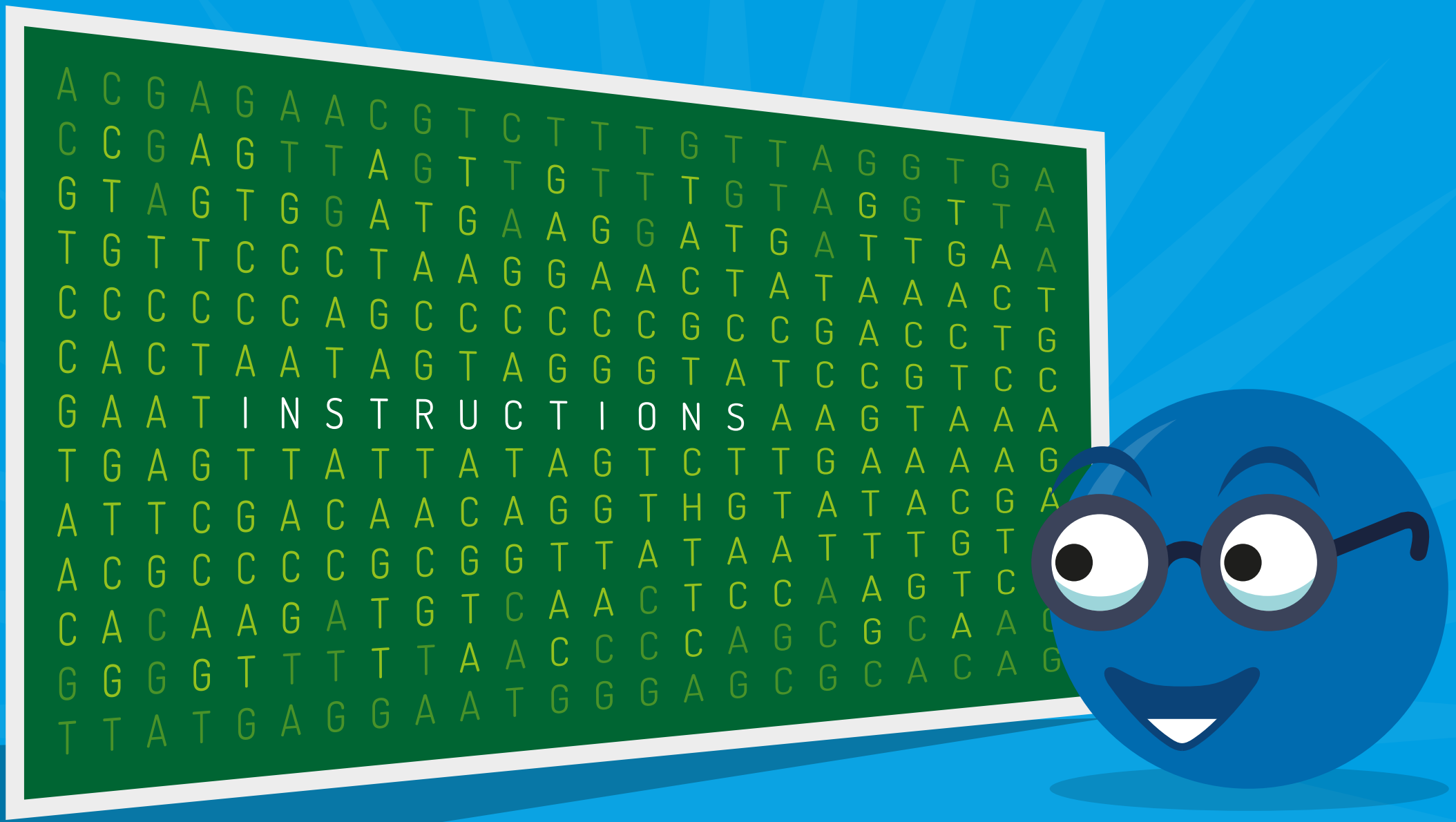
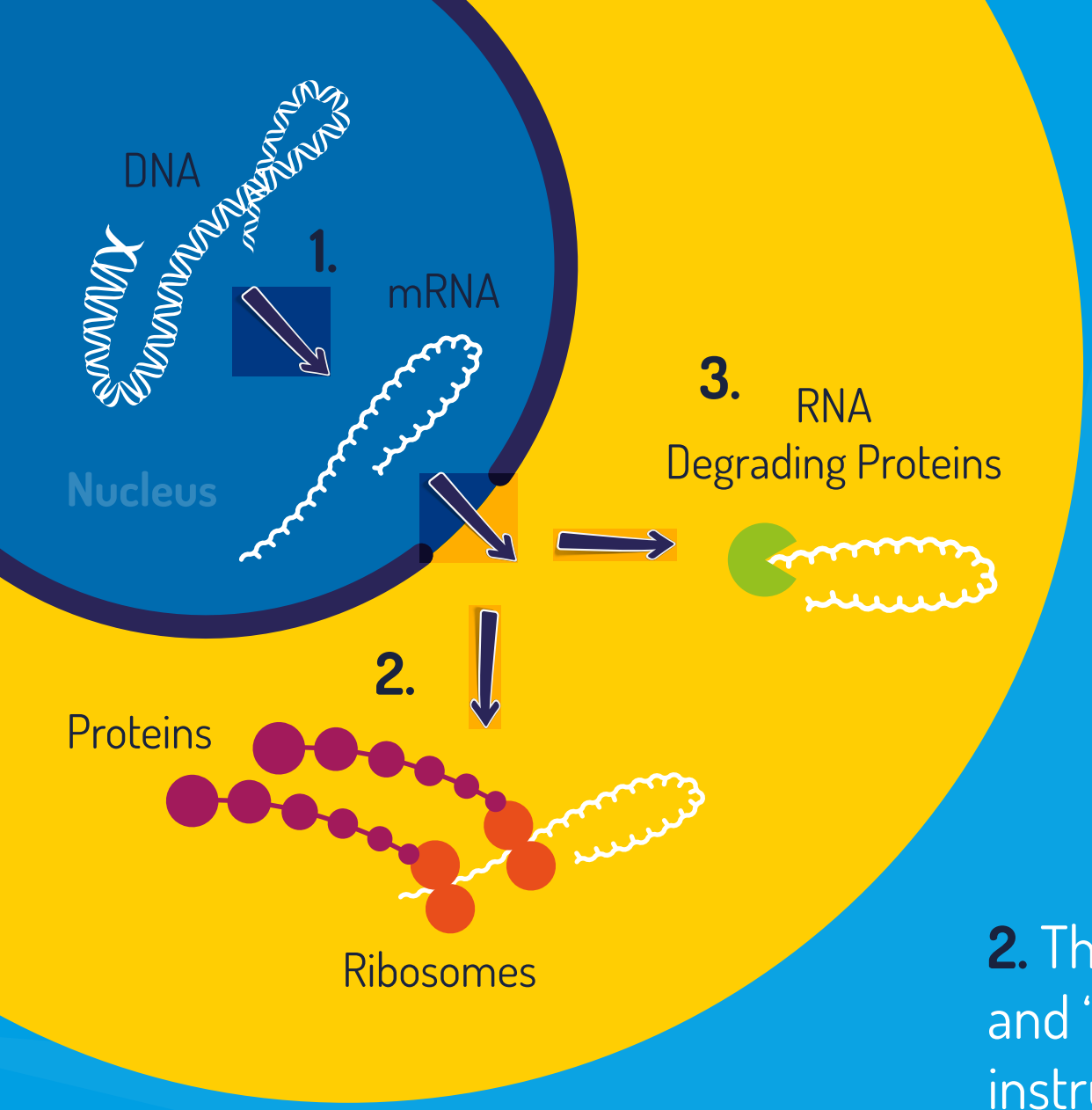
The development and function of immune cells

Our research focusses on the development and function of immune cells.

For cells to develop and carry out their jobs properly, instructions must be read and translated from our DNA.





Protein-coding genes contain the instructions to make proteins, which are involved in lots of processes including DNA synthesis, the immune cells response, cell structure and more!

The instructions are read like this:

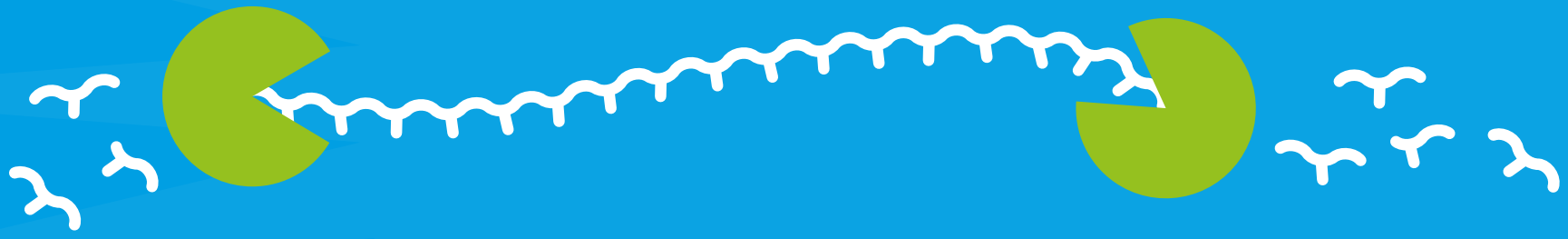
1. Information in DNA is transferred to messenger RNA (mRNA)

2. The mRNA leaves the nucleus and 'ribosomes' translate the instructions in to proteins

3. Sometimes, the mRNA is not needed and so RNA degrading proteins are recruited

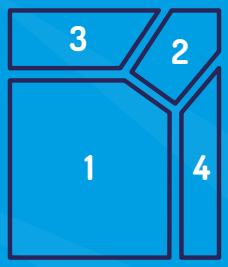
We study two RNA binding proteins called **ZFP36L1** and **ZFP36L2** which bind to the mRNA...

...and recruit the **'RNA degrading proteins'** to break up the mRNA.



To understand how important the RNA binding proteins were to immune cell development, we generated mice that don't make these proteins in their T cells or B cells.

We use markers on the surface of the cells to determine which cells we are looking at. Each dot on the plot represents an individual cell.

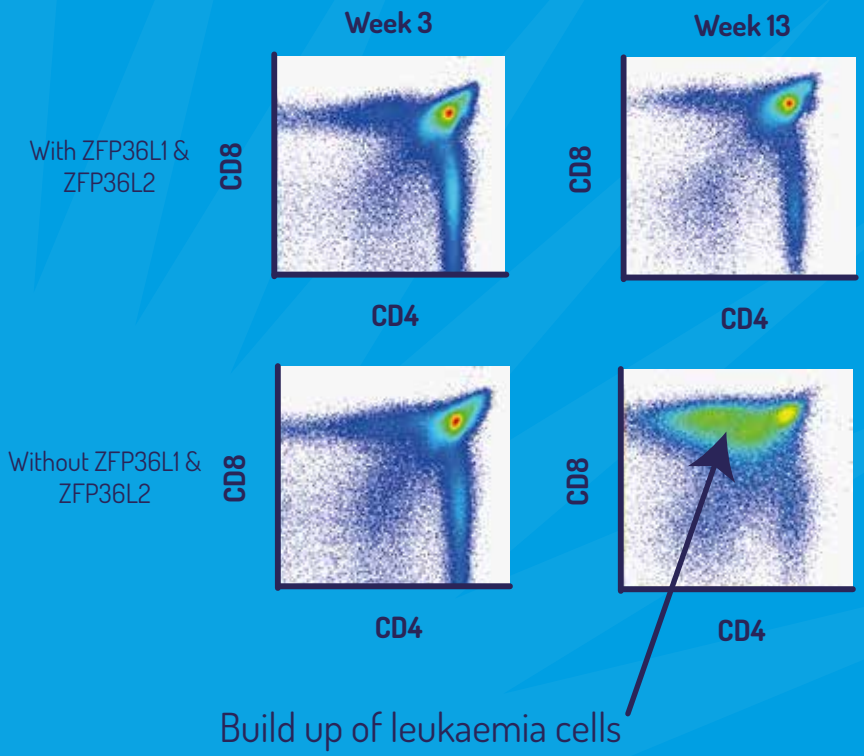


1. **Double negative cells:**
the earliest stage of T-Cell development in the thymus, make the first half of their T-Cell receptor.

