HOSPITAL Assuta RAISING HEALTH STANDARDS

Understanding the Biology of Erdheim-Chester Disease

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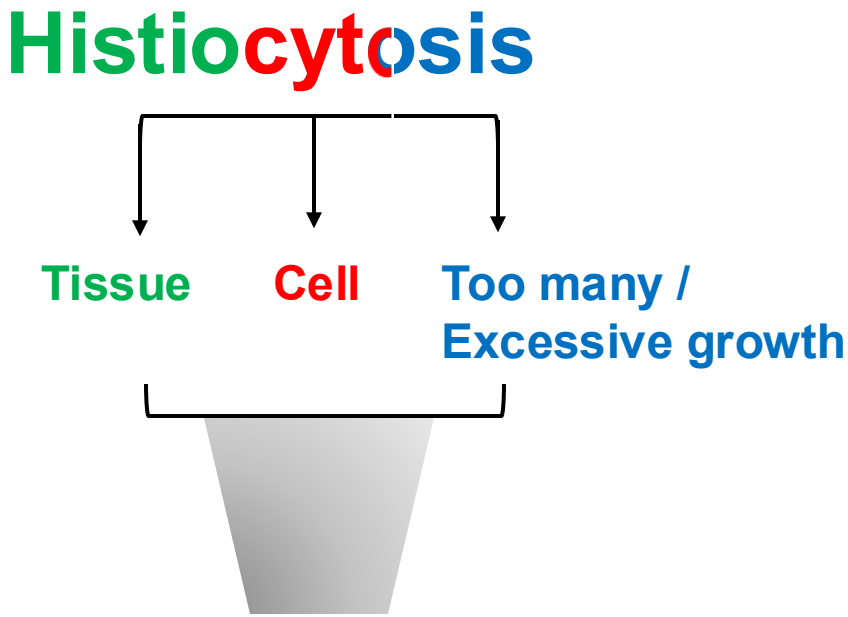
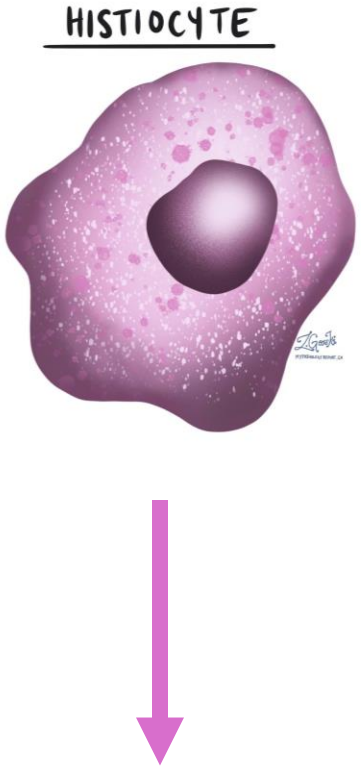
ECD belongs to a group of diseases called histiocytosis

- **Histiocytosis** refers to a condition involving **histiocytes**, a type of **immune cell**
- The word comes from Greek origins:



Histiocytosis refers to an abnormal buildup of histiocytes (immune cells) in tissues



These cells normally help fight infections and clean up waste. But when they build up too much, they can damage healthy organs

Think of histiocytes like janitors in a school 🏫 normally, they clean up and keep everything running smoothly.

<u>But in histiocytosis:</u>

- The janitors don’t stop working 🧹
- Instead of removing trash, they pile it up in hallways 🚧
- Over time, this clogs the school, making it hard to function

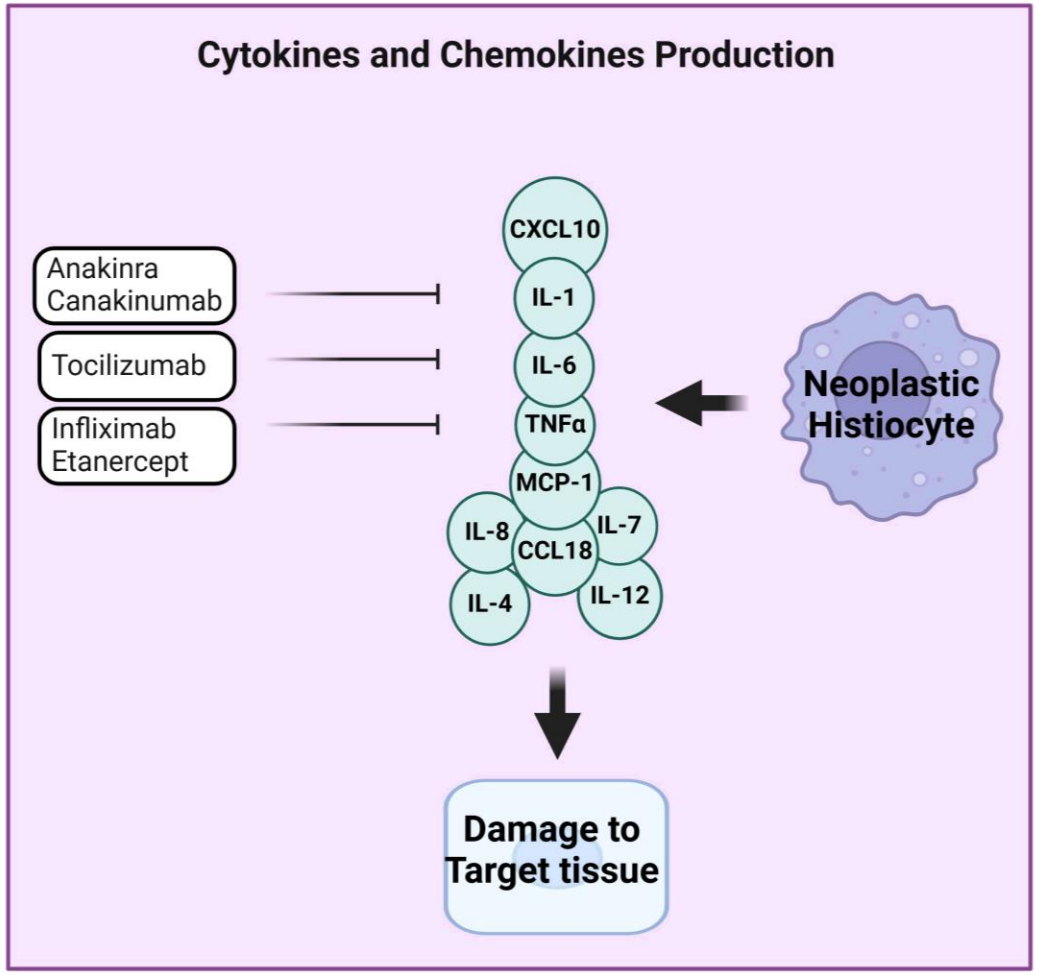
Meaning: Histiocytosis occurs when histiocytes [immune cells] proliferate and accumulate where they shouldn’t, leading to inflammation and tissue damage

