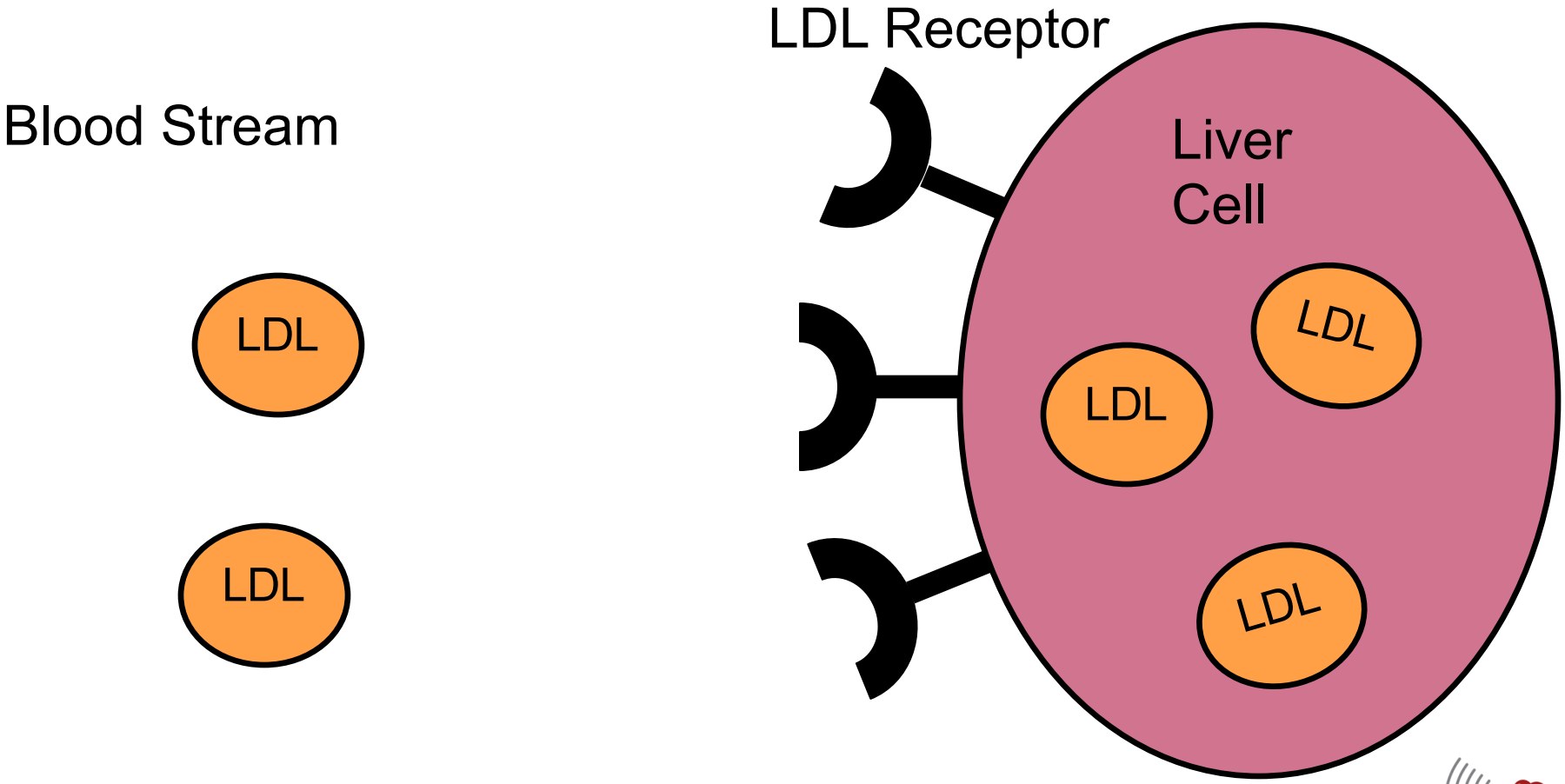
Cholesterol in the blood is in LDL