2. **Double positive cells:**
later in development finish making their T-Cell receptors.

3. **CD8 single positive:**
contain immature T-Cells between the double negative and double positive stage of development as well as killer T-Cells.

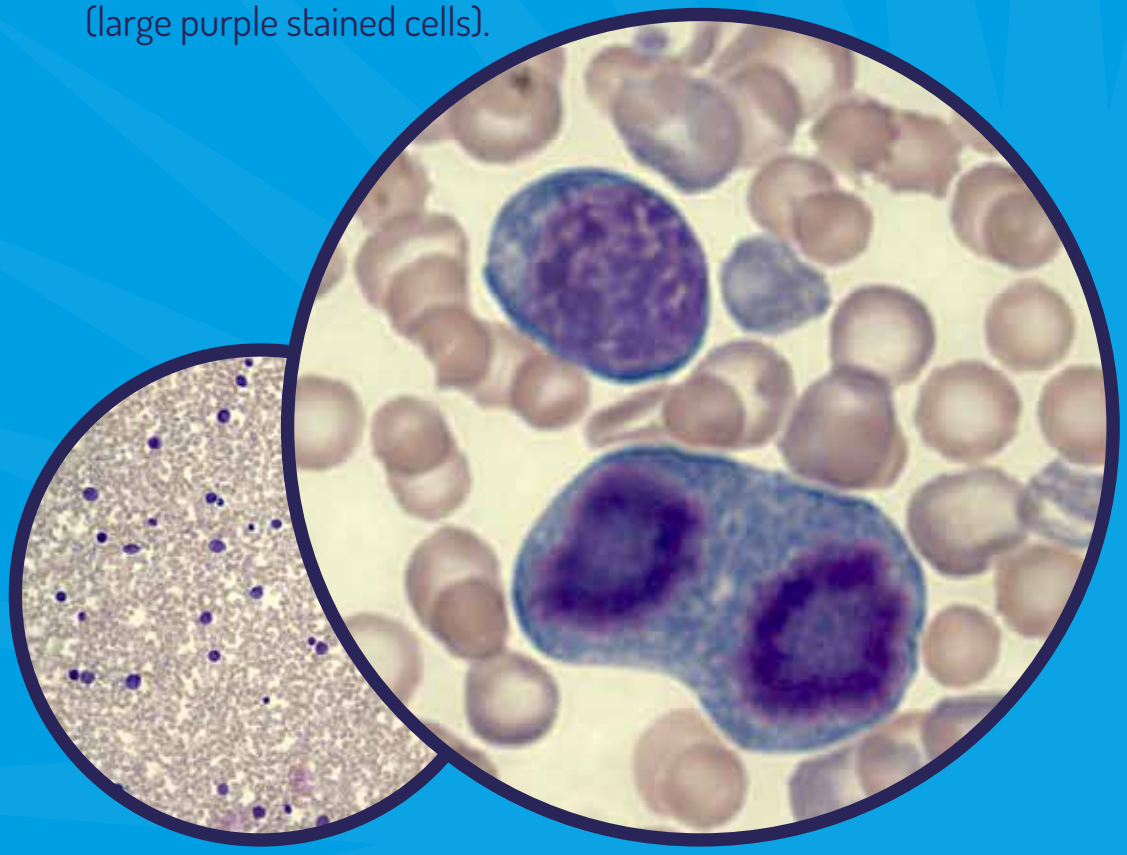
4. **CD4 single positive:**
contain the helper T-Cells.



We found that these mice developed leukaemia (cancer of white blood cells) at about 14 weeks of age.

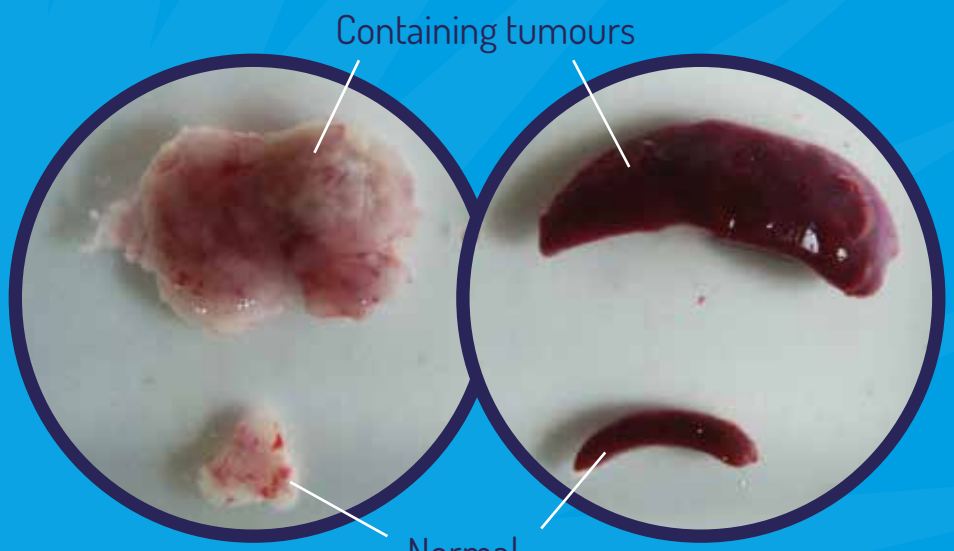
The leukaemic cells formed tumours in the thymus and spread to other immune cell organs such as the spleen and lymph nodes.

Blood smears showing leukaemic cells (large purple stained cells).



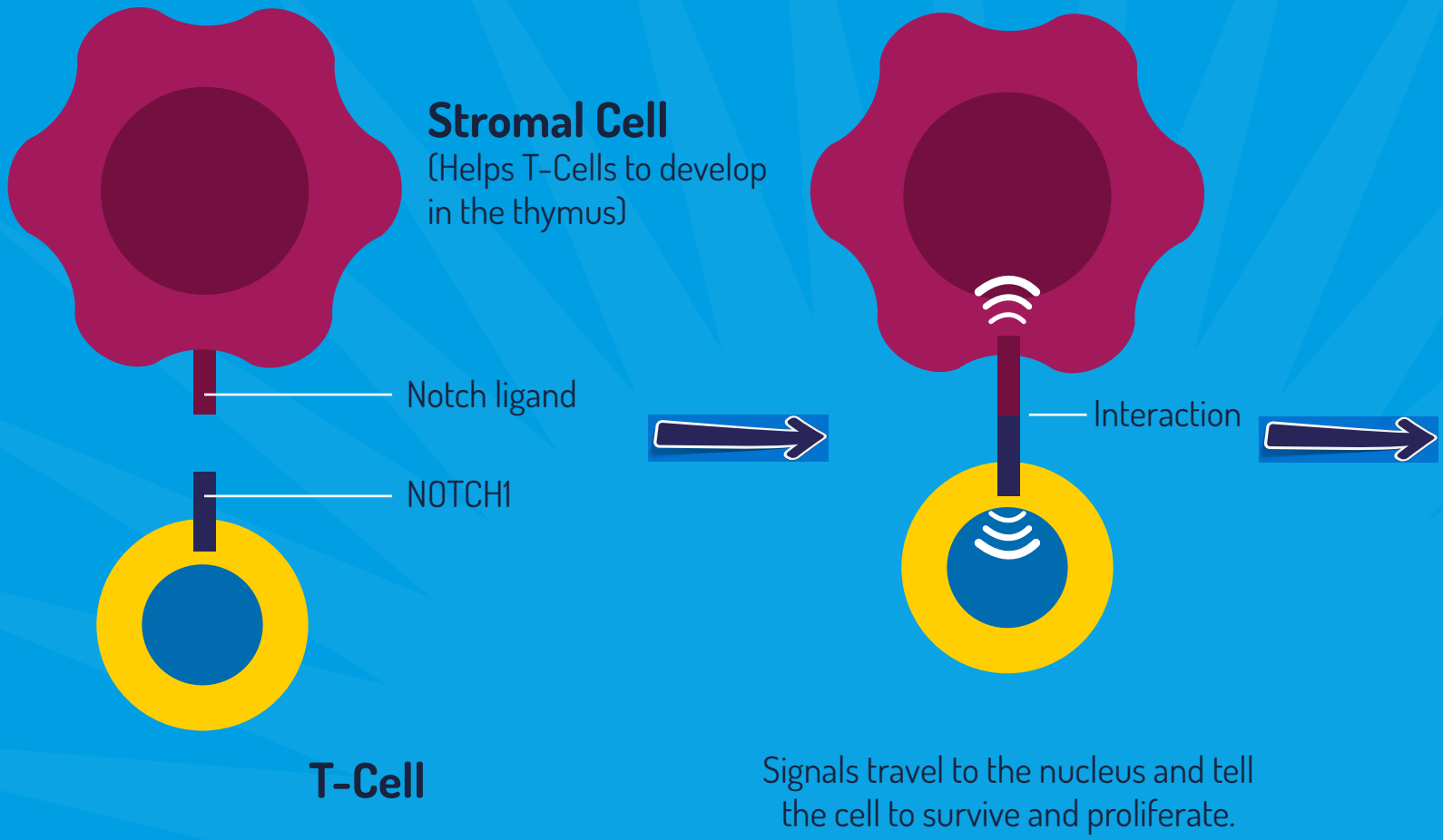
Low Magnification **High Magnification**

Images of thymus and spleen showing tumours



Thymus **Spleen**

Upon further study we found that the T cells which lacked these two RNA binding proteins had an increase in a protein called NOTCH1.



This protein is important in T-Cell development.
But, when it is over-active it can cause leukaemia.

We found that the NOTCH1 mRNA has a site where ZFP36L1 and ZFP36L2 can bind and recruit RNA degrading enzymes.

So, if ZFP36L1 and ZFP36L2 are not active during T cell development this can cause leukaemia.

This is just one mechanism by which these RNA binding proteins control immune cell development and functions. We are working to understand how these RNA binding proteins and their target mRNAs are regulated in immune cells.

Martin Turner Laboratory

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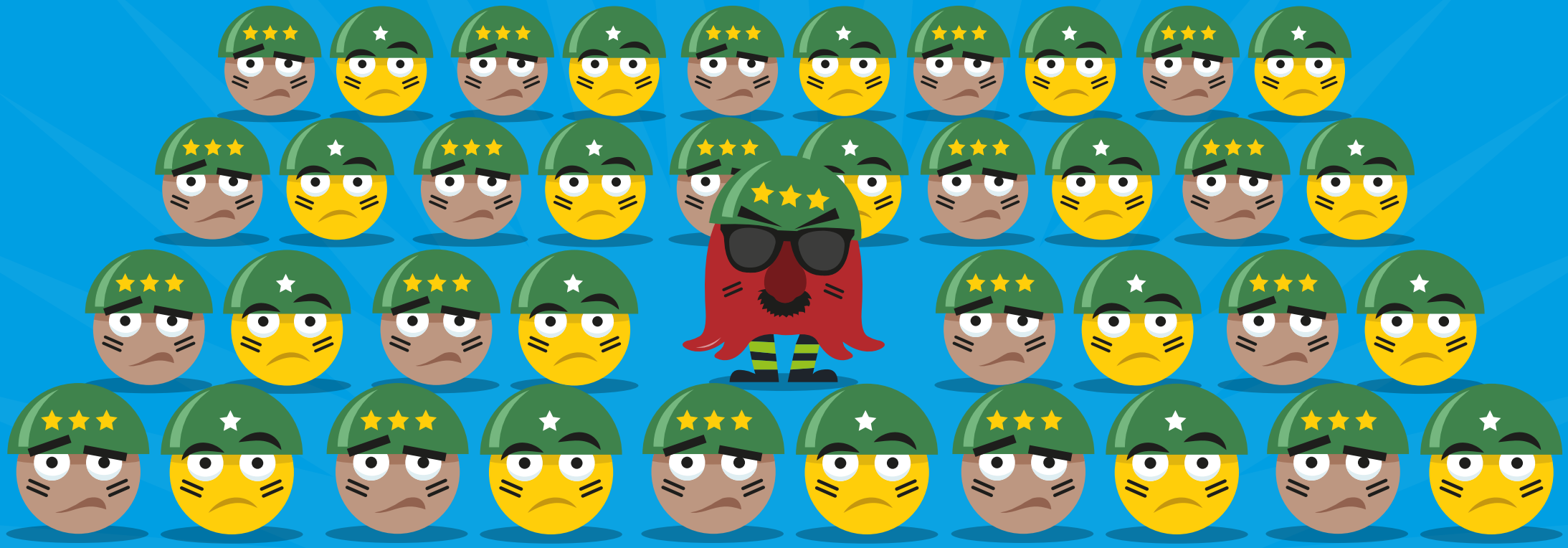
Research in the Turner Lab focuses on understanding the fundamental mechanisms that control immune cell development and function throughout the life-course.
www.babraham.ac.uk/our-research/lymphocyte/martin-turner

For more information on this research:
www.ncbi.nlm.nih.gov/pubmed/20622884

The Immune Army vs. Cancer

Did you know your immune system can fight cancer? But, sometimes harmful cancers grow and spread because they have ways to fool the immune system into letting them survive.