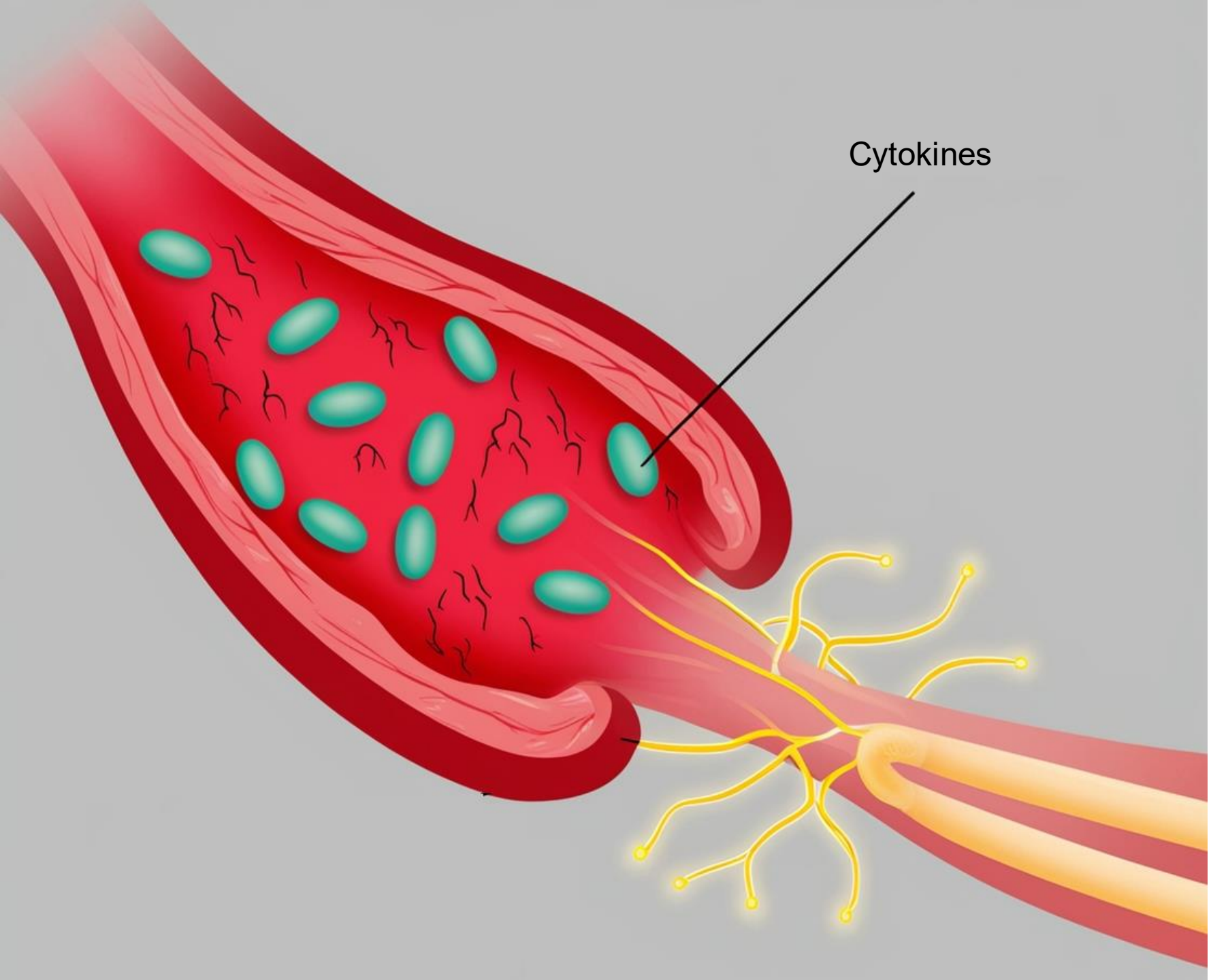
Over expression of cytokines and chemokines leads to chronic inflammation

The accumulated histiocytes in the tissue release **cytokines and chemokines** – small proteins the body uses to “send messages” to recruit more immune cells into the tissue.

Since the histocytes release too many of these messages (cytokines) it leads to chronic inflammation and damage of healthy tissues.

Before targeted treatments were discovered, the main way to reduce inflammation was using drugs that block cytokines.



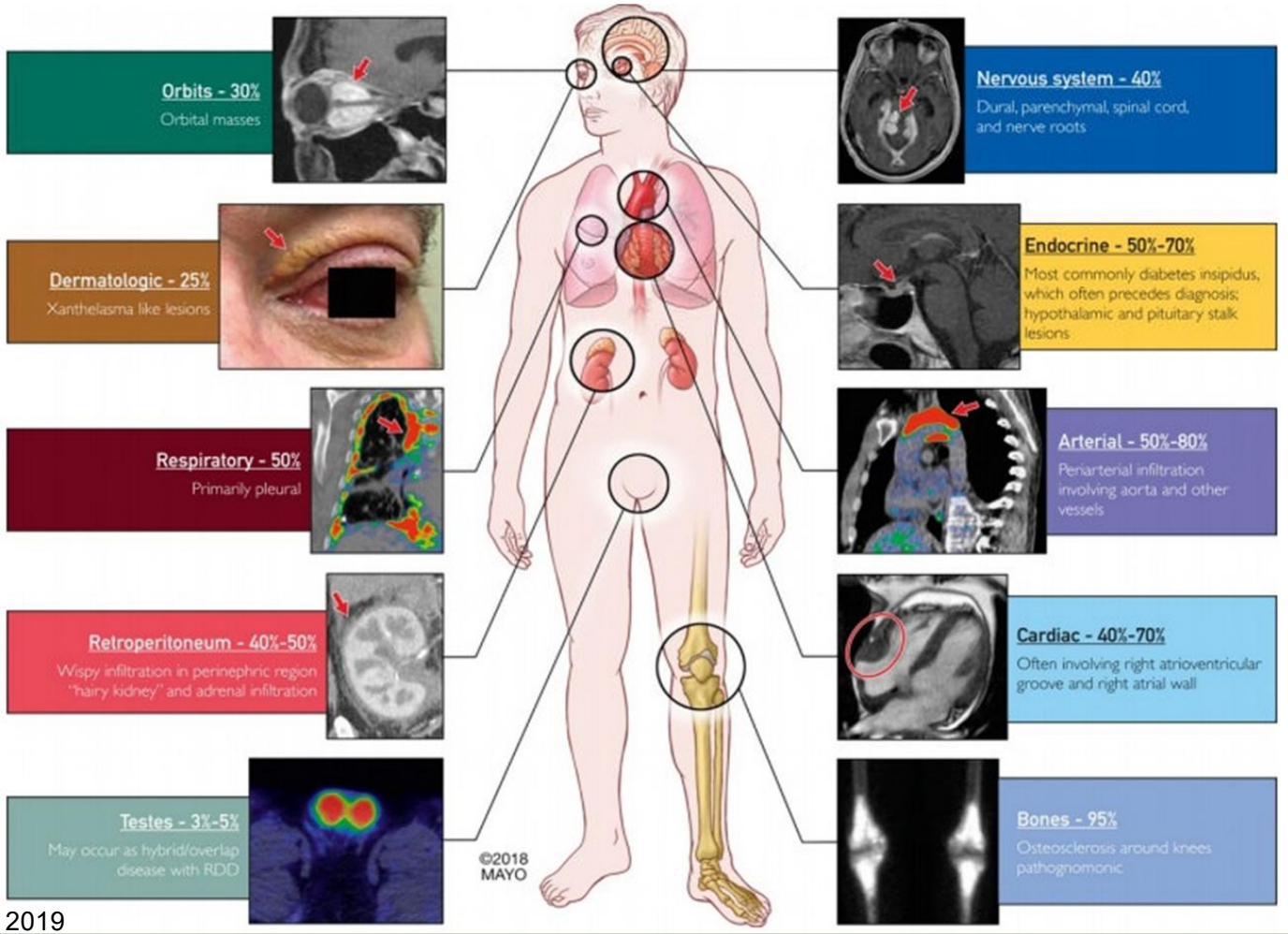


- Chronic inflammation due to excessive cytokine release can cause **pain**
- This is usually the first symptom that leads patients to see a doctor

Erdheim-Chester Disease (ECD)

In ECD, histiocytes accumulate in various organs - including the bones, heart, lungs, kidneys, and brain.

This infiltration disrupts normal organ function and causes chronic inflammation and pain



Mayo Clinic proceeding, 2019

Types of Research

To understand disease biology, we need research

Basic Research

Investigating the biological mechanisms of the disease

- Studies in animal models, cells, and tissues (laboratory models of the disease)
- Genetic testing & Molecular analyses (DNA, RNA, Protein)

Clinical Trials

Evaluating new drugs on patients

- These studies are based on laboratory research
- The goal is to evaluate potential side effects of new drugs, as well as how effective they are