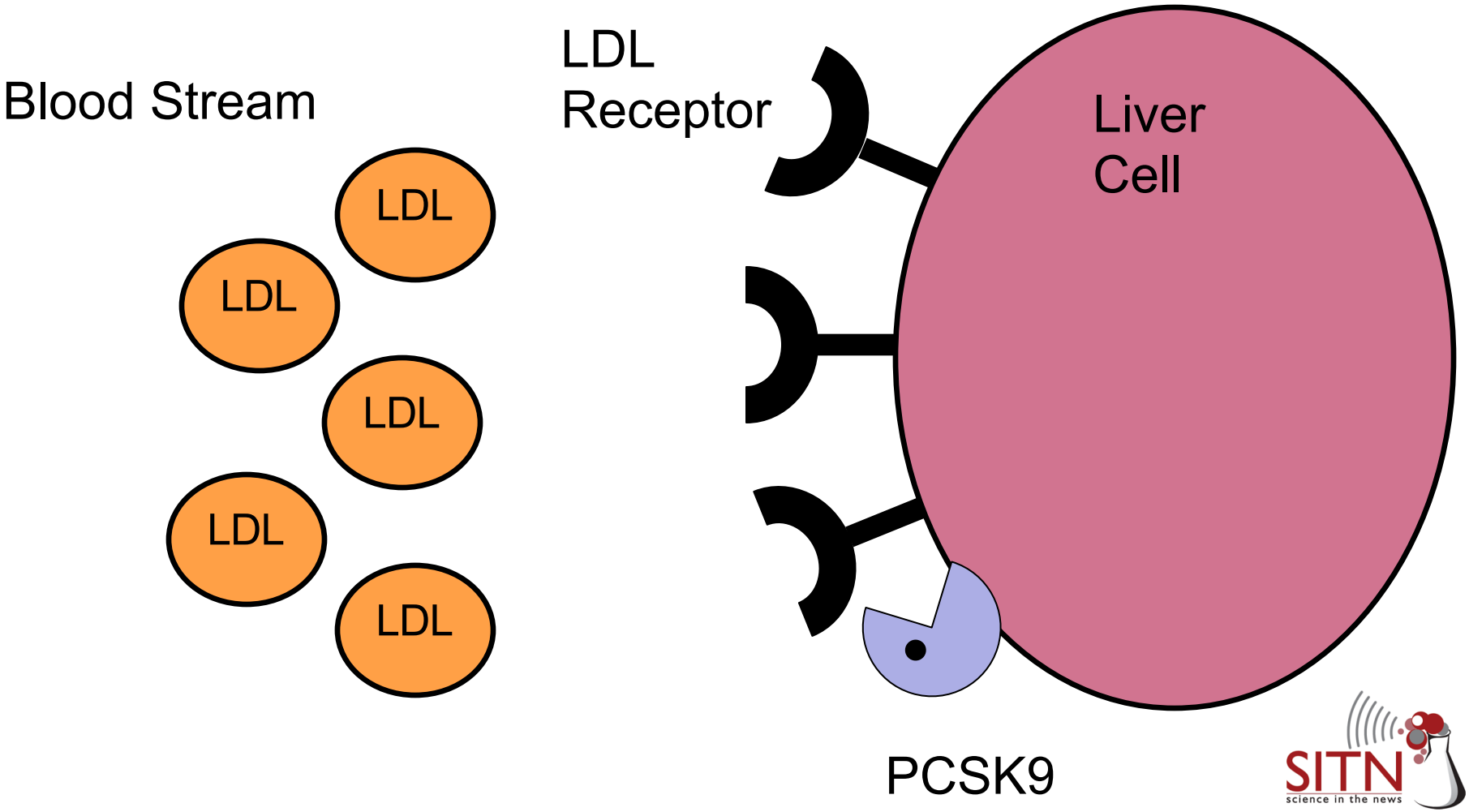
LDL Binds to LDL Receptor



Liver cells take LDL out of blood