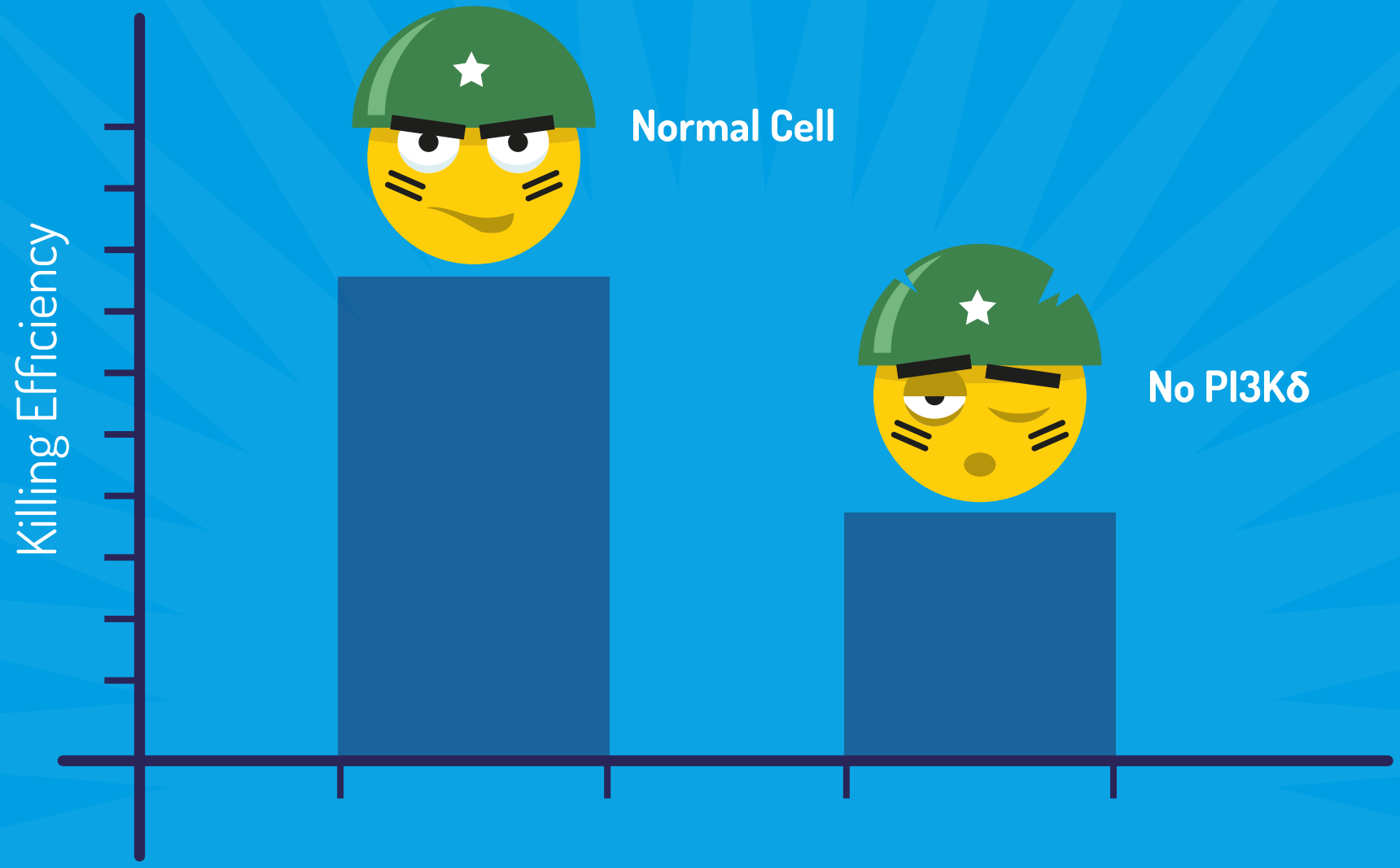
One way they do this is to **hide** from the immune system, altering their expression of **genes** so that they are not recognised as dangerous.

Alternatively, they can **recruit regulatory T-cells** to shield them, essentially corrupting the police officers into protecting them.

However, we've discovered that deactivating a protein called **PI3Kδ** in immune cells slows tumour growth.

But why does this happen?

At first we thought the change was in **killer T-cells**, but when we removed them from the body and gave them tumour cells to kill, the **cells lacking PI3Kδ did worse!**



Could it be instead that the **regulatory T-cells** are being turned off? And that the killer T-cells can get rid of cancer cells like they should (with a weaker attack)?

Regulatory T-cells usually stop our immune system from **running out of control** and damaging our bodies.

We are currently trying to build detailed **profiles** of both killer T-cells and regulatory T-cells to pinpoint the **effects of PI3Kδ deficiency** in each.

T-CELL (Killer)

Babraham Institute

CD44	10
CD62L	2
PD-1	6
G_zB	9

T-CELL (Regulatory)

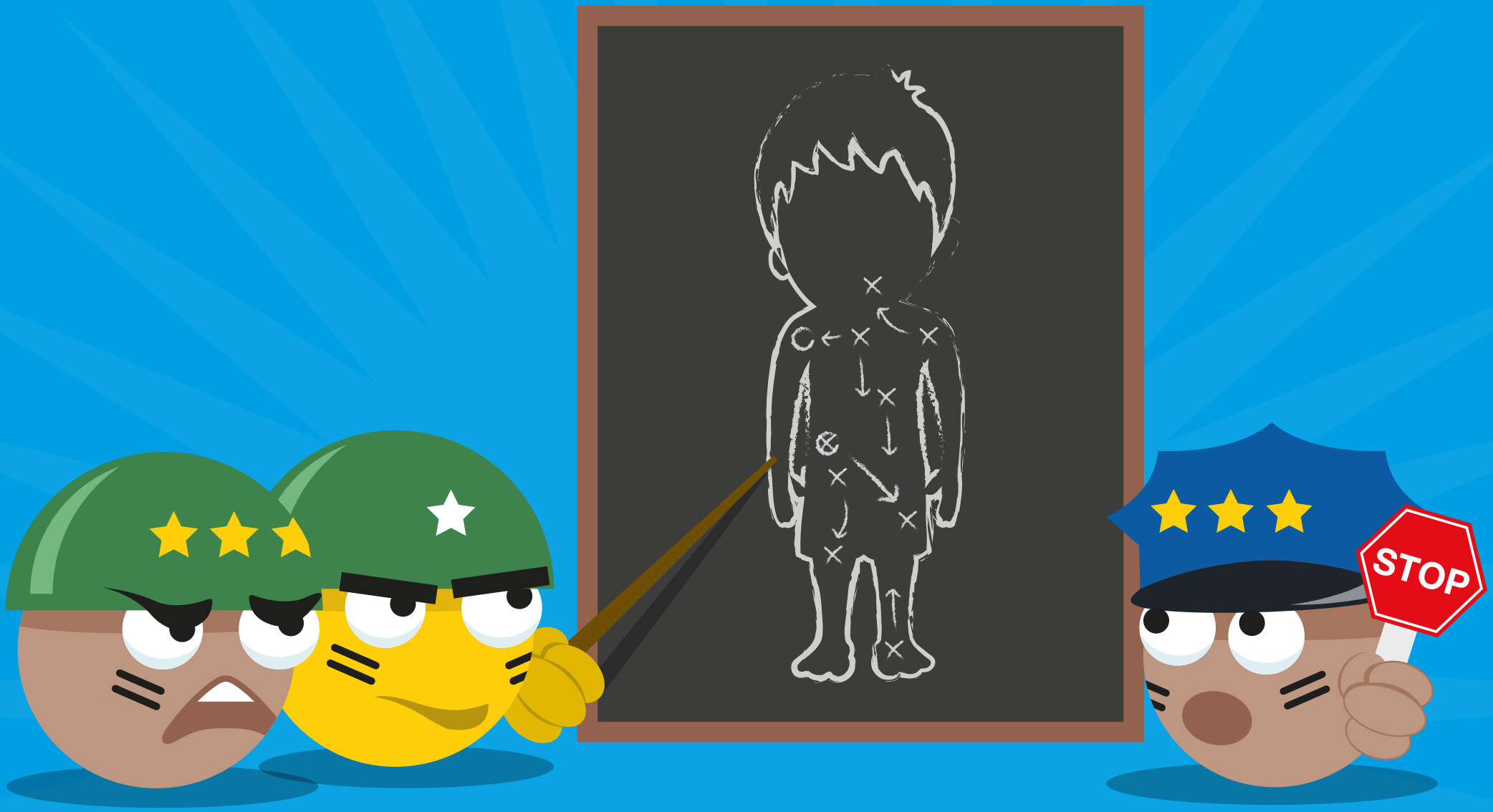
Babraham Institute

CD25	9
CTLA-4	10
PDL-1	6
G_zB	4

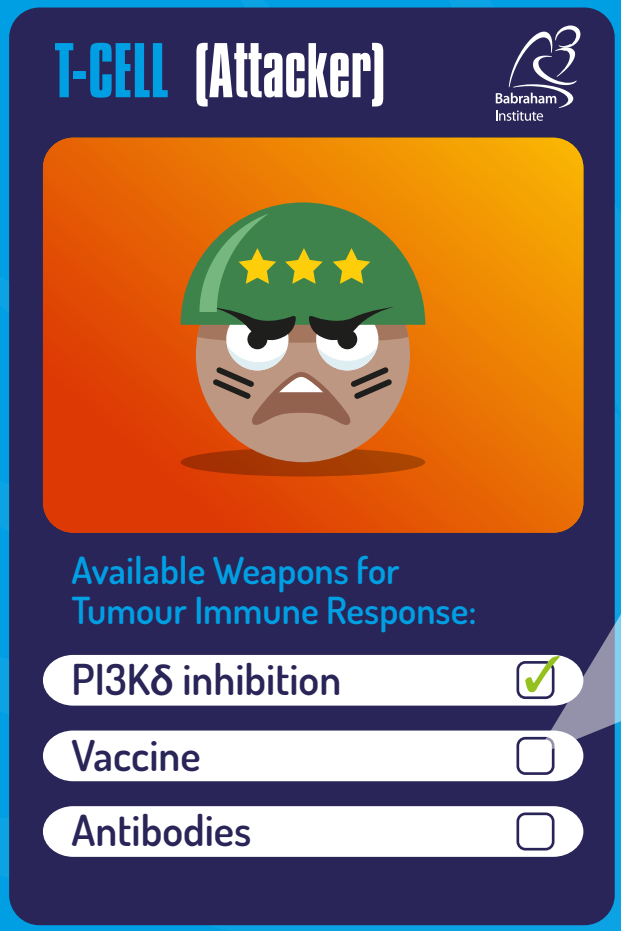
To complicate matters, **no two tumours are the same...**

...and PI3Kδ inhibition **doesn't work equally** against all of them.

We are trying to develop PI3Kδ inhibitors into a **cancer therapy**. Understanding why some cancers respond better than others will allow us to use inhibitors in the most effective way.



We may be able to improve the effect of PI3Kδ inhibition by combining it with other treatments, such as tumour vaccines or antibody therapies.



such as tumour vaccines or antibody therapies.