Data Research

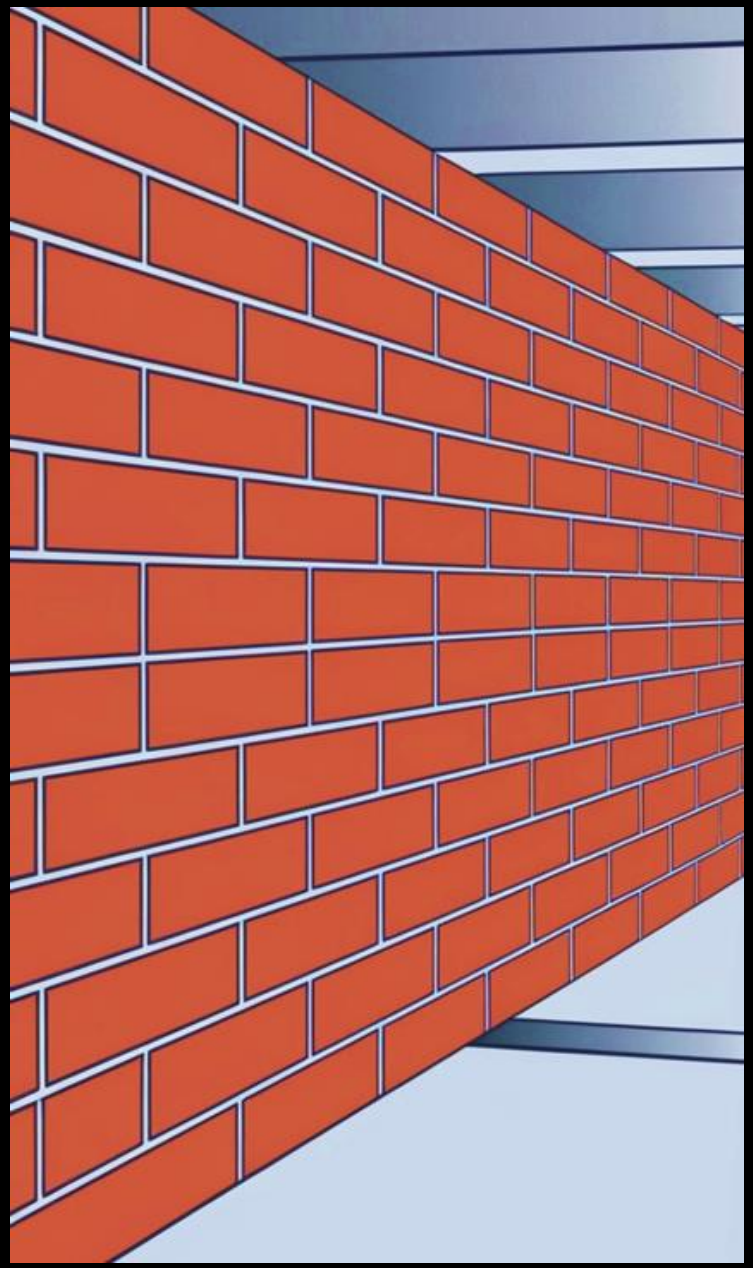
Collecting Data for Clinical Insights

- Using medical records and registries
- Analyzing the collected data to improve outcomes

Research lab - a bridge connecting the basic science to the clinical practice

Discoveries start in the laboratory setting are developed into potential treatments and reach ECD patients in clinical practice

Just as a building is made of bricks



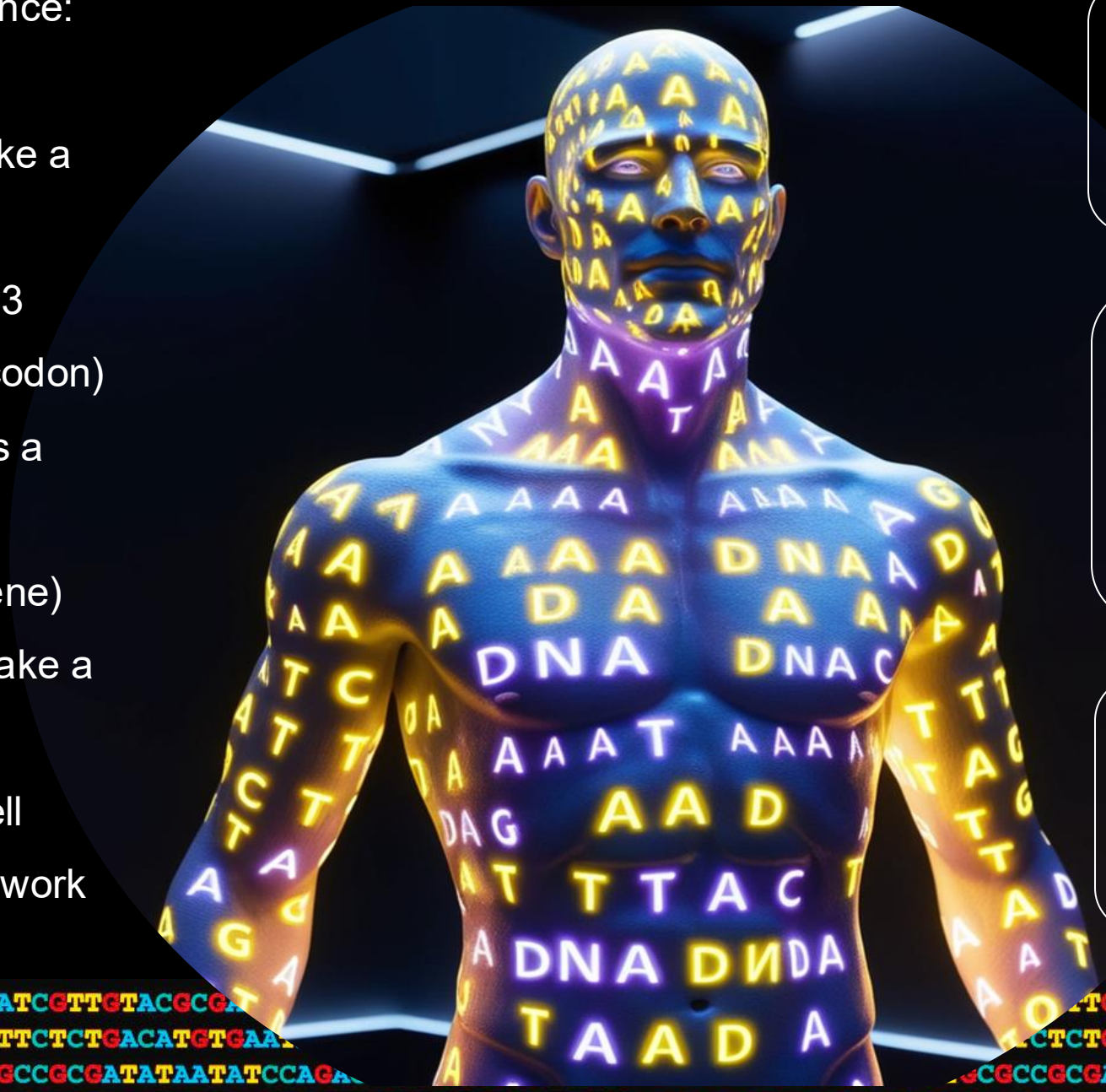
The human body is made of cells

Inside each of the cells in our body there is genetic material – DNA

Contains the complete instructions needed to create a healthy human

DNA is a very long sequence:

- consists of four letters: **A**, **T**, **C**, and **G** - just like a language
- In this language every 3 letters form a “word” (codon)
- A group of words forms a "sentence” (a gene)
- The "sentence” (the gene) gives instructions to make a protein
- Proteins instruct the cell what to do and how to work properly



Today, in the lab, we can read our entire DNA from beginning to end

Changes in one of the letters in a significant region of the DNA can lead to diseases

These changes are what we call in the scientific language "**mutations**”

What is a Mutation?

1 Definition

A small change in a significant region of our genetic code (the DNA), like **a typo** replacing a letter in a word changing the meaning entirely

2 Examples:

English

Book → **C**ook

Spanish

Perro → **C**erro

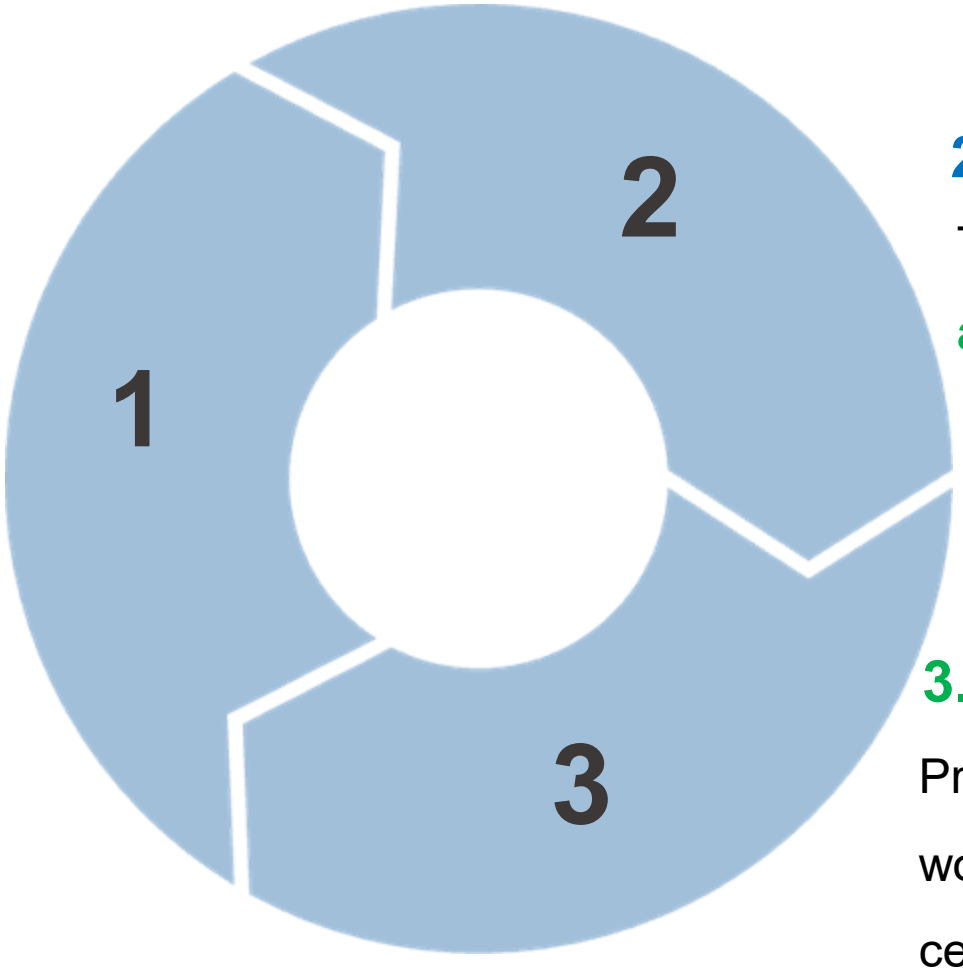
That's just one letter - but it turns into a completely different word with a different meaning

3 Biological Impact

a change in the DNA sequence can impact a biological mechanism because now the sequence is no longer understood correctly

How does a mutation affect a biological mechanism?