PCSK9 degrades LDL Receptors



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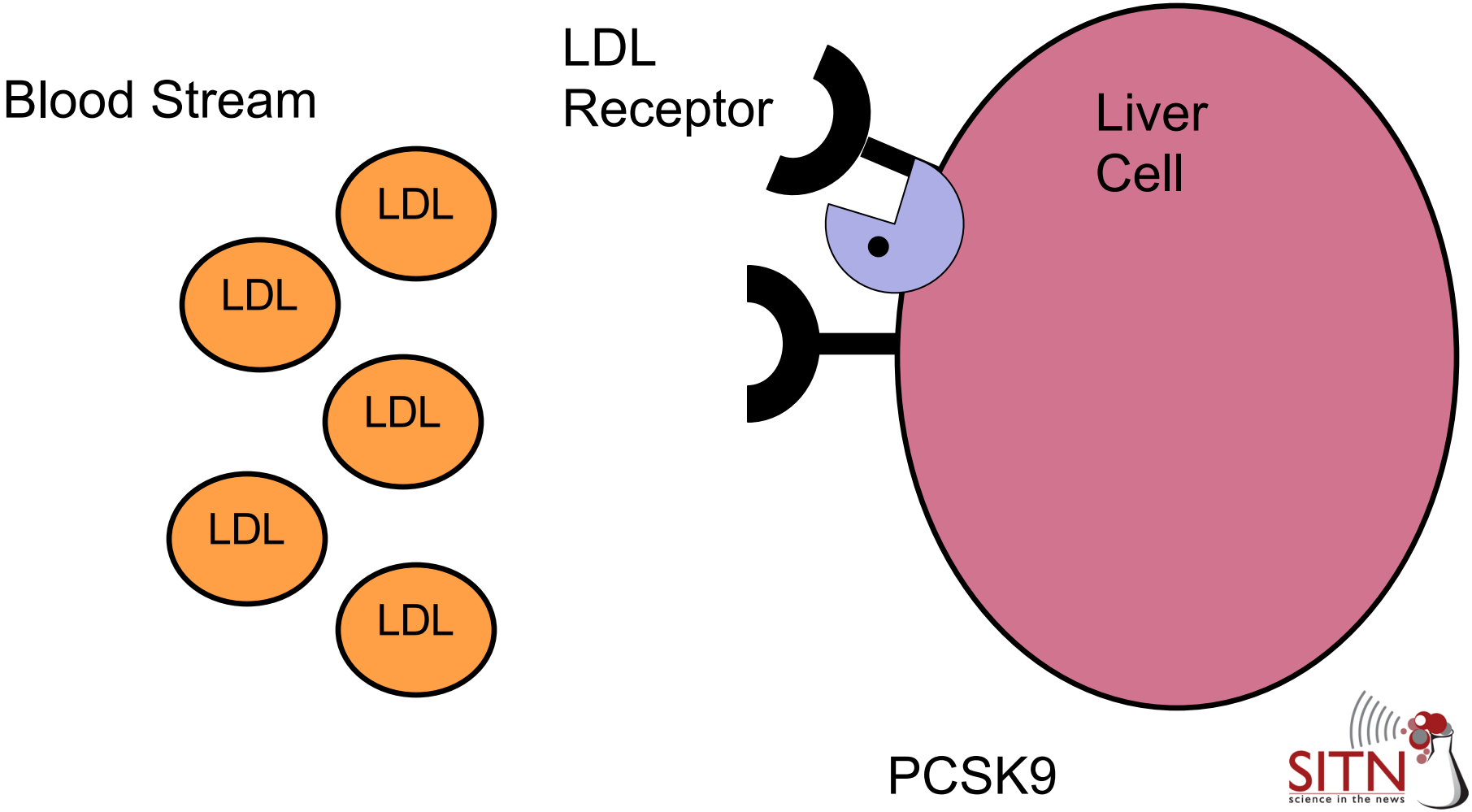