Klaus Okkenhaug Laboratory

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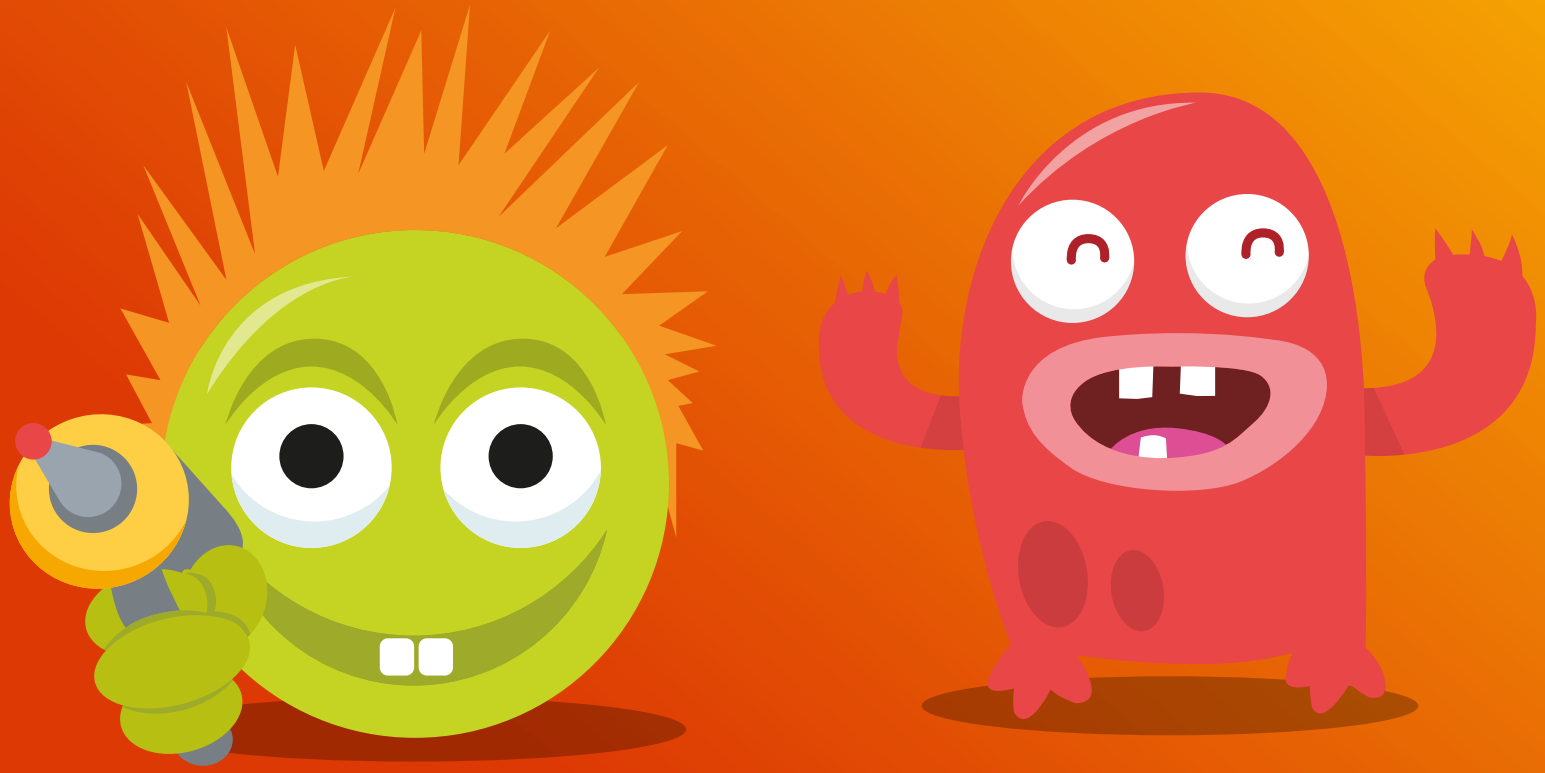
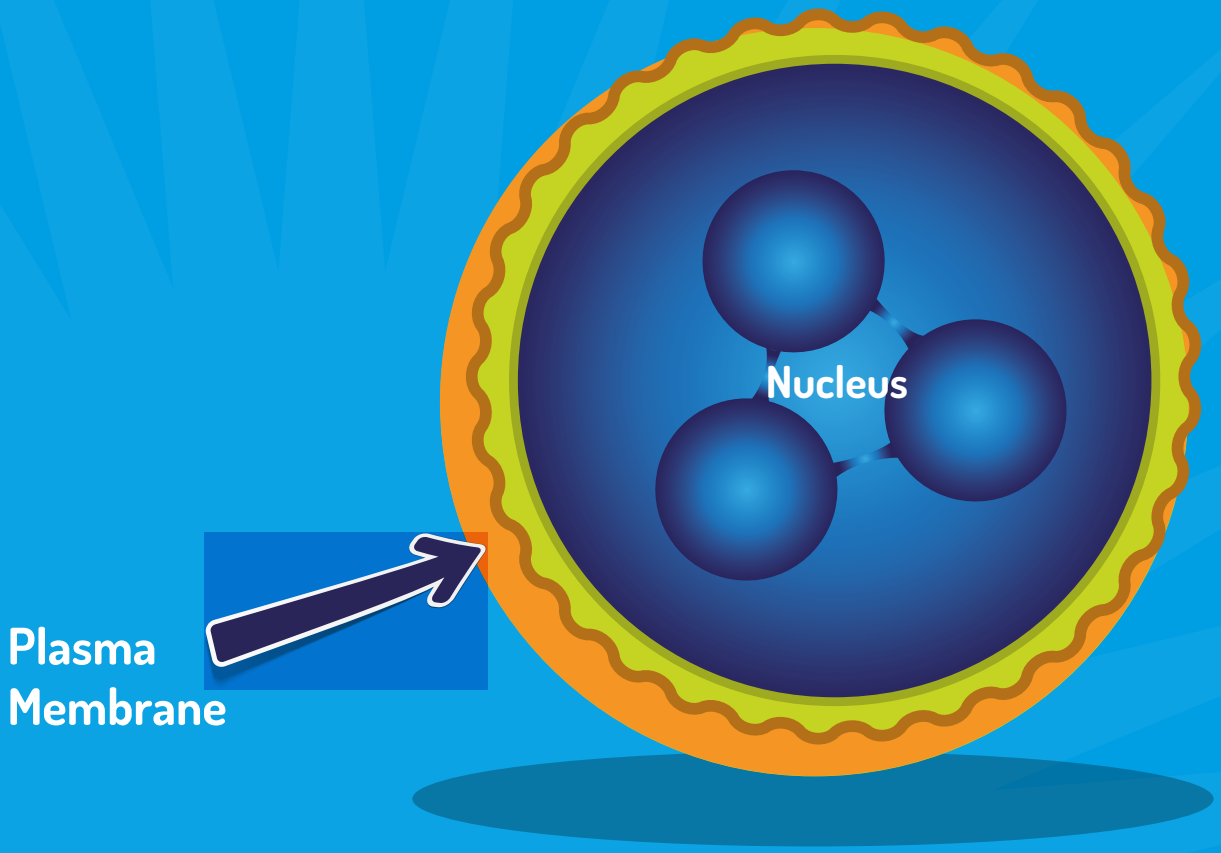
Research in the Okkenhaug Lab focuses on how a group of enzymes called PI3Ks are used by cells of the immune system.
www.babraham.ac.uk/our-research/lymphocyte/klaus-okkenhaug

Measuring Rac Activation in Neutrophil Chemotaxis



Neutrophils are the body's **first line of defence** and are the first cell to be called upon in an immune response.

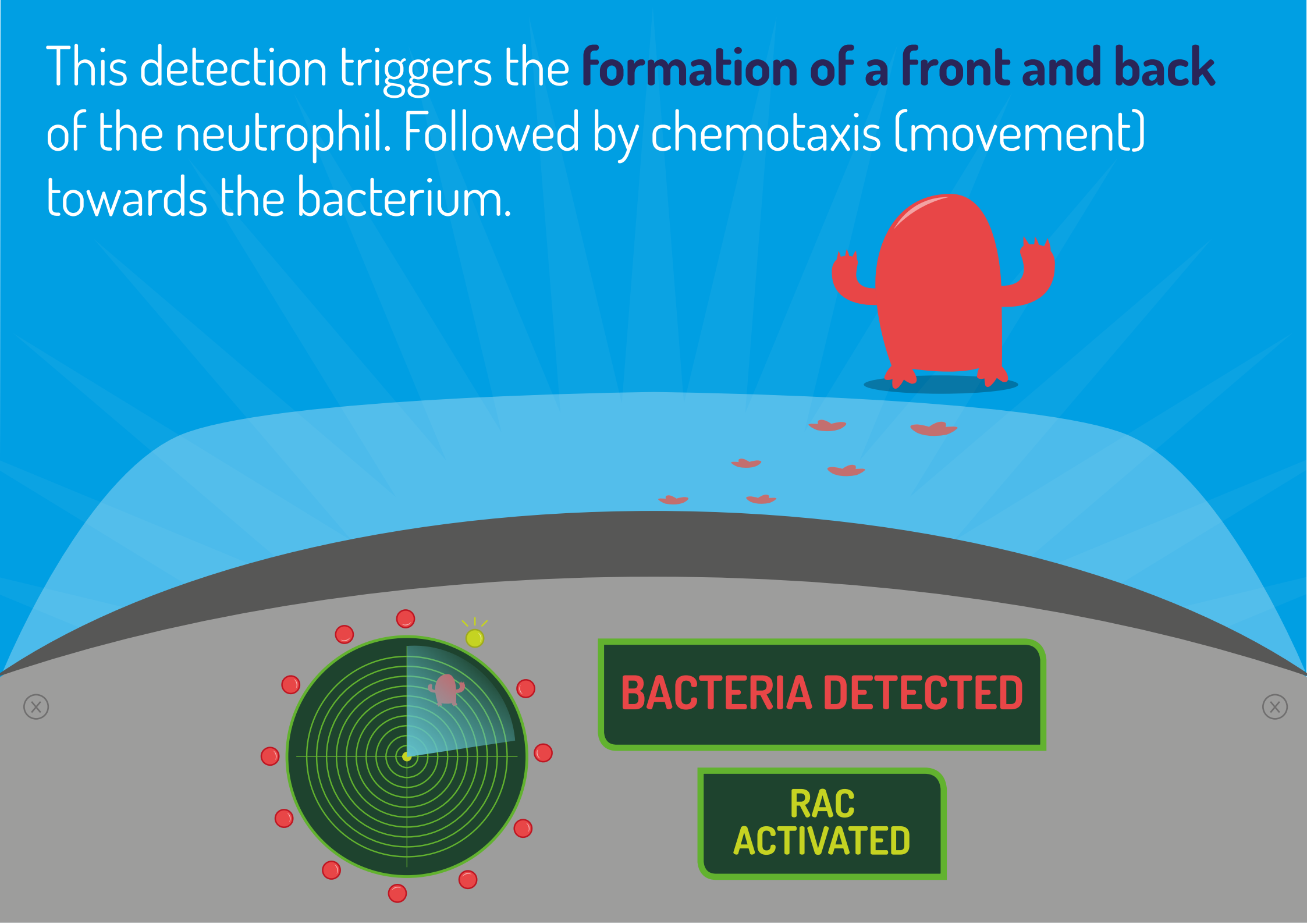


They contain a **nucleus divided** into 2–5 lobes.