A normal transfer of information - inside the cell



1. DNA

A unit of information from our DNA is converted into a molecule called **RNA**

[DNA - Contains genetic instructions]

2. RNA (gene)

Then, RNA is used to make **a protein**

3. Protein

Proteins are what actually do the work in our cells. They control how cells grow, divide, and function

When a mutation occurs in the DNA, it disrupts this flow.

This can impact biological pathways, such as those controlling cell division

How mutation changed ECD treatment?

For many years,
ECD was a medical mystery

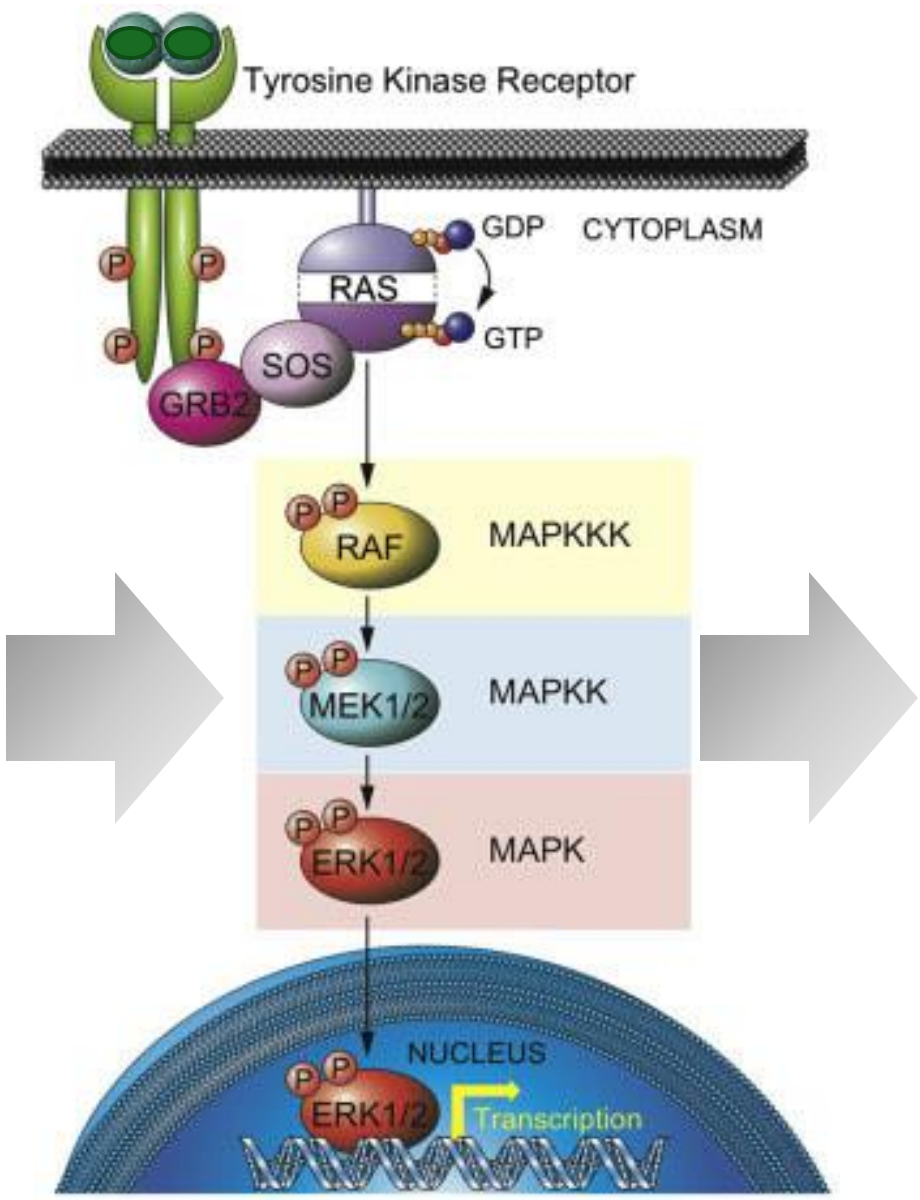
Physicians saw patients with abnormal immune cell growth, but they didn't fully understand why it happened or how to treat it effectively

That changed dramatically when researchers discovered that many patients with ECD have **a mutation** in a gene called **BRAF** [specifically, **BRAF V600E**]

This mutation leads to activation of a biological pathway called **MAPK pathway**, leading to abnormal cell growth

Mutations driving disease progression by activation of MAPK pathway

In fact, researchers have found additional mutations in genes that activate **the MAPK pathway** (MAP2K1, RAS and others)



When we have a mutation in these genes it leads to abnormal cell growth. These cells release **cytokines** that trigger **chronic inflammation** - and this combination is what truly **drives disease progression**

Conclusion from basic science research

Mutations in the MAPK pathway drive disease progression !

What can we do in the clinical practice ?

From basic research to the clinical practice

Based on these laboratory findings, clinical trials were initiated in patients - first with BRAF (VE-BASKET), and later with MEK inhibitors

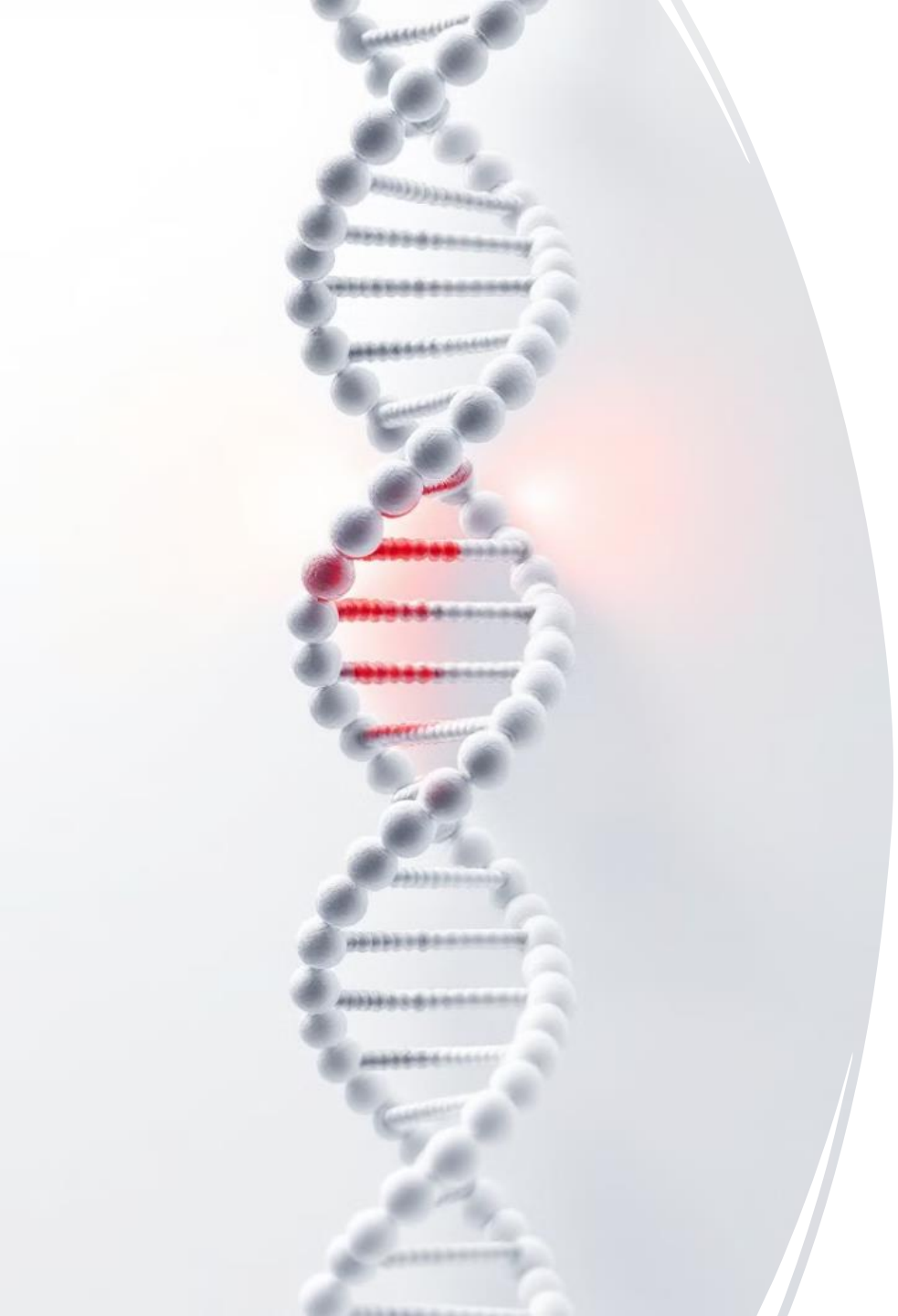
These treatments aim to block the MAPK pathway - activated by the mutation, helping to reduce inflammation and slow disease progression