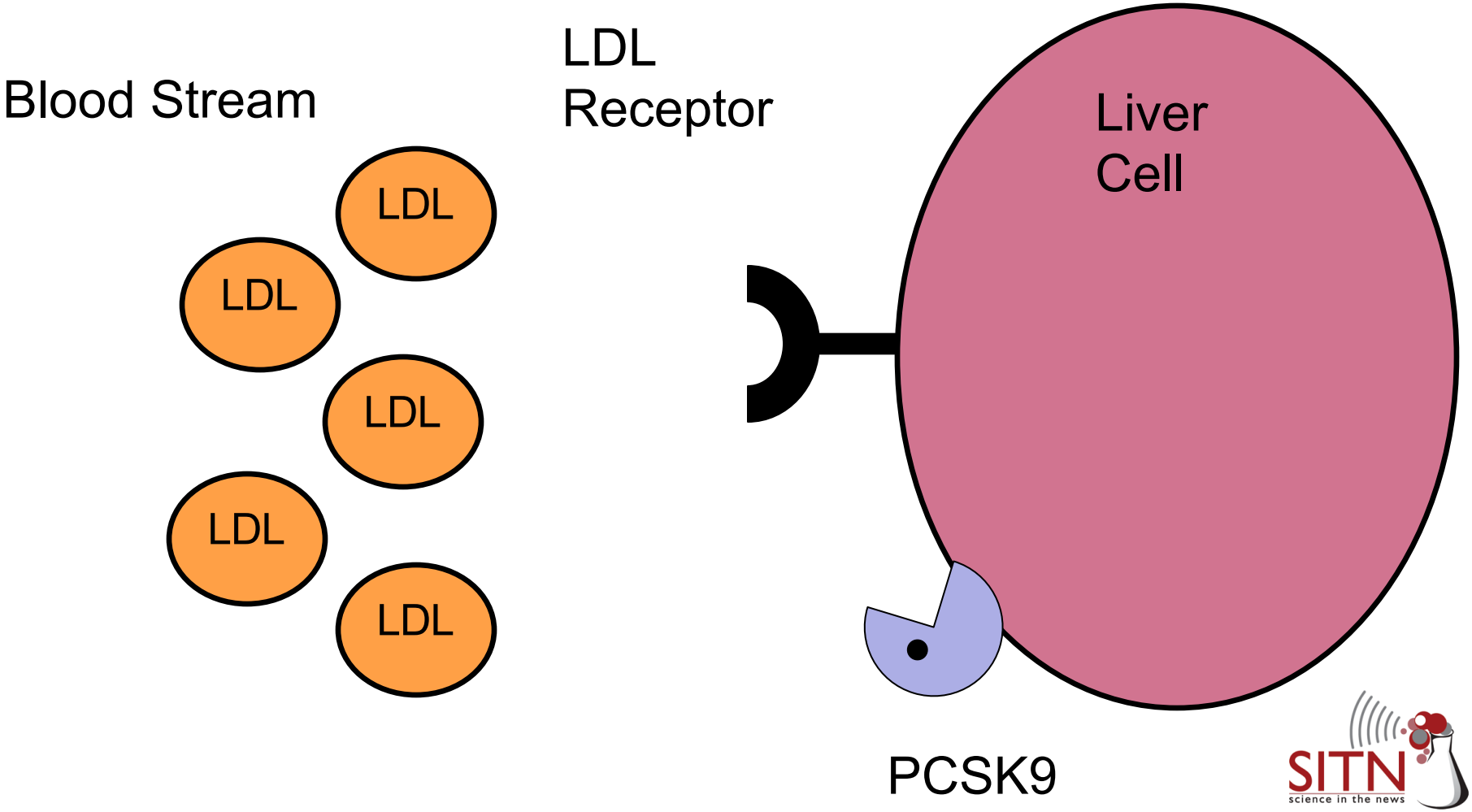
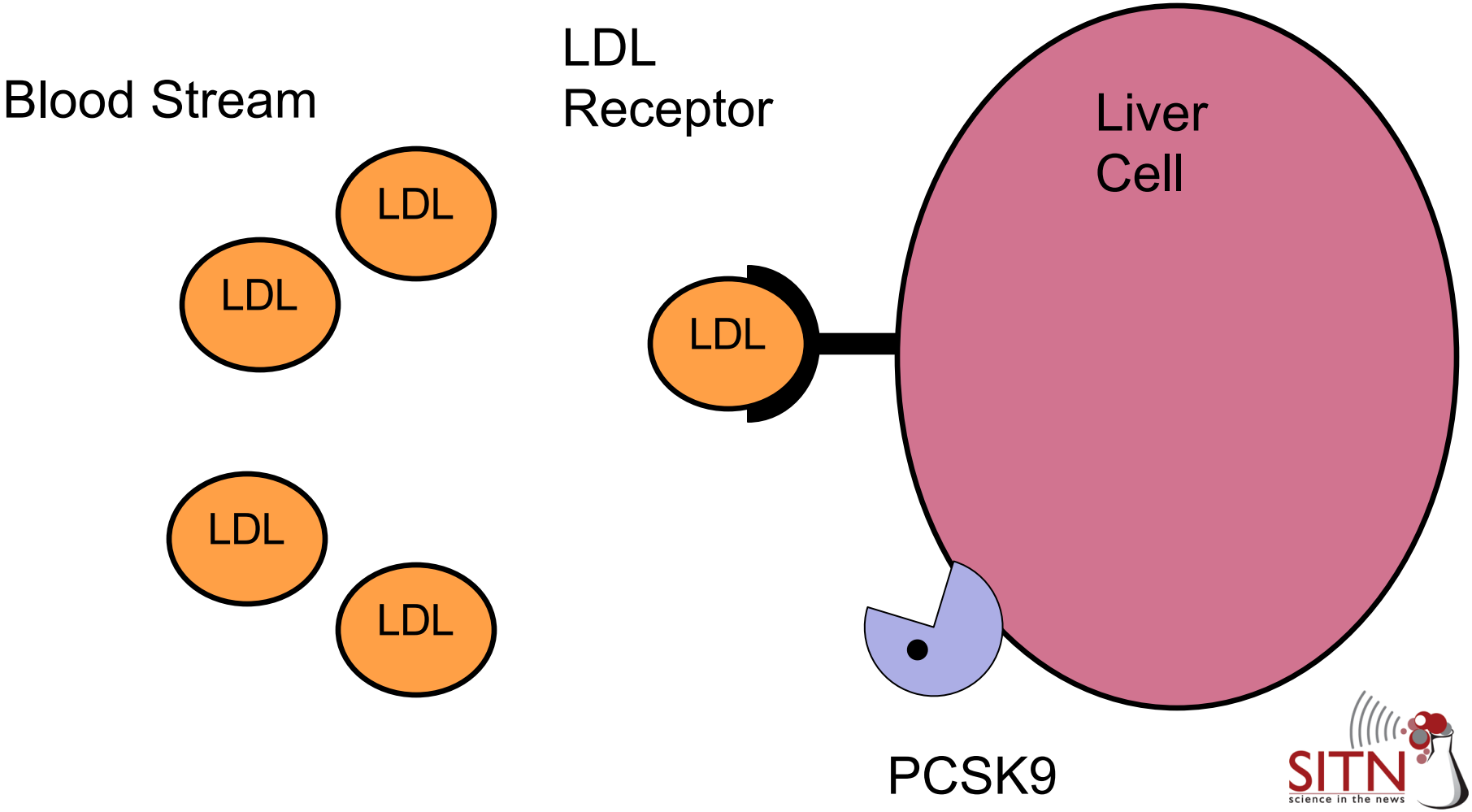