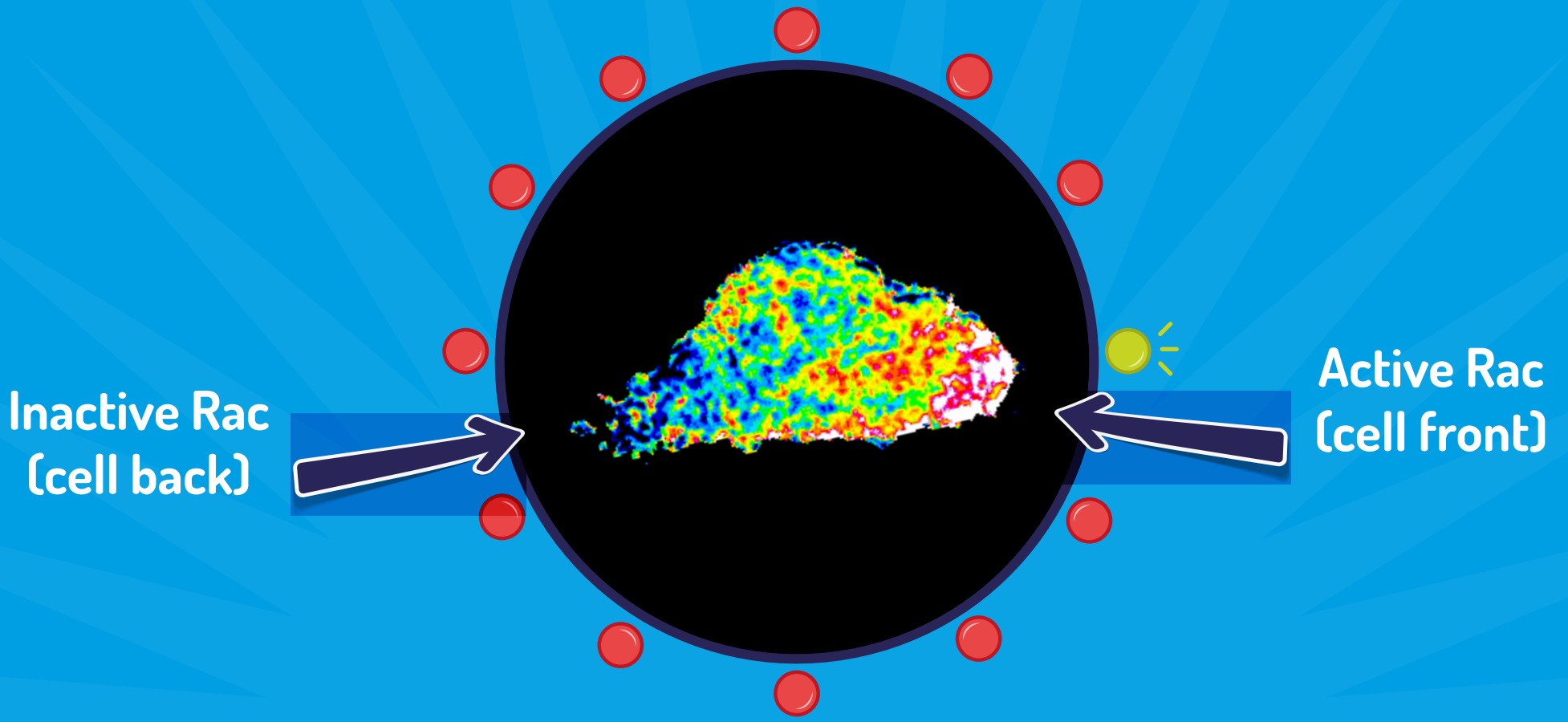
Neutrophils have **no sense of direction** or defined ‘front’ and ‘back’ in their normal state.

However, neutrophils sense the **debris trail** left behind by a bacterium or **distress signals** from other cells and move towards the trouble.

This detection triggers the **formation of a front and back** of the neutrophil. Followed by chemotaxis (movement) towards the bacterium.

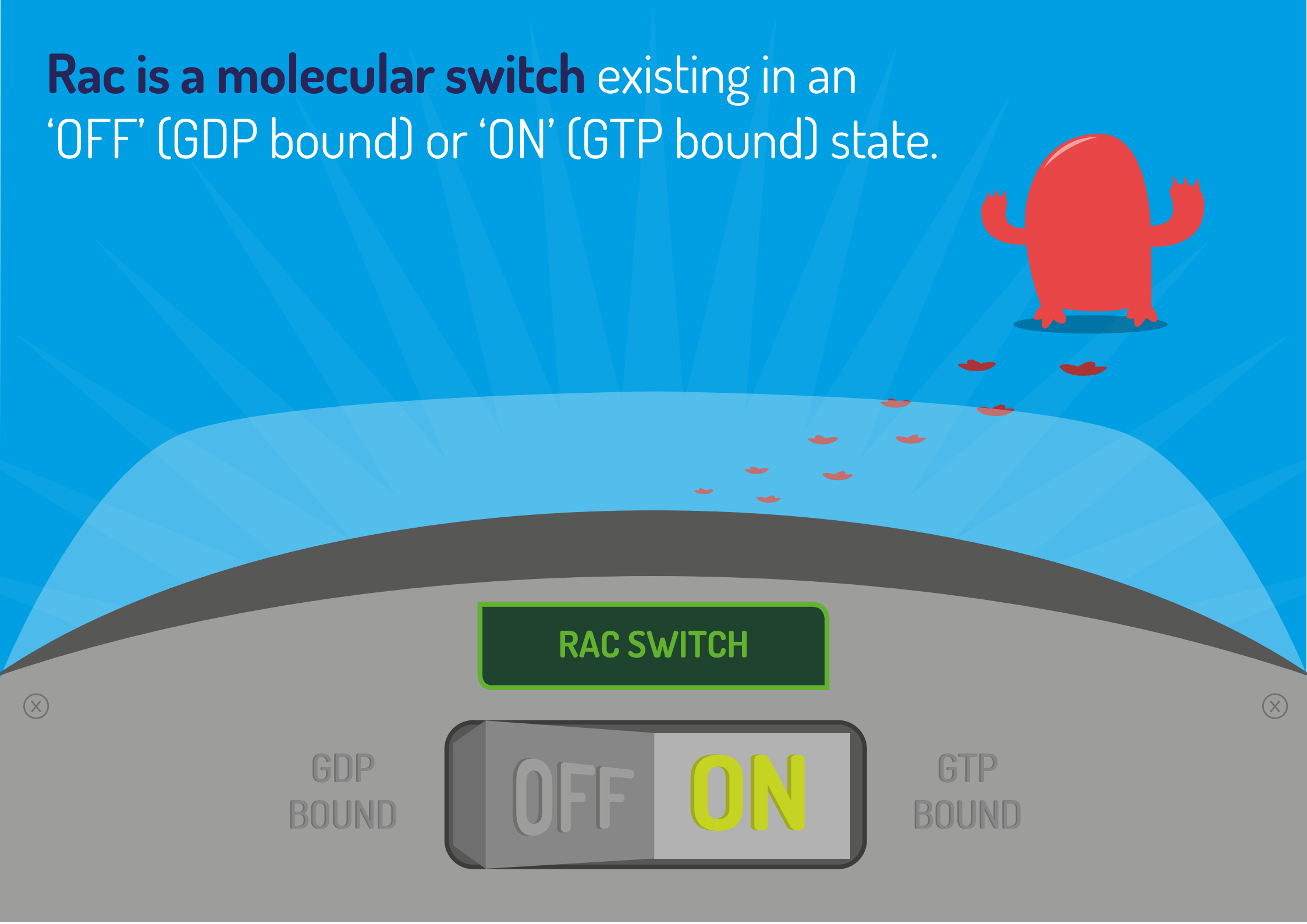


In order for chemotaxis to take place
Rac must be active in the cell.

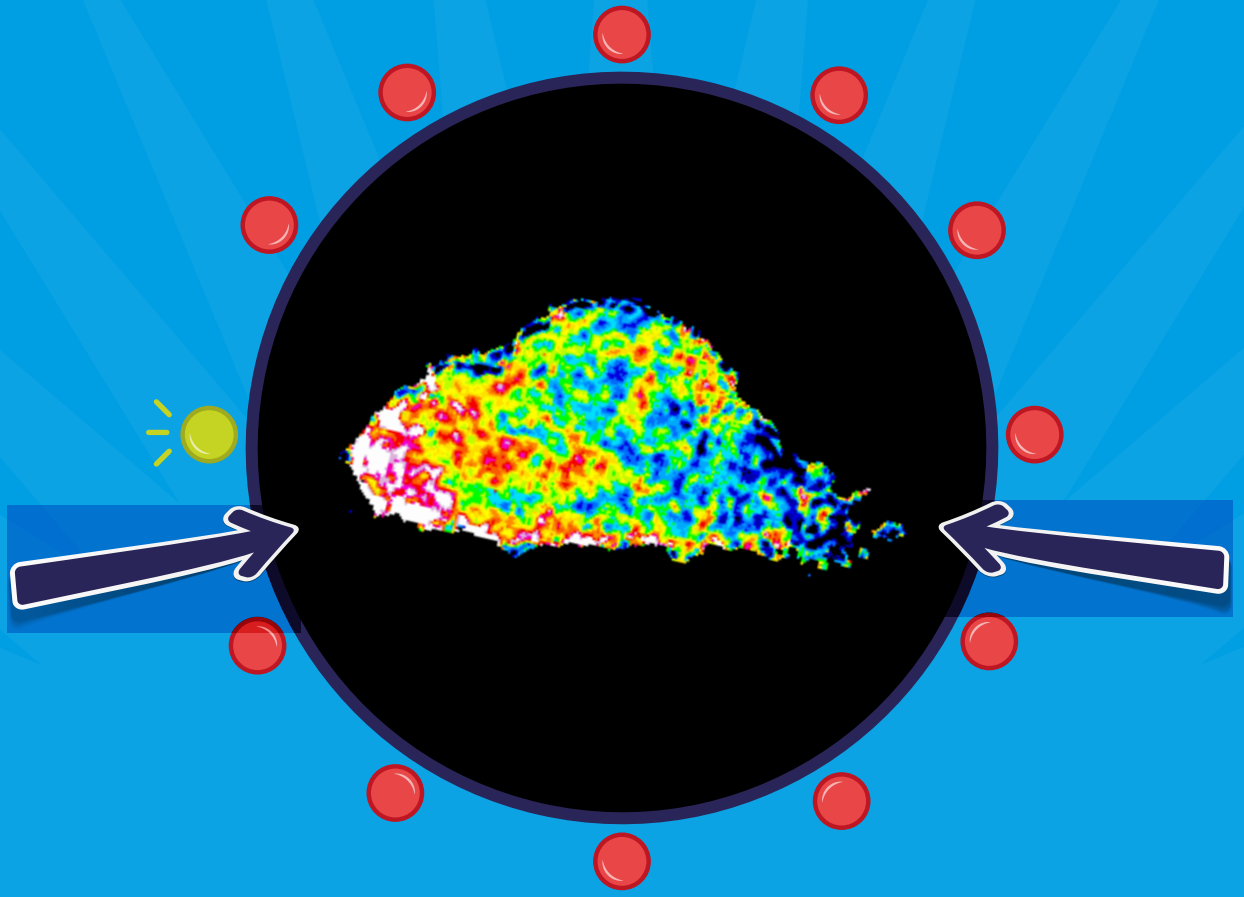


Rac gives the cell a front and back,
as shown in the above heat map of active Rac.

Rac is a molecular switch existing in an 'OFF' (GDP bound) or 'ON' (GTP bound) state.



Rac is stimulated by the debris trail left behind by a bacterium and **migrates towards it**.