These studies led to FDA approval of BRAF and MEK inhibitors for the treatment of ECD

Clinical Trials in Histiocytic Neoplasms

New clinical trials testing new biological drugs based on different mutations - are ongoing in multiple sites - reports are pending…

Clinical Trials Treatments	Institutions	Status (End of 2024)
Anakinra or denosumab + everolimus (mTOR inhibitor)	MD Anderson (Houston)	Completed
DCC-2618 (c-Kit inhibitor)	Multiple	Completed
Ulixertinib or BVD-523 (ERK inhibitor)	Multiple	Completed
Selinexor + choline salicylate	Mayo Clinic, MN	Recruiting
Virotherapy	Mayo Clinic, MN	Recruiting
CSF1R inhibitor	Mayo Clinic, MN	Not recruiting
PLX8394 (BRAF inhibitor)	Multiple (11 sites)	Active, not recruiting
HH2710 (ERK1/2 inhibitor)	Multiple	Terminated
Lenalidomide (immunomodulatory agent)	Dana Farber (Boston)	Active, not recruiting
HLX208 (BRAF inhibitor)	China	Recruiting
Cobimetinib	NACHO (Baltimore, Dallas, DC, Houston, Madison, Memphis, Orange)	Recruiting
Dabrafenib (BRAF inhibitor) or trametinib (MEK inhibitor)	National Institute of Health (Bethesda)	Completed
Nivolumab (PD1 antibody)	Multiple (52 sites)	Completed
LY3023414, selumetinib, ensartinib, olaparib, palbociclib, ulixertinib, selpercatinib	Children's Oncology Group: Pediatric MATCH trial; multiple US sites	Recruiting
Ulixertinib	Memorial Sloan Kettering	Recruiting
Vemurafenib and cobimetinib	Multiple (UK)	Recruiting