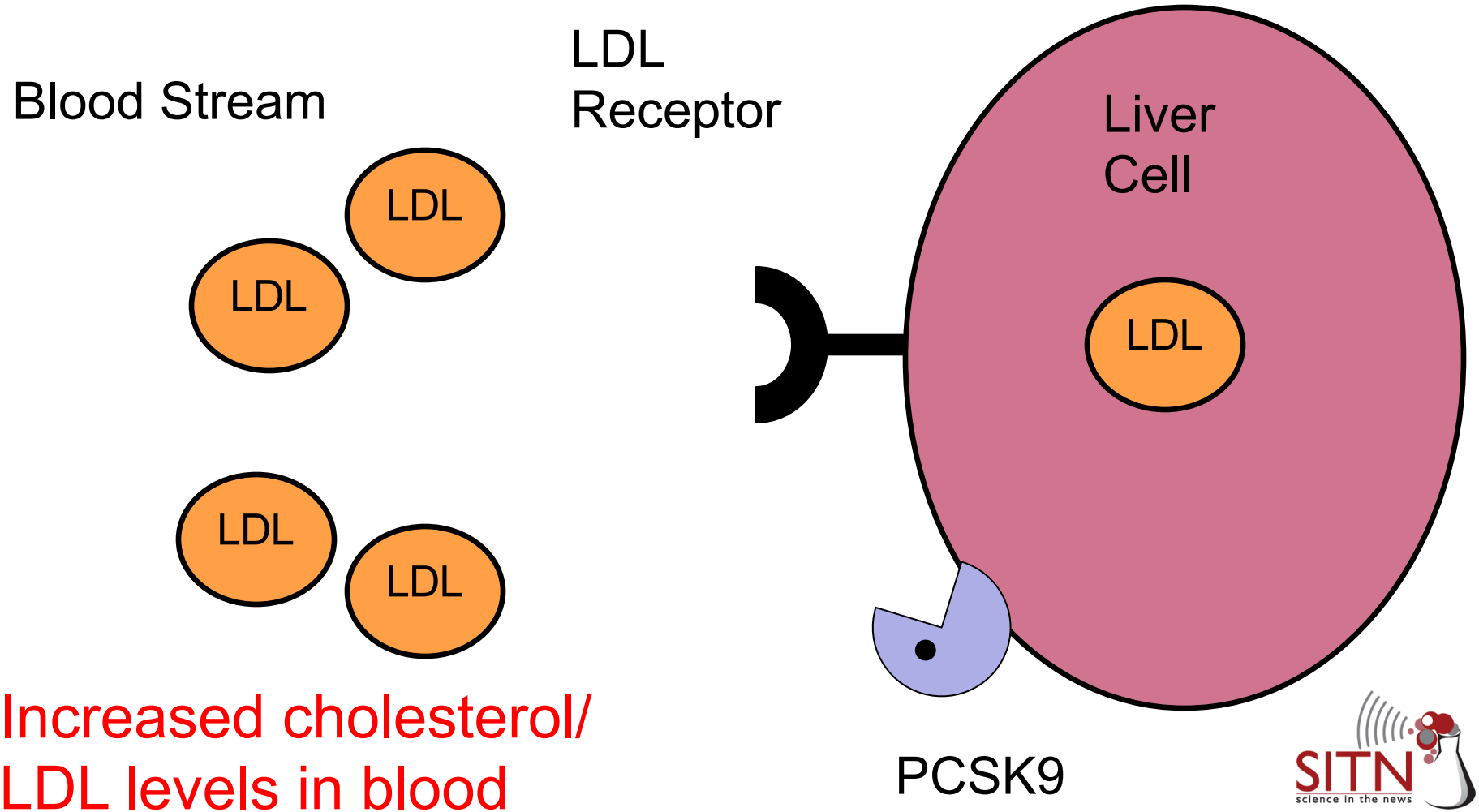
PCSK9 degrades LDL Receptors



Less LDL receptors to bind LDL



Less LDL receptors to bind LDL



Increased cholesterol/
LDL levels in blood

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