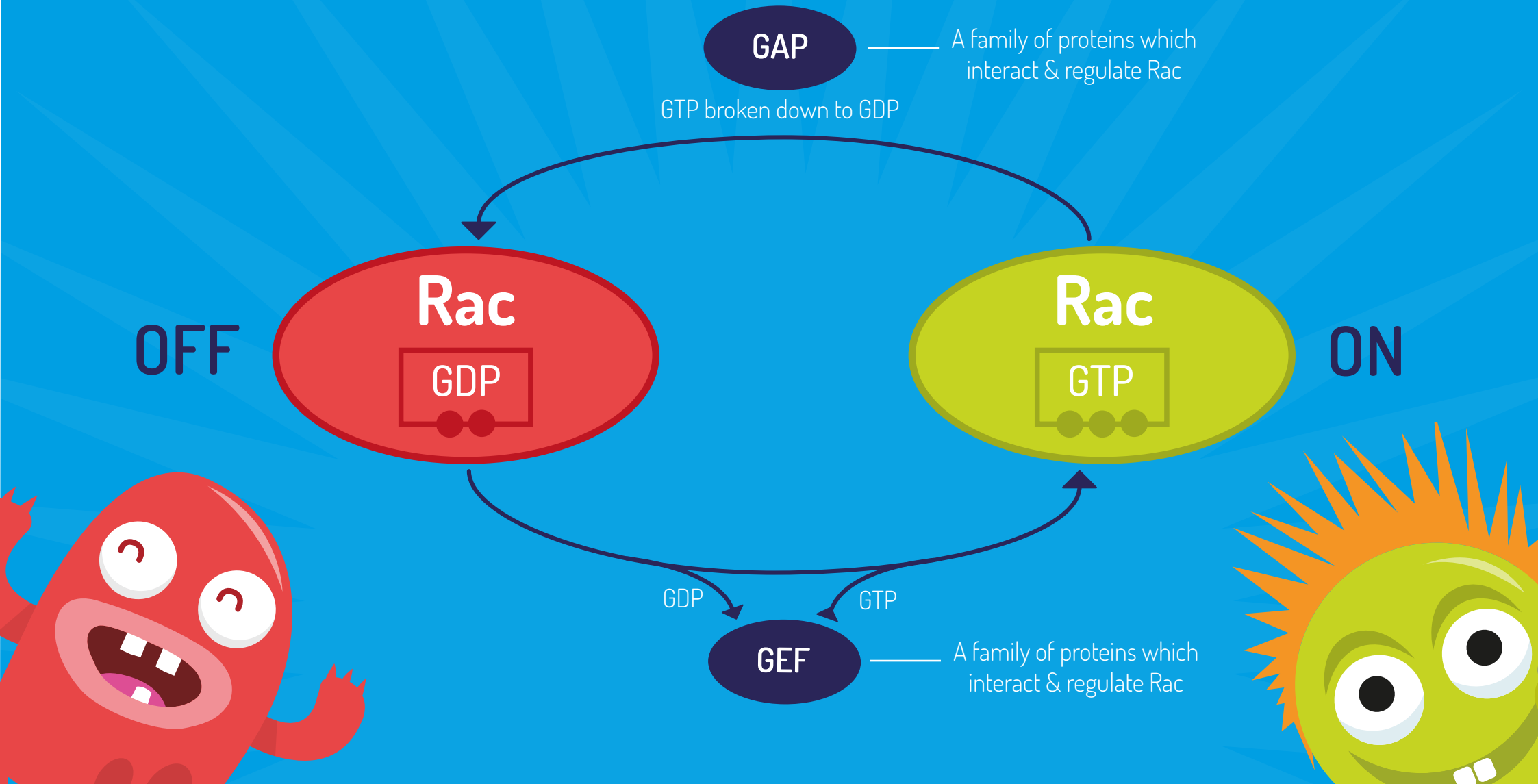


The cell won't turn to follow the trail, it will simply create a new front

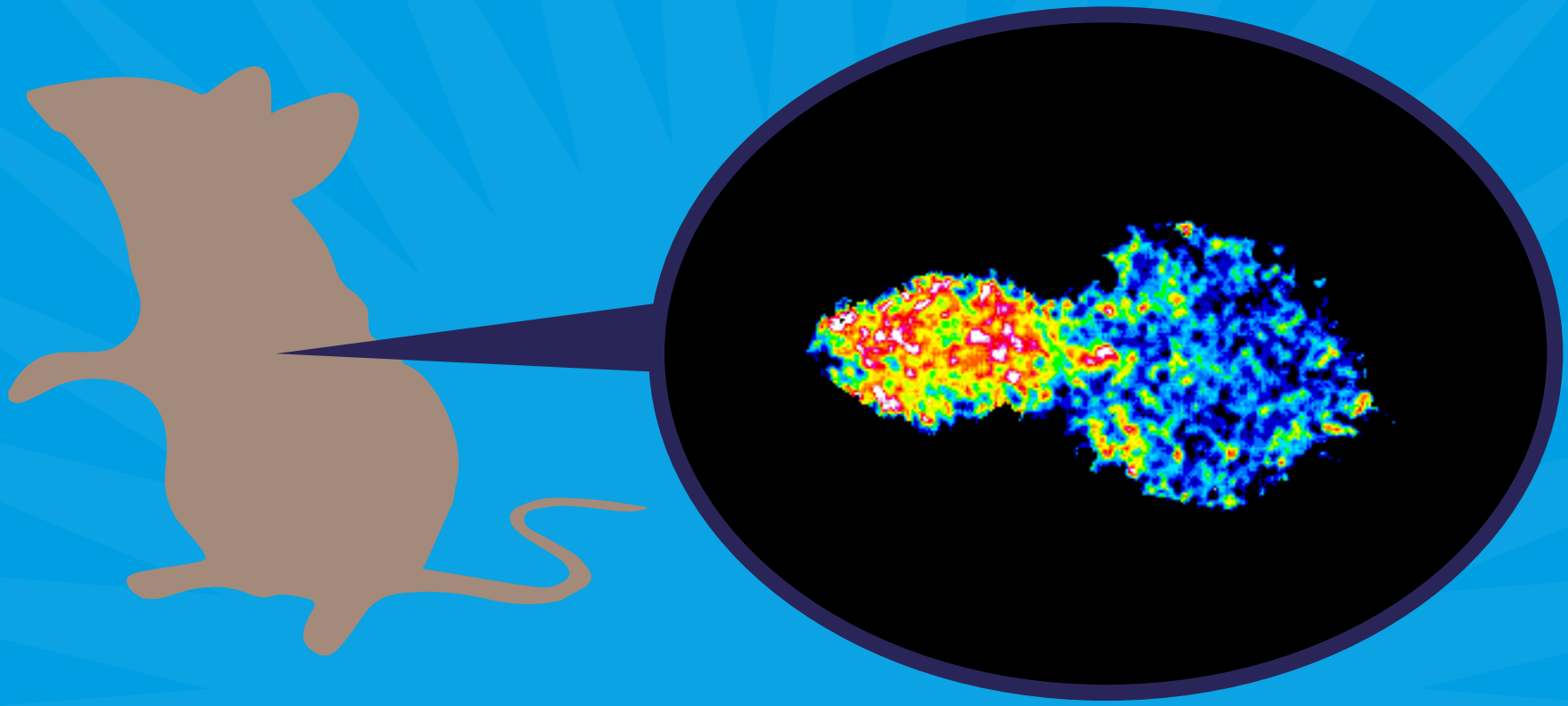
If Rac is **dysfunctional** then neutrophils **can't migrate**.

They also **can't produce oxygen radicals** which are used to break down pathogens

We study the **regulation of the Rac switch**, specifically how it is **turned on**, so that we can better understand how neutrophils function.



To advance our understanding of the function of Rac, we have developed mice with a **sensor inside their neutrophils**, which allows us to see when Rac is switched on or off.



Heidi Welch Laboratory

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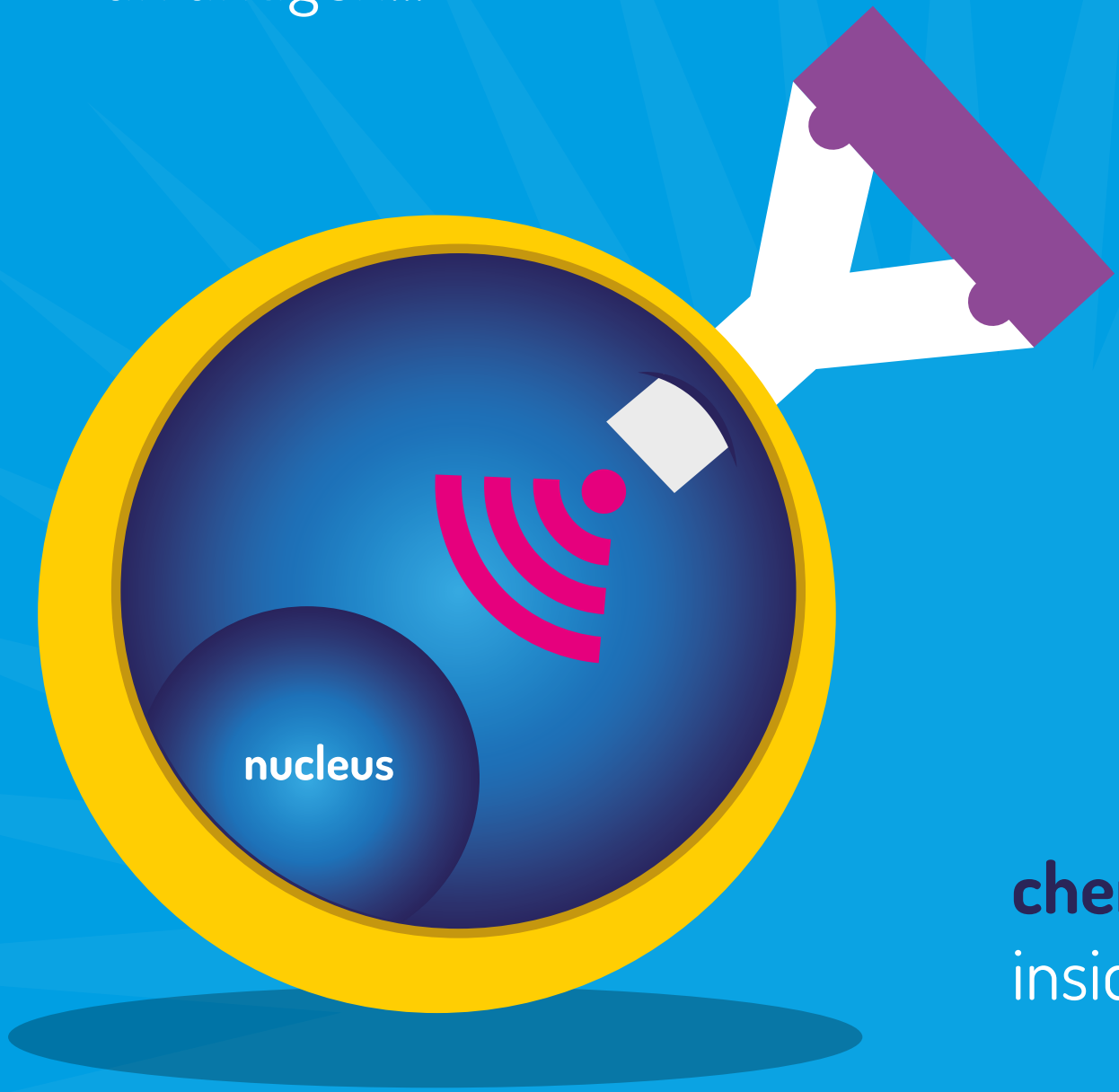
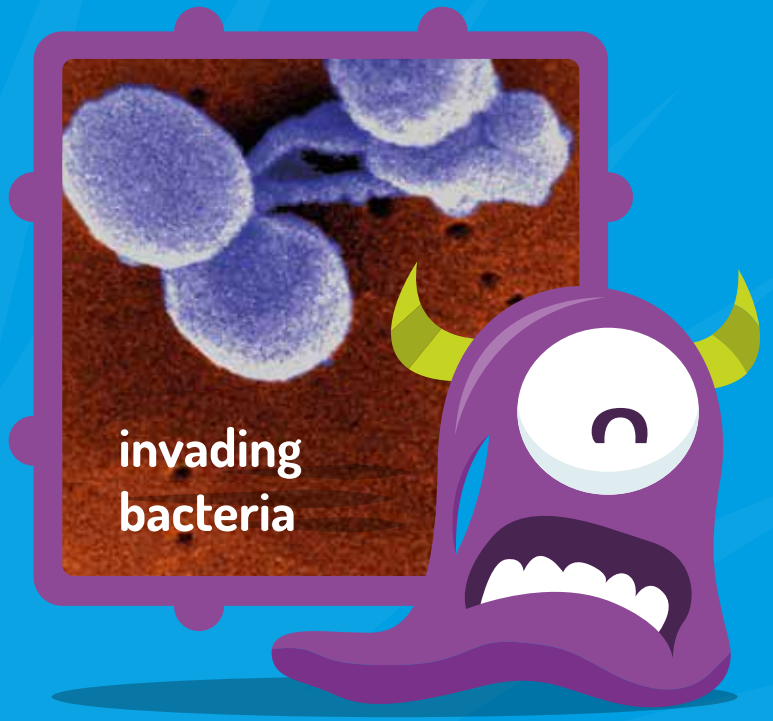
Research in the Welch lab focusses on the molecular mechanisms that regulate Rac, in particular the proteins which activate Rac, so called Rac-GEFs:
www.babraham.ac.uk/our-research/signalling/heidi-welch

The vital role of PI3Kδ in Antibody Production

Antibodies on the B cell surface are called **‘B Cell Receptors’**.