In recent years -

Beyond DNA mutation,

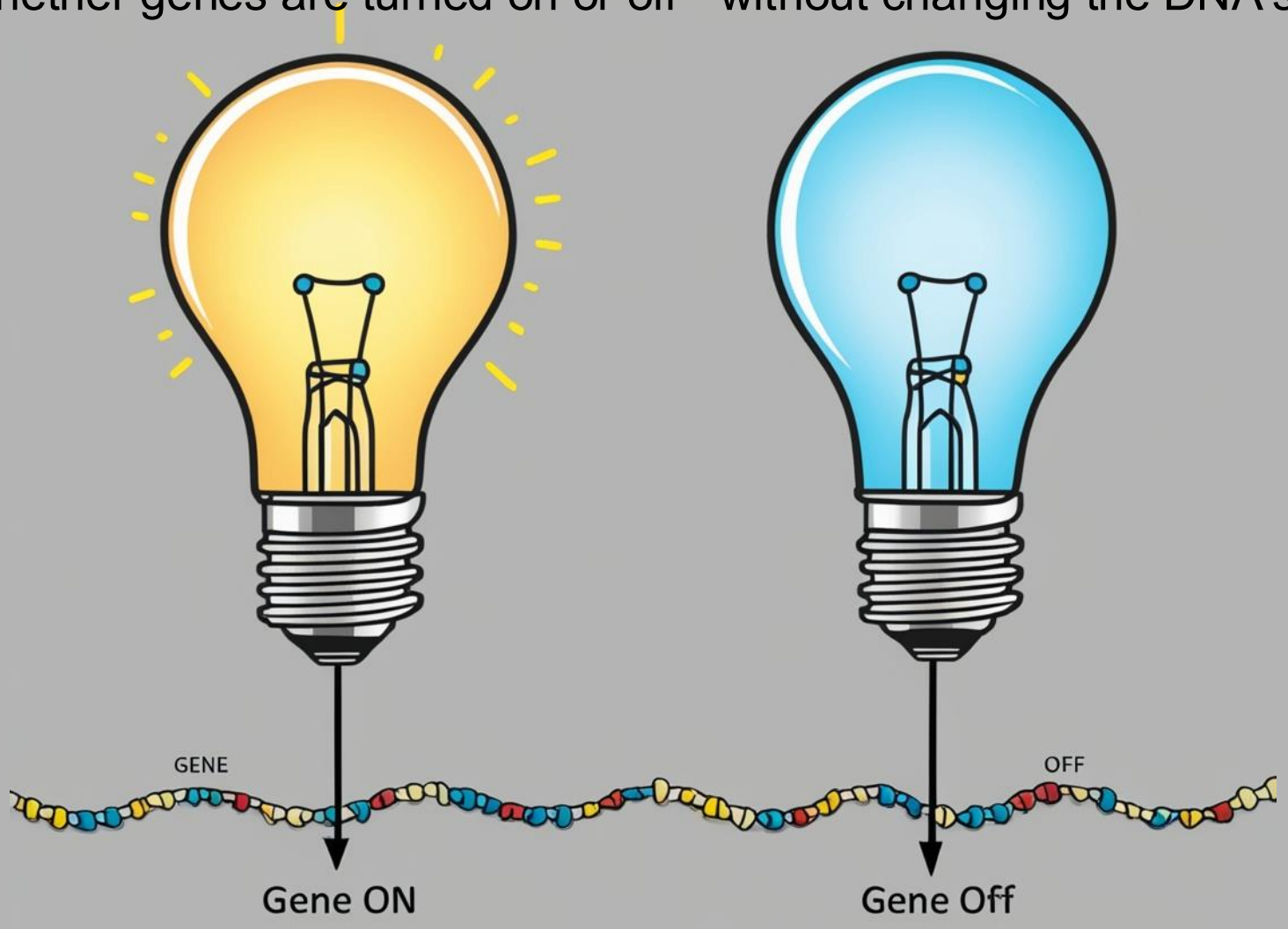
some progress has been

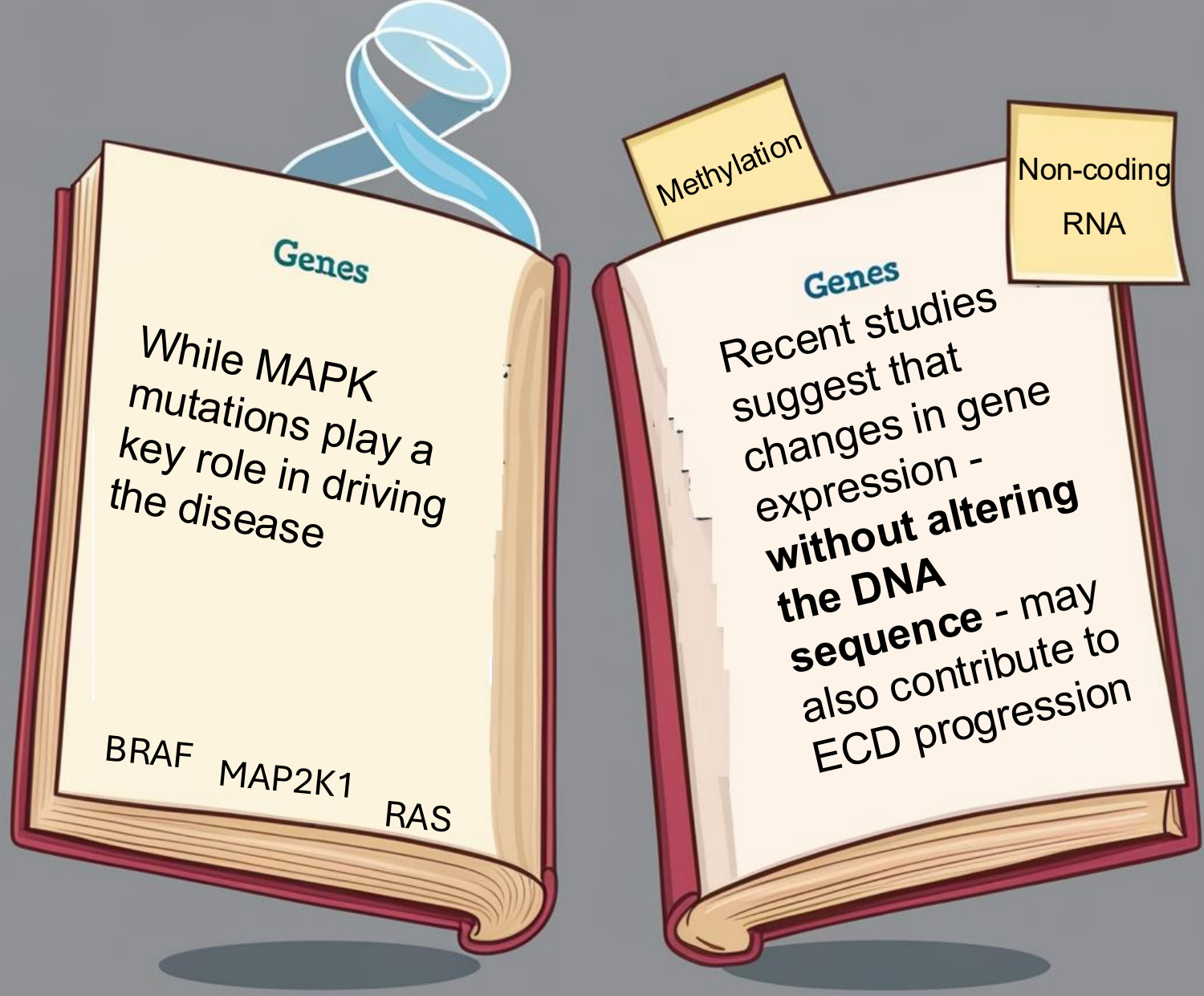
made in a field called

Epigenetics

Epigenetics

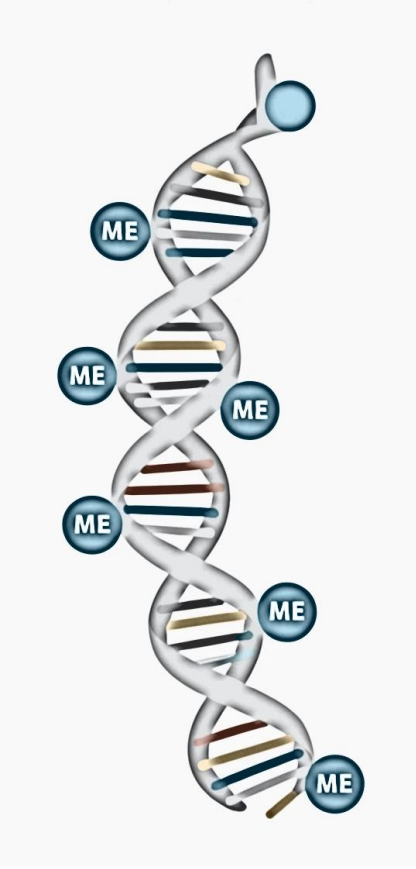
Controls whether genes are turned on or off - without changing the DNA sequence





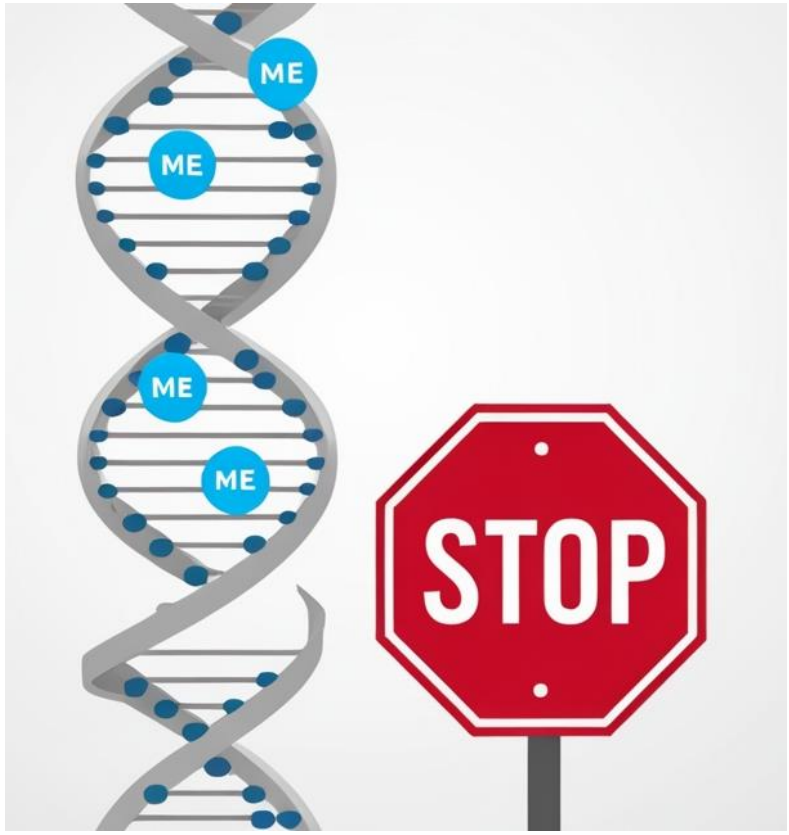
Genetic mutation **Epigenetic regulation**

Epigenetics - influence gene expression without altering the DNA sequence



For example:

Addition of a chemical group (methyl) on top of the DNA – called DNA methylation can determine either a certain gene will be expressed or shut down



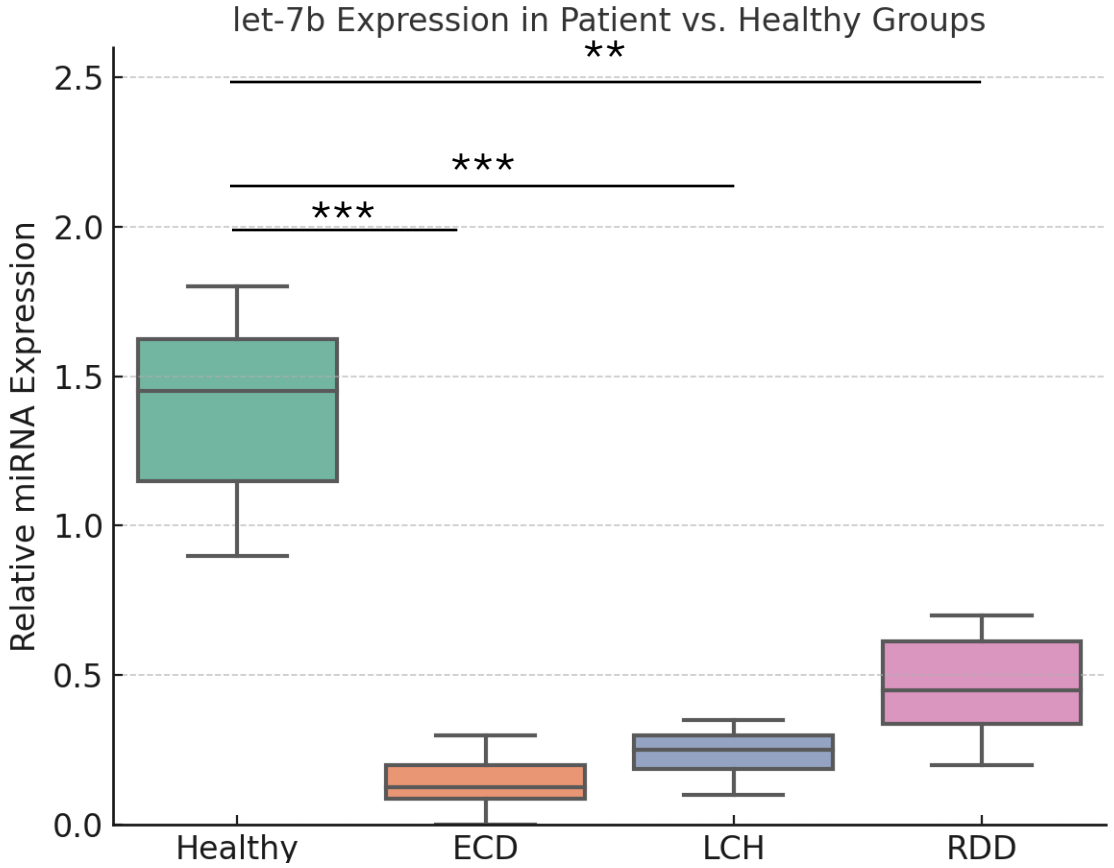
When we have the methyl group (DNA methylation) on top of the DNA the gene will be **NOT** be expressed (like a stop sign)