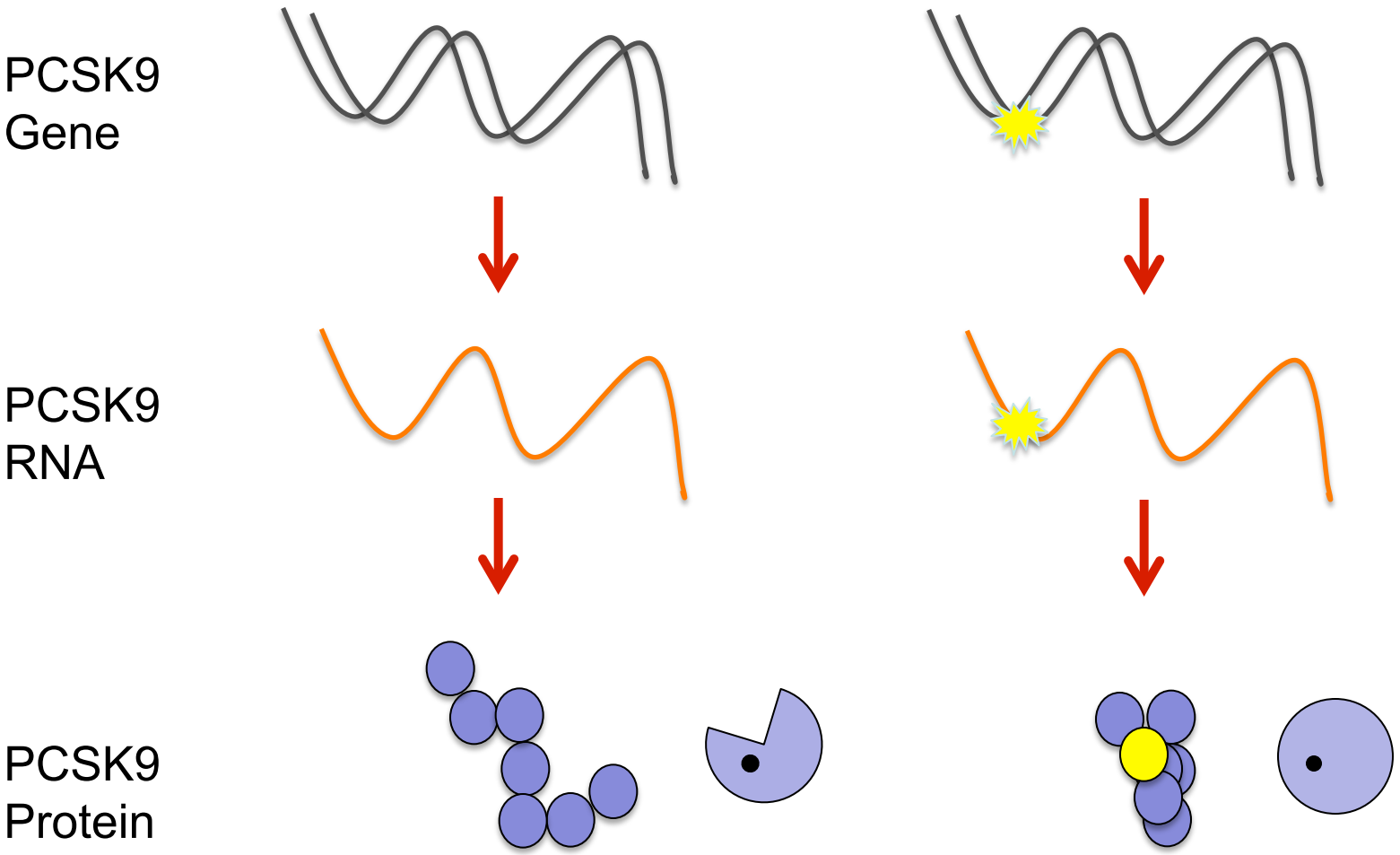
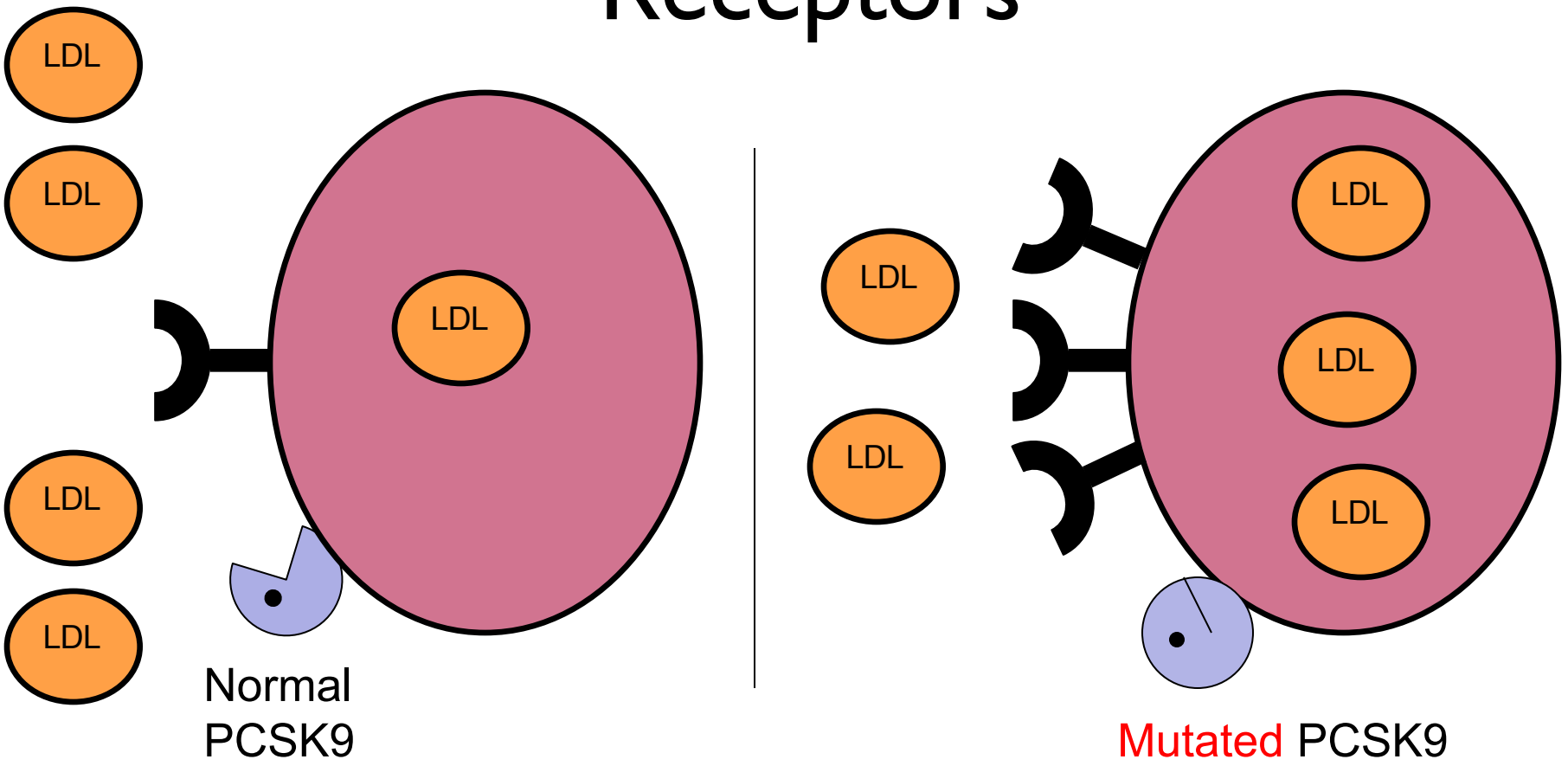
Some people have mutation in PCSK9



PCSK9 mutation leads to more LDL Receptors



LOW Cholesterol/LDL levels in blood!