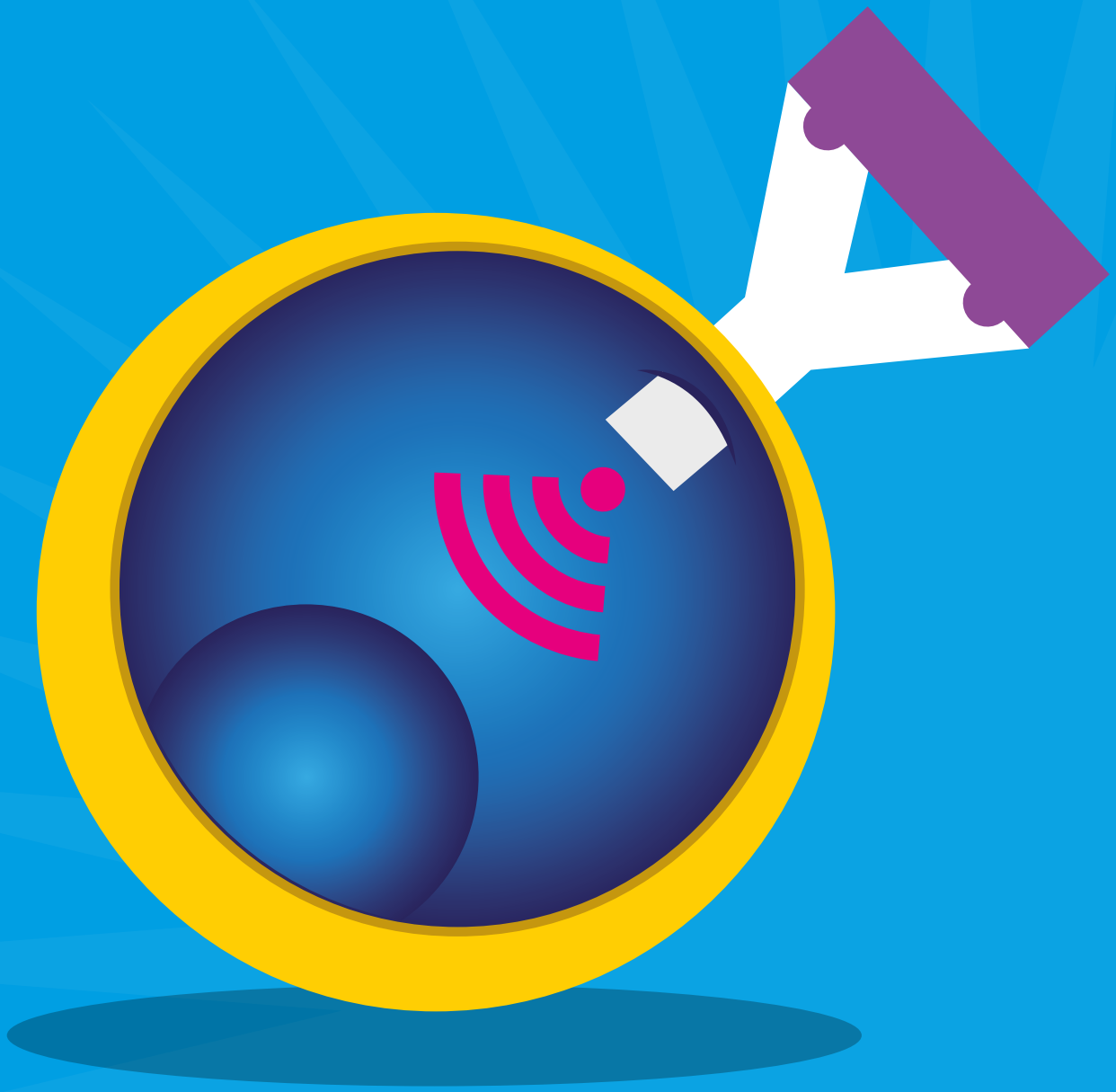
When a **B Cell Receptor** binds to an antigen...





chemical signals are generated inside the B Cell.

These signals can tell the B Cell to:

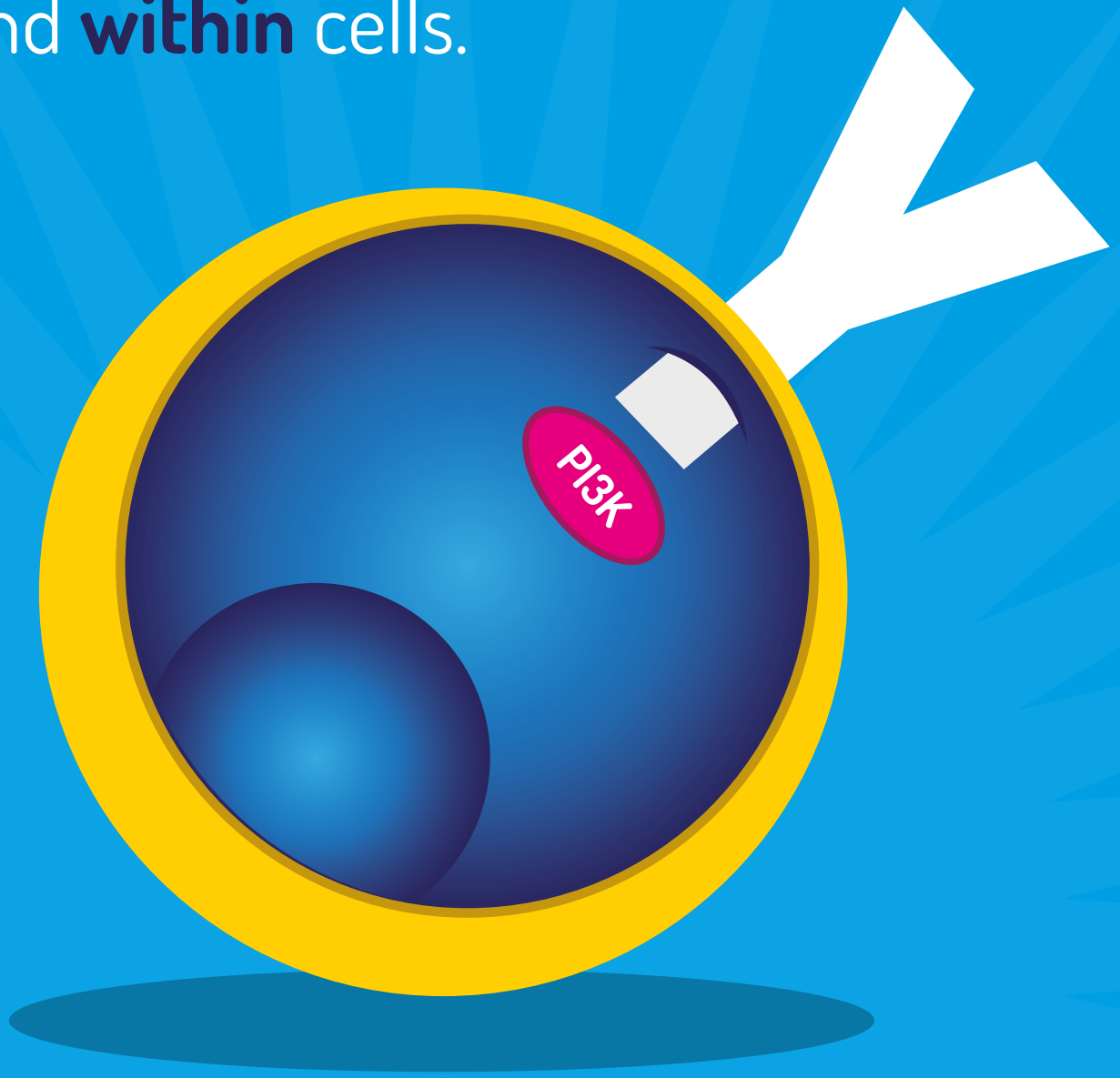


Stay alive!