We found that a specific gene named **MIRLET7B** is methylated in patients with histiocytosis (ECD, LCH and RDD)

Since this gene is methylated (STOP sign) it is not being expressed

Because of that, it does not generate its mature form - a small molecule called let-7b

We found that patients with histiocytic neoplasms have low levels of Let-7b (miRNA) compared with healthy individuals



Healthy (n=10); ECD (n=25), LCH (n=7), RDD (n=8)

MAPK pathway
under control

In normal cells:

- The microRNA let-7b is expressed
- It suppresses key genes in the MAPK pathway, helping keep this pathway under control

leads to MAPK
overactivation

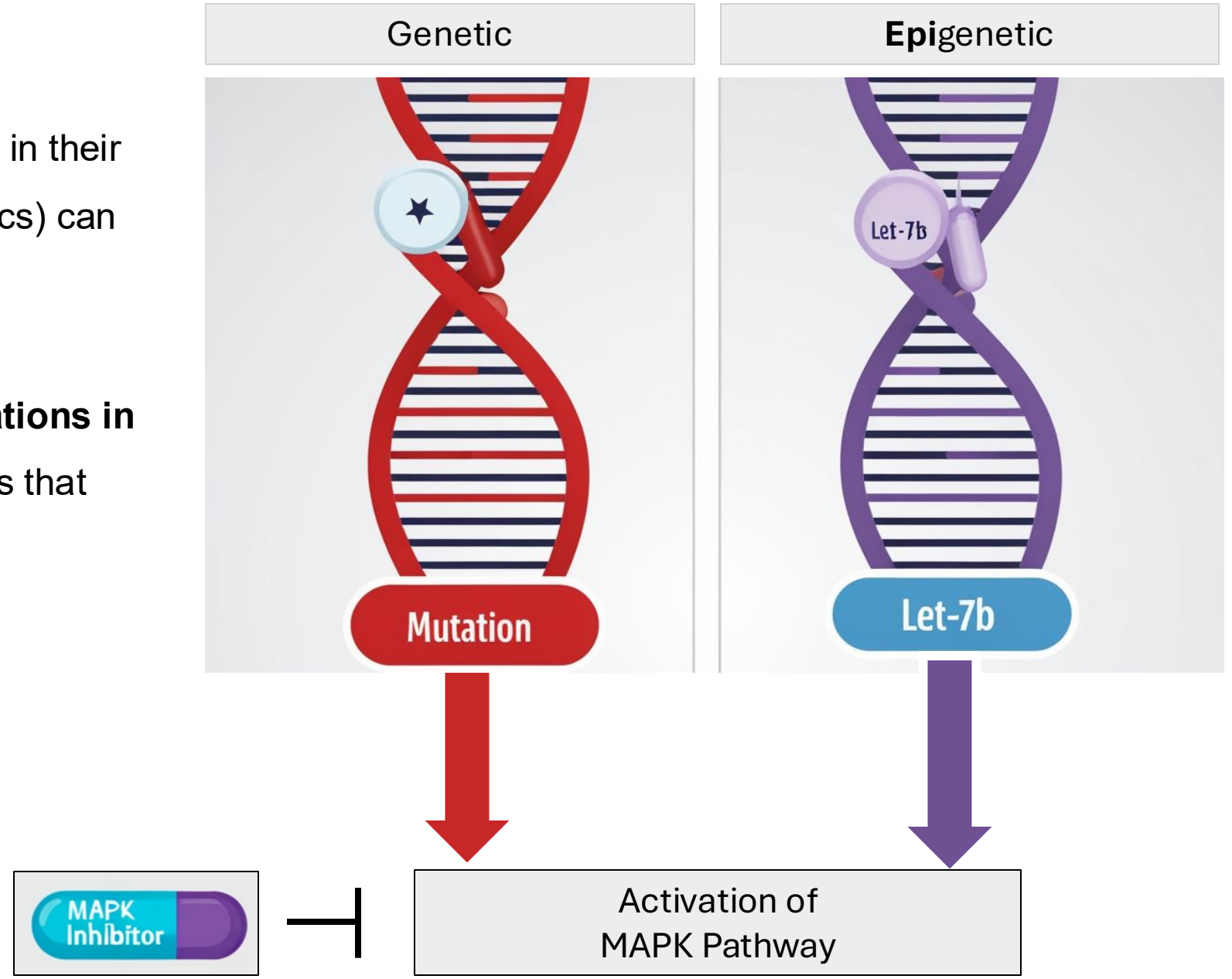
In ECD:

- let-7b is downregulated (reduced expression)
- As a result, it can no longer suppress the MAPK pathway
- This leads to MAPK overactivation - even in the absence of DNA mutations

Why it is important?

- Even if a patient doesn't have a mutation in their DNA, changes in gene activity (epigenetics) can still turn the MAPK pathway "on"

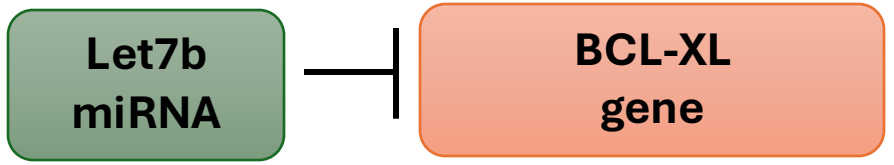
- This means some patients **without mutations in their DNA** may still benefit from the drugs that block this pathway



Let-7b controls BCL-XL gene

We also identified that let-7b keeps a gene named BCL-XL under control

BCL-XL is a gene that **helps cells stay alive and grow**

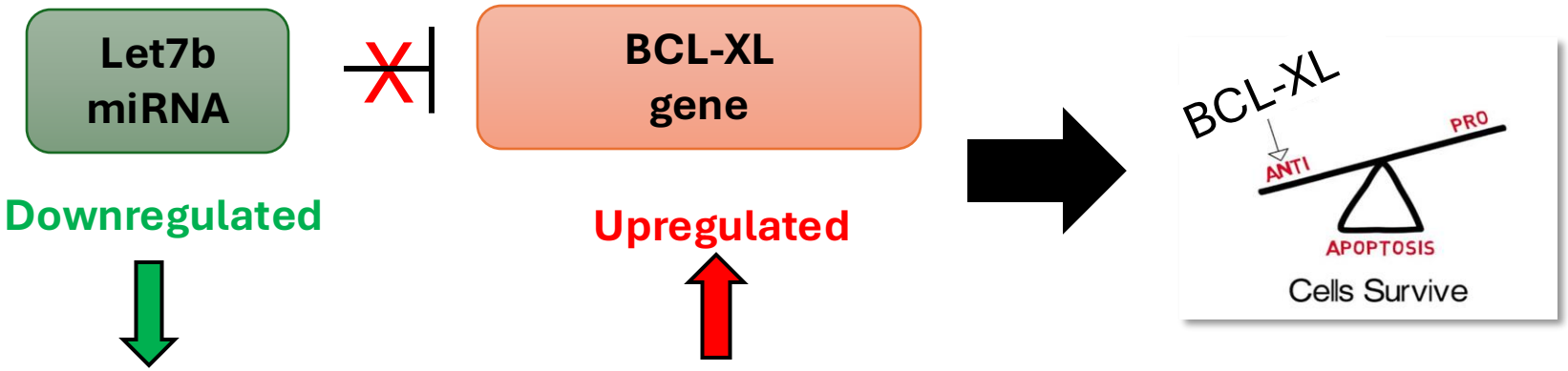


What happen when let-7b is missing?