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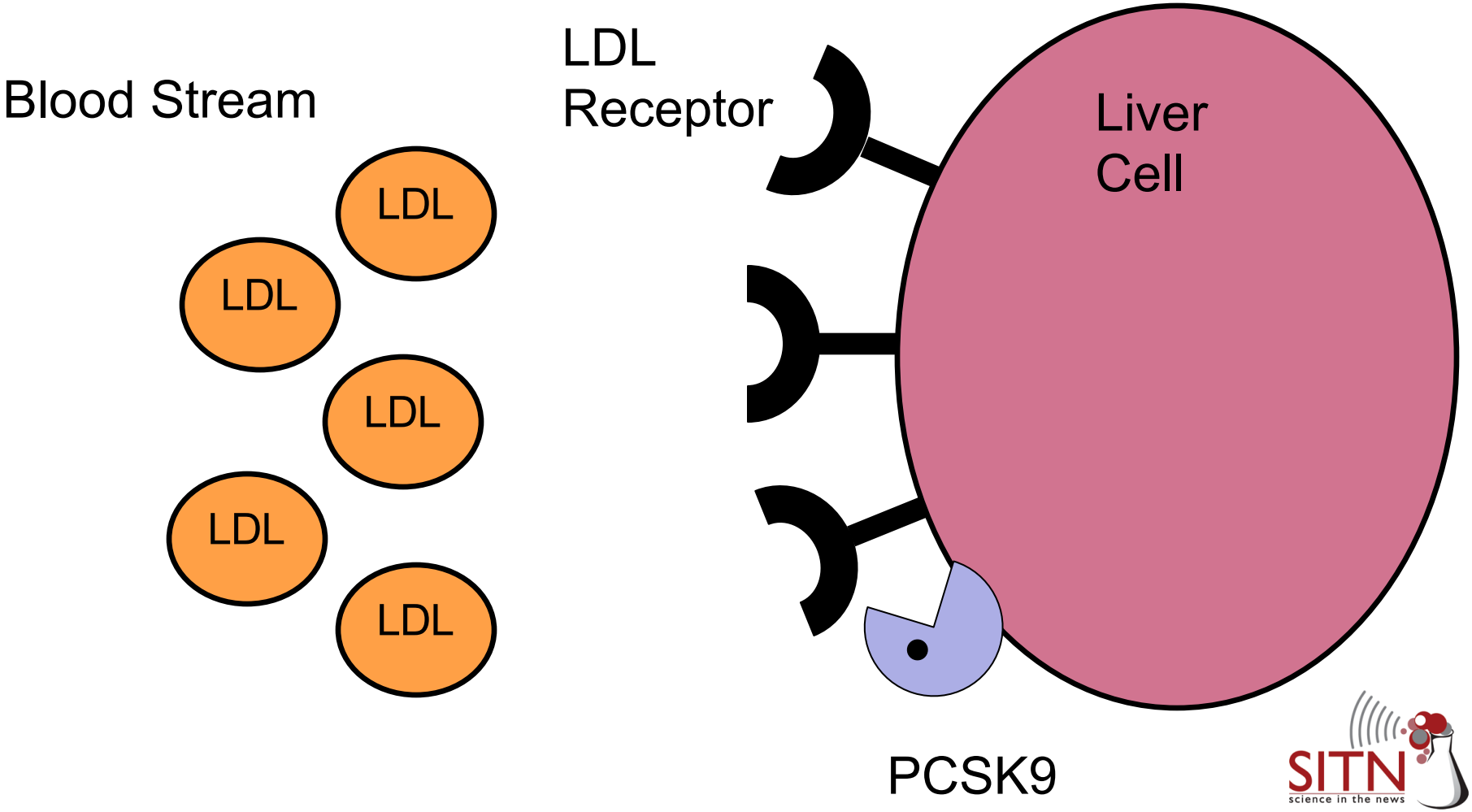
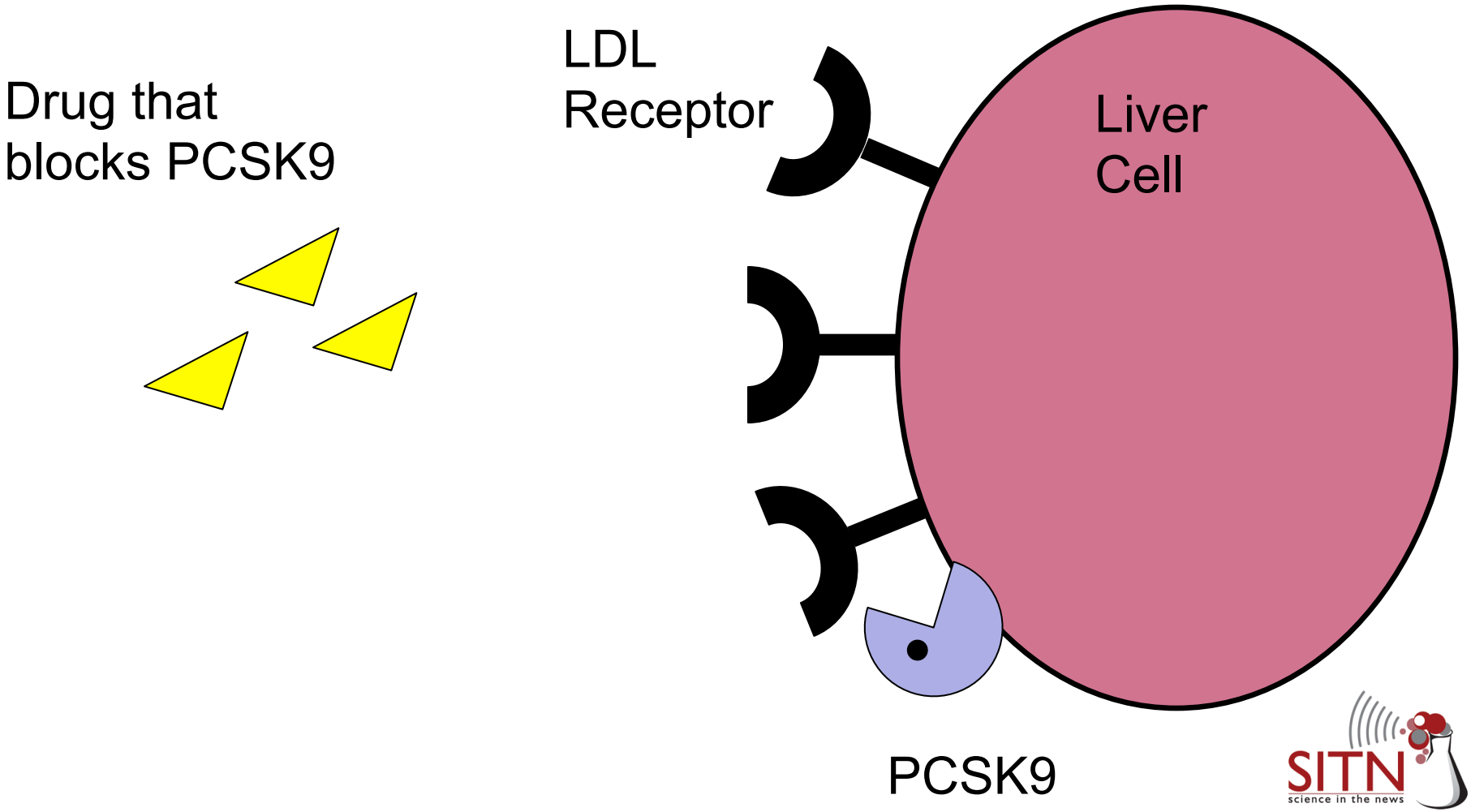
Can we use our knowledge of PCSK9 mechanism?