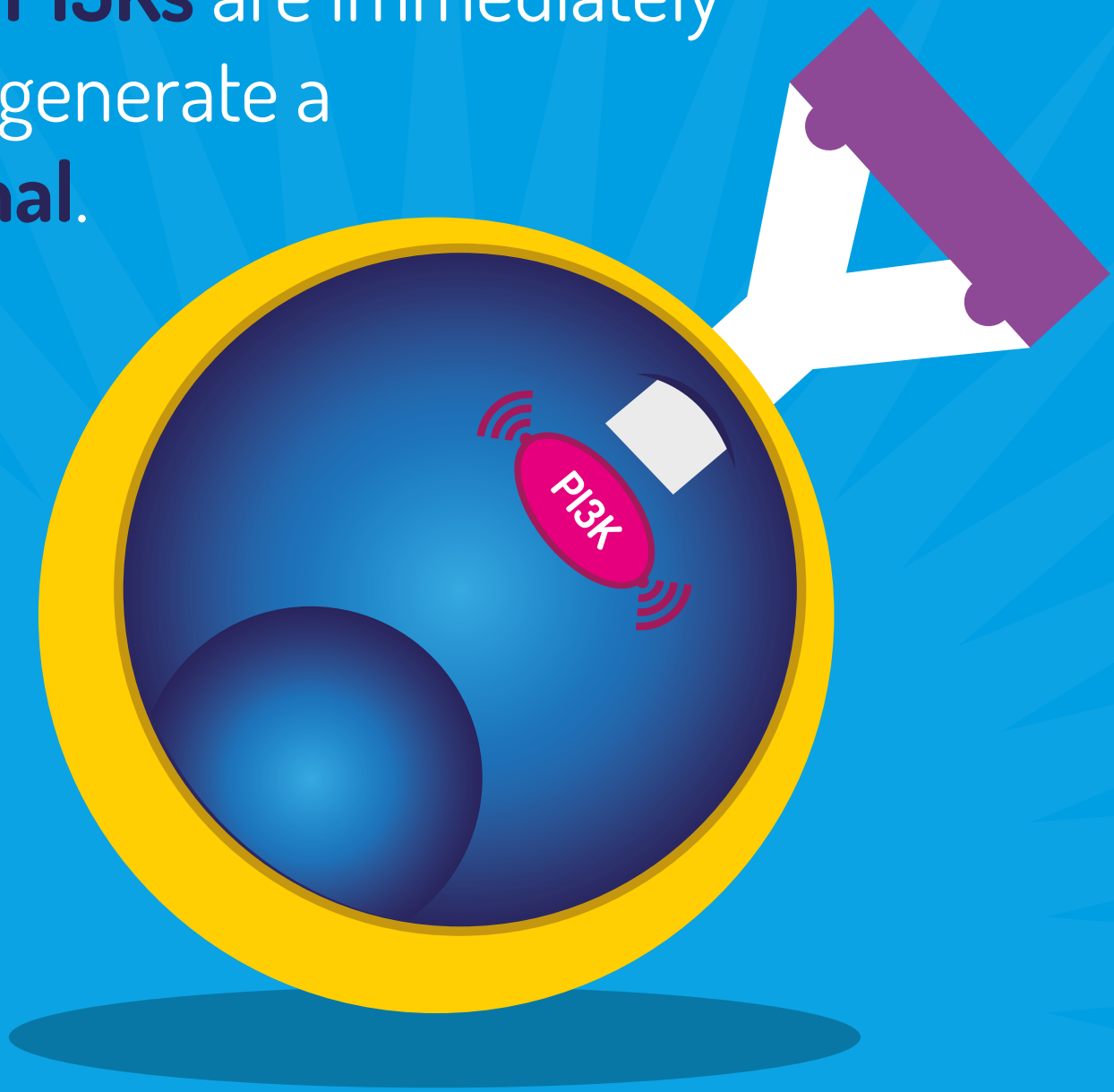
Continue to develop

Make more antibodies

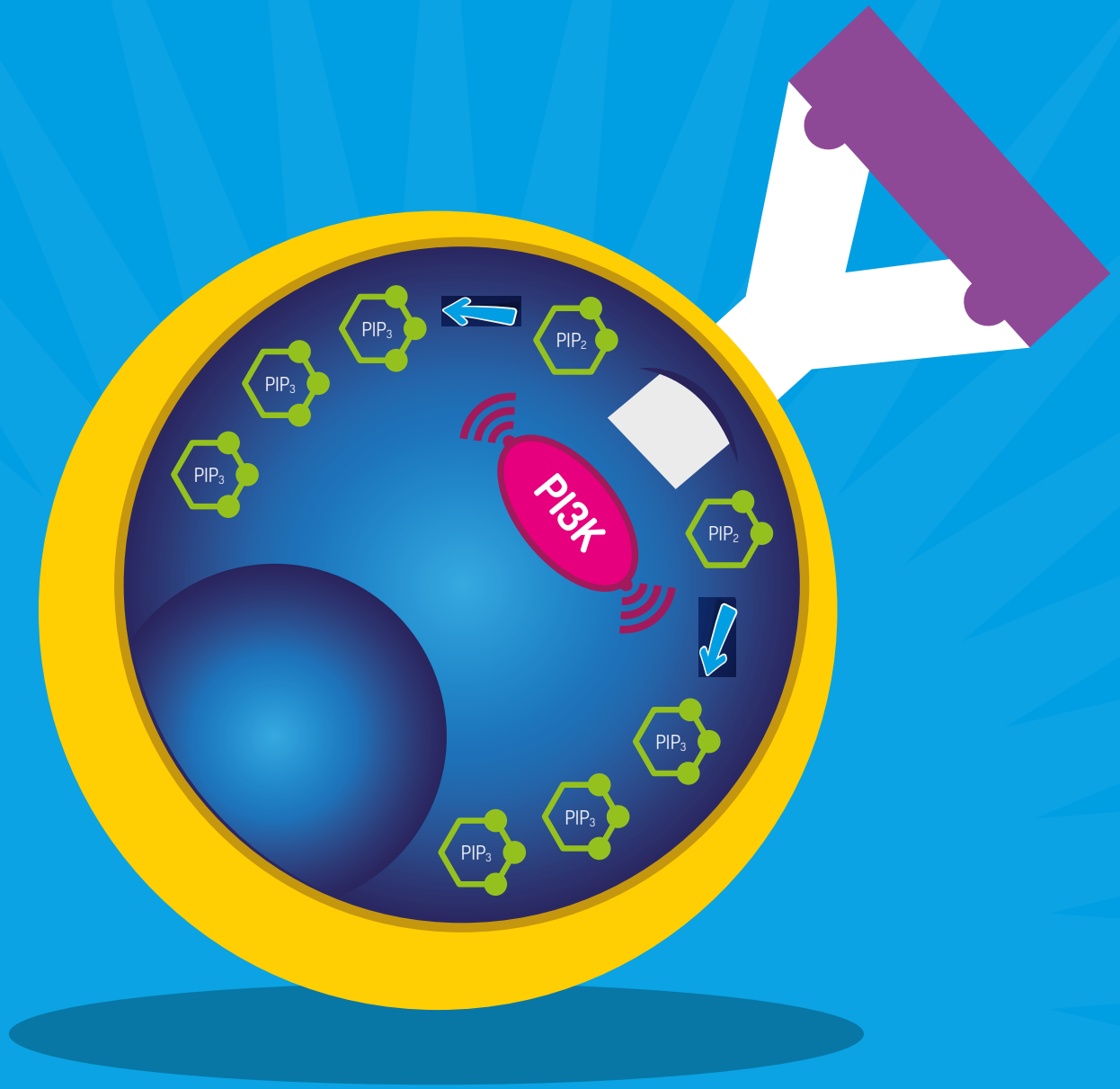
PI3-Kinases (PI3Ks) are a family of proteins found **within** cells.



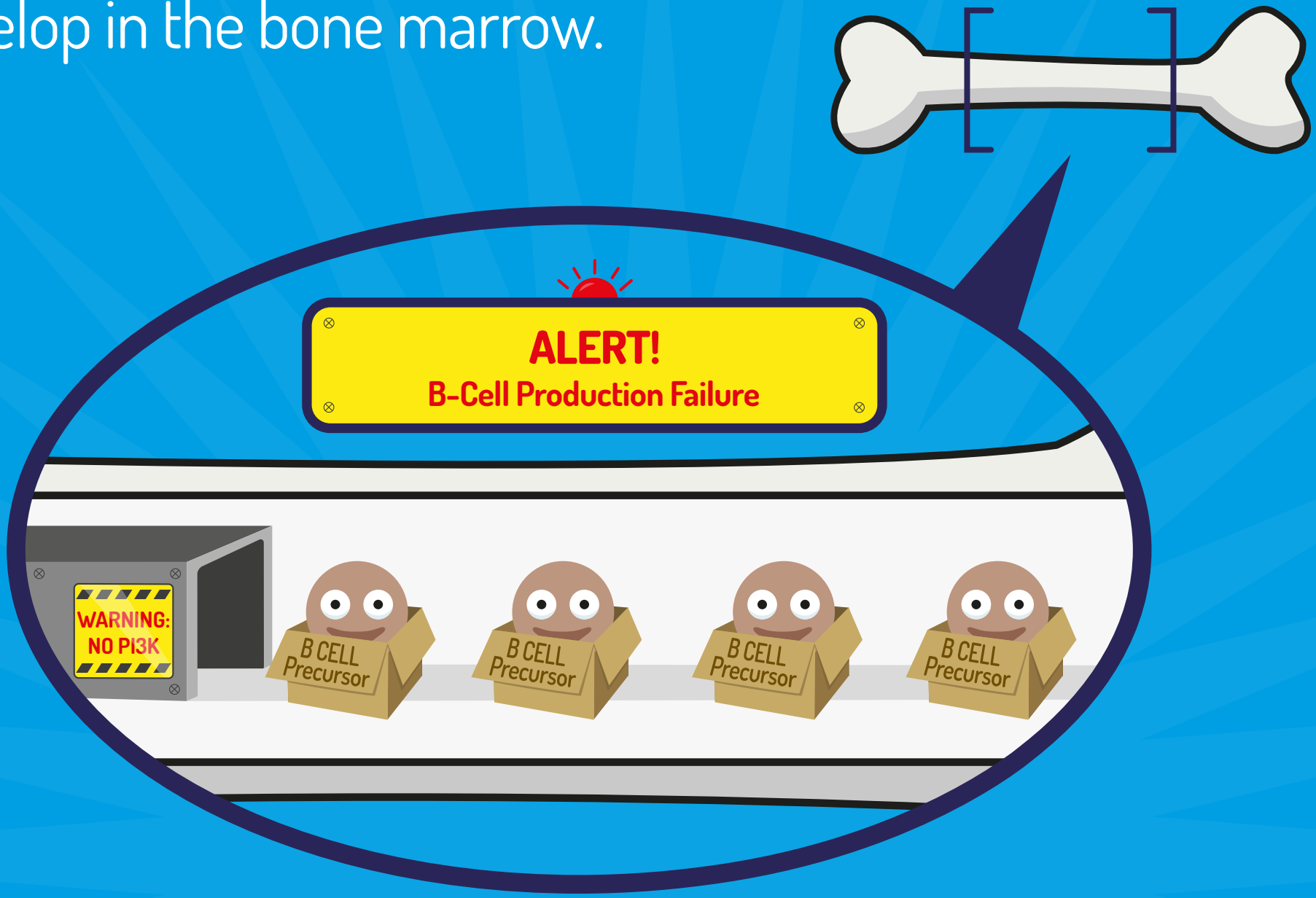
When the B Cell Receptor detects an antigen these **PI3Ks** are immediately activated and generate a **chemical signal**.



This signal is called '**PIP_3**' and forms at the **cell membrane**.



B cells need PI3K signals to develop in the bone marrow.



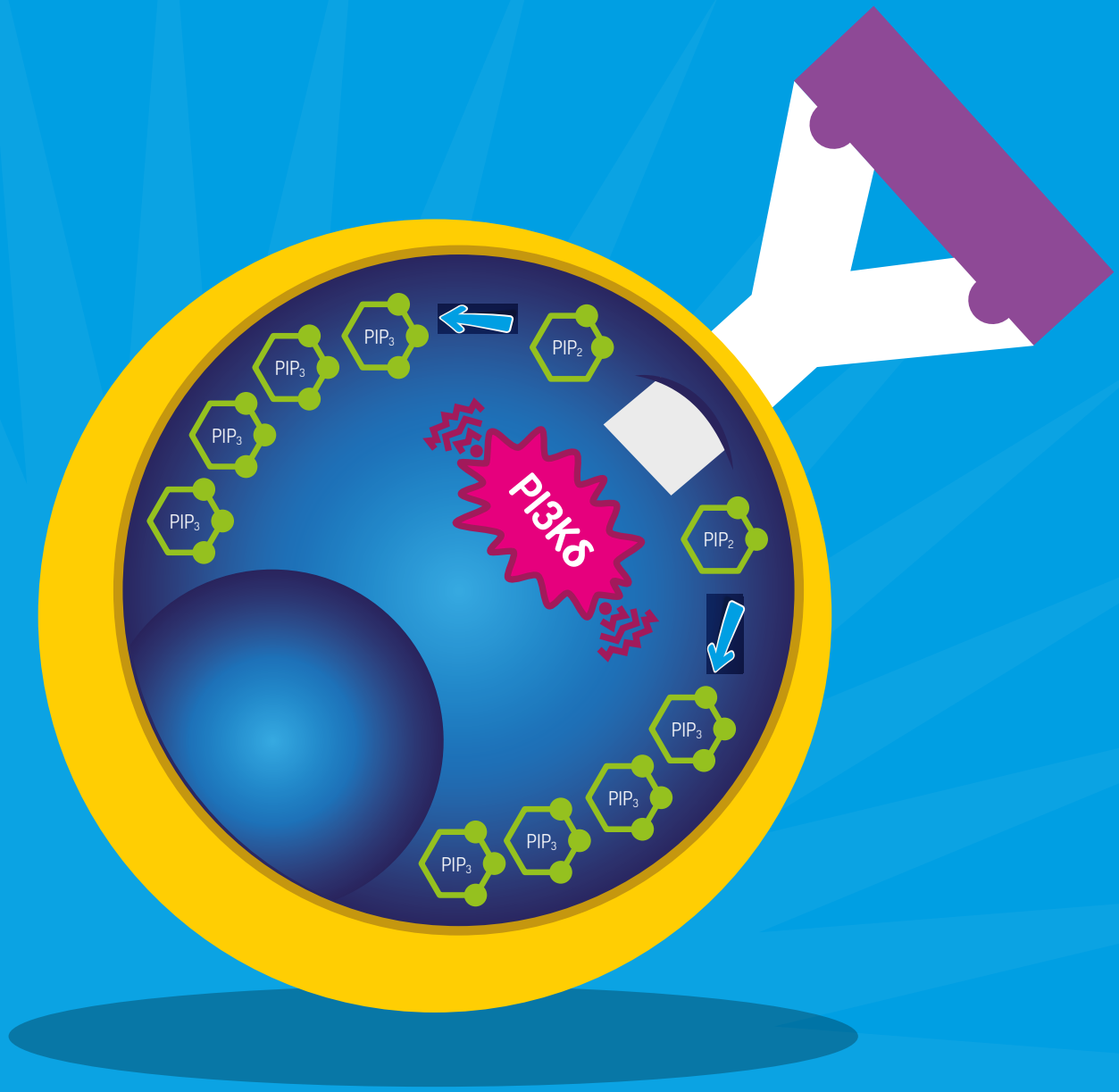
Surprisingly, patients have been identified with **too much PI3K activity** inside their B Cells!

These B Cells are a bit frantic – like they've had too much caffeine.

In these patients the B Cells develop (they can be found in the blood) but they **don't make enough antibodies** - or their antibodies are **not specific enough** to fight infections.

We have called this disease **Activated PI3K Delta Syndrome** (APDS) because of the specific type of PI3K which is over-activated.

APDS is rare, but several individuals in the UK have been identified with this heritable disease.