In patients, let-7b levels are low, so it can't control BCL-XL

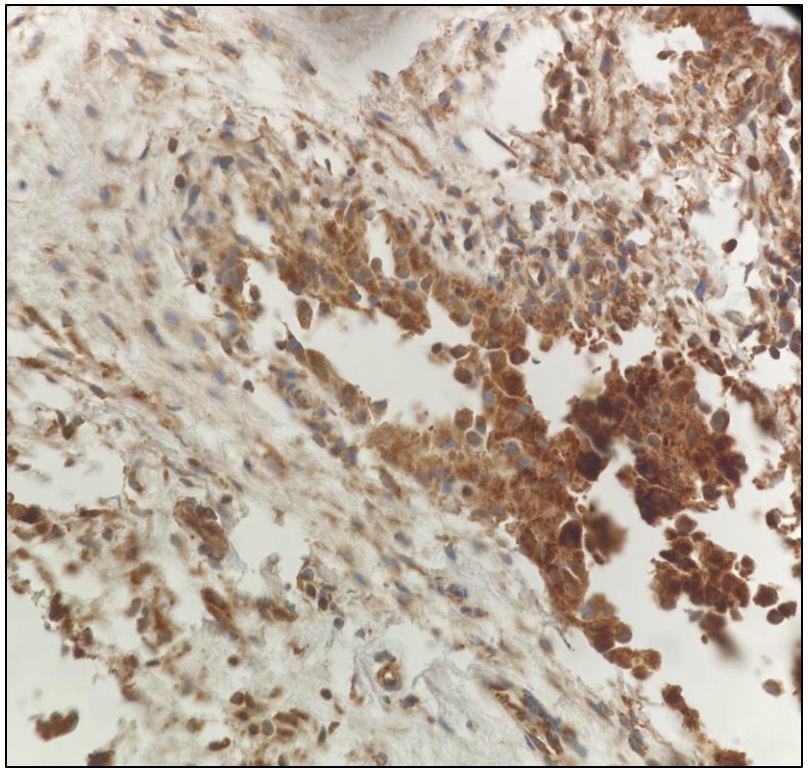
As a result, BCL-XL becomes too active

This may cause **cells to survive,** and **make the disease worse**

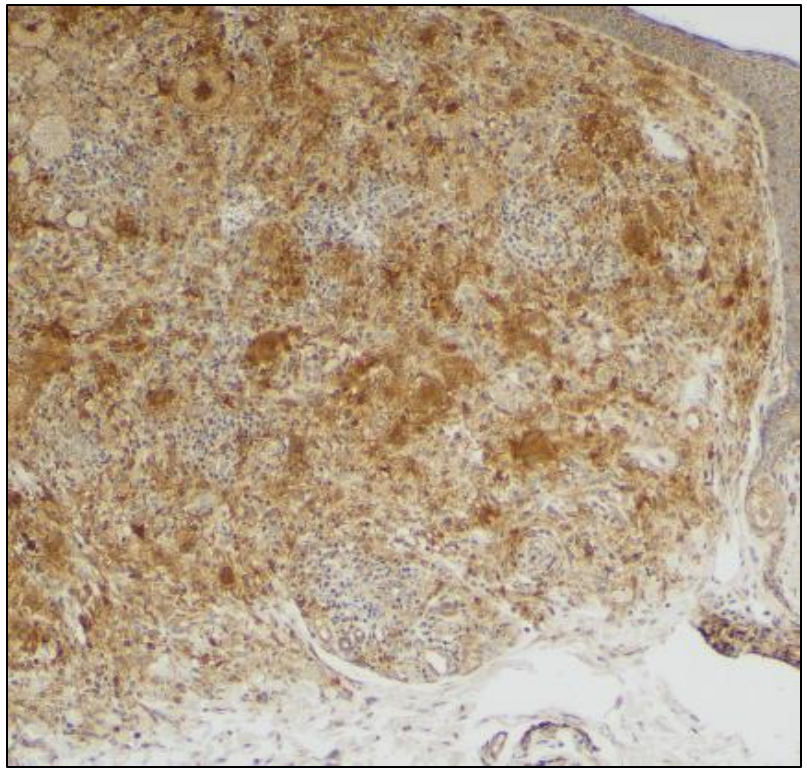


We identified in tissue samples from patient biopsies that **BCL-XL** levels were extremely high in the patients' tissues

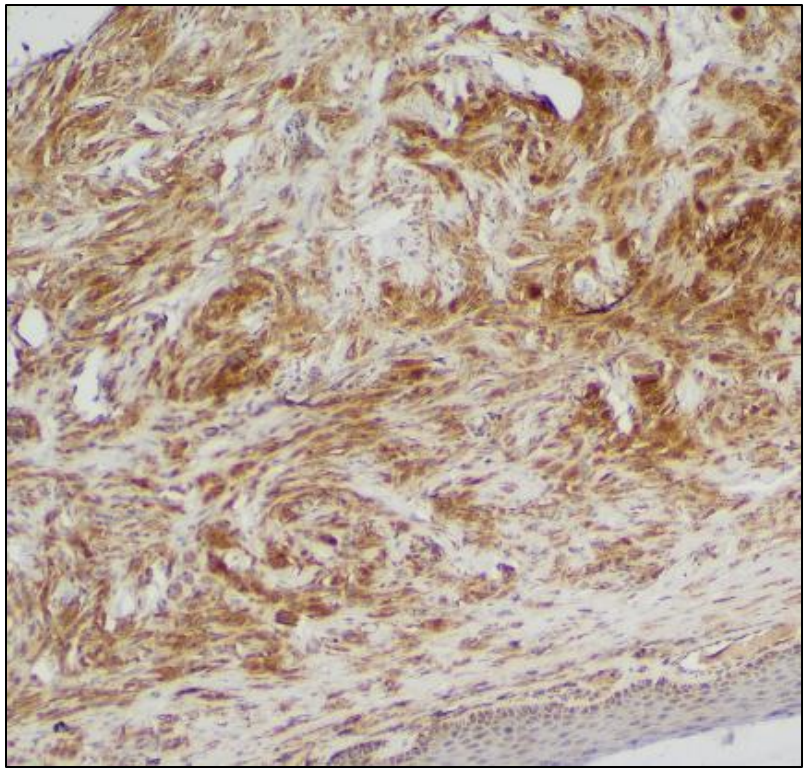
ECD Patient #1_Tissue Biopsy



ECD Patient #2_Tissue Biopsy



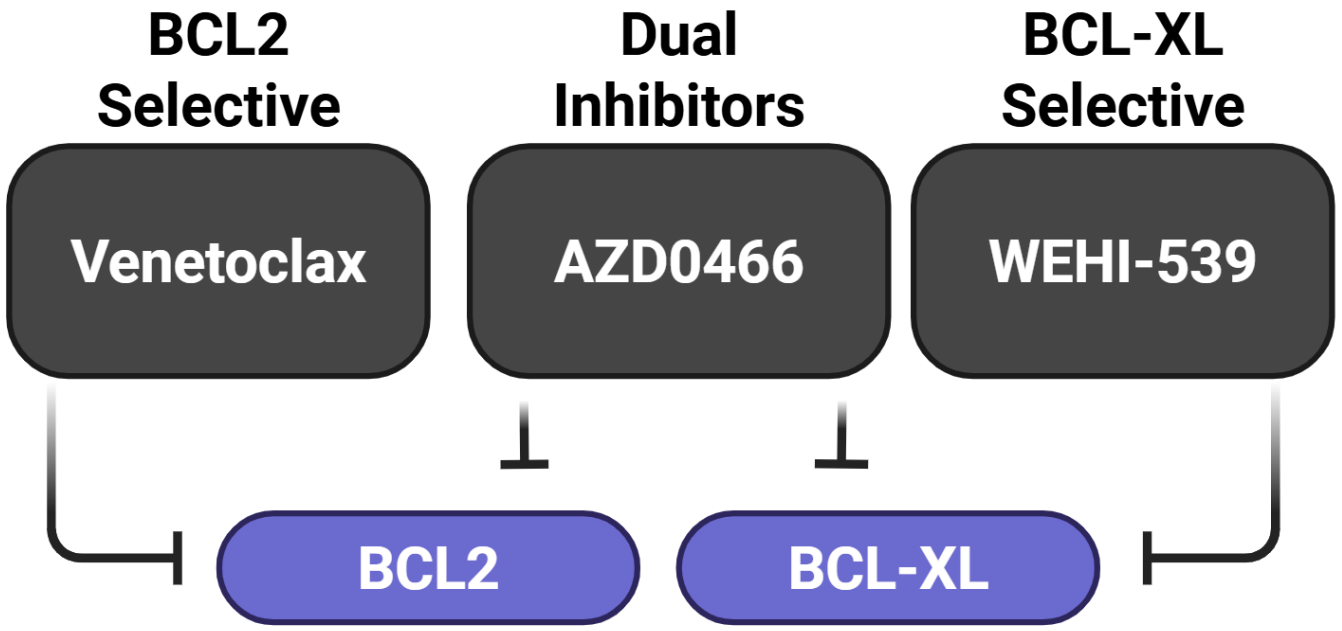
ECD Patient #3_Tissue Biopsy



We also identified another protein, called **BCL2**, that is overexpressed in some patients

BCL-XL/BCL2 Inhibitors

Today, there are BCL2 and BCL-XL inhibitors already in use or in clinical trials



This supports the need for ongoing research into this treatment approach, which may lead to new therapies in the future

Summary

- ECD arises from **abnormal growth of immune cells** called histiocytes, leading to inflammation and tissue damage.
- Genetic **mutations**, mainly in the **MAPK pathway**, drive abnormal cell growth, over production of cytokines and inflammation.
- Understanding these mutations led to **targeted treatments** blocking this pathway.
- **Other treatment** are currently under clinical investigation.
- ECD is characterized by a complex network of **genetics and epigenetics** mechanisms. Some are already targetable, some will be in the future.

Thank you for listening

Quotations ?