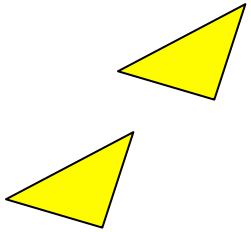


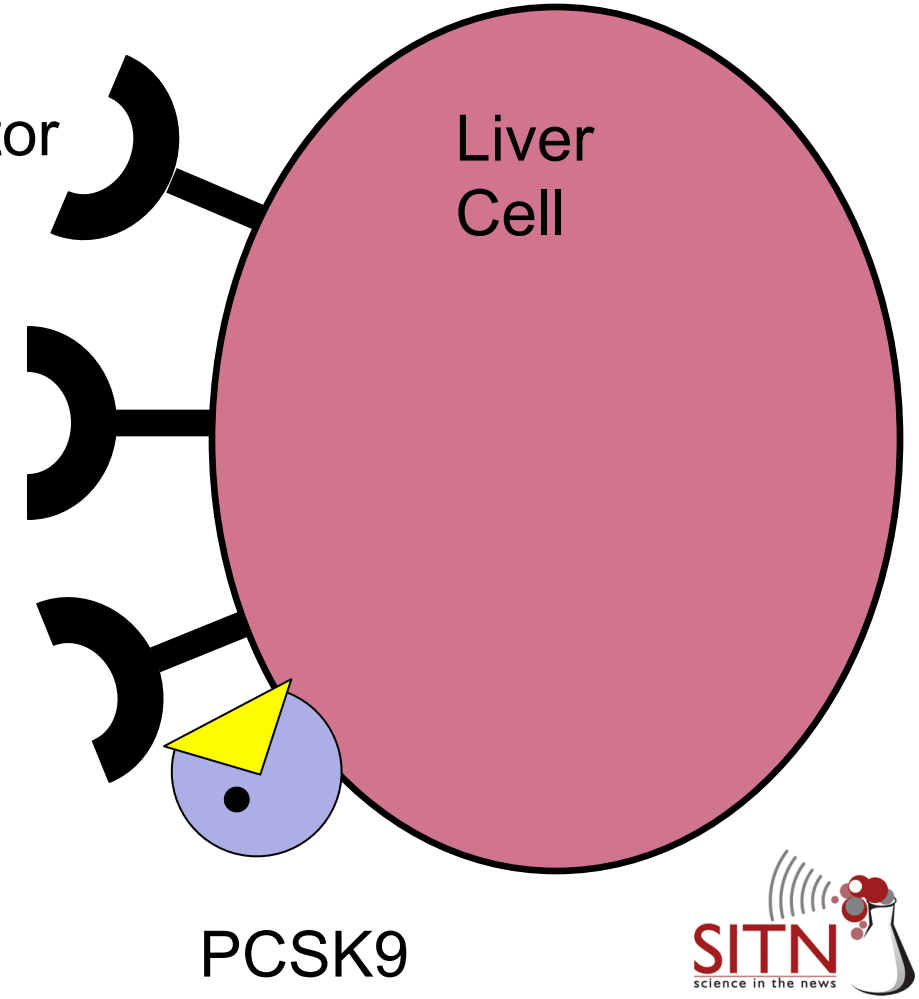
PCSK9 inhibitor



PCSK9 inhibitor

Drug that blocks PCSK9





PCSK9 inhibitor drug mimics PCSK9 mutation

Low LDL/Cholesterol!

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Conclusions

-People have different DNA
-Combination of genes and environment cause disease
-We can find genetic variants that are associated with disease risk
-We can use knowledge of genetics to find new drugs

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QUESTIONS?

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Thank you!

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

Harvard Integrated Life Sciences

HILS

addgene

The nonprofit plasmid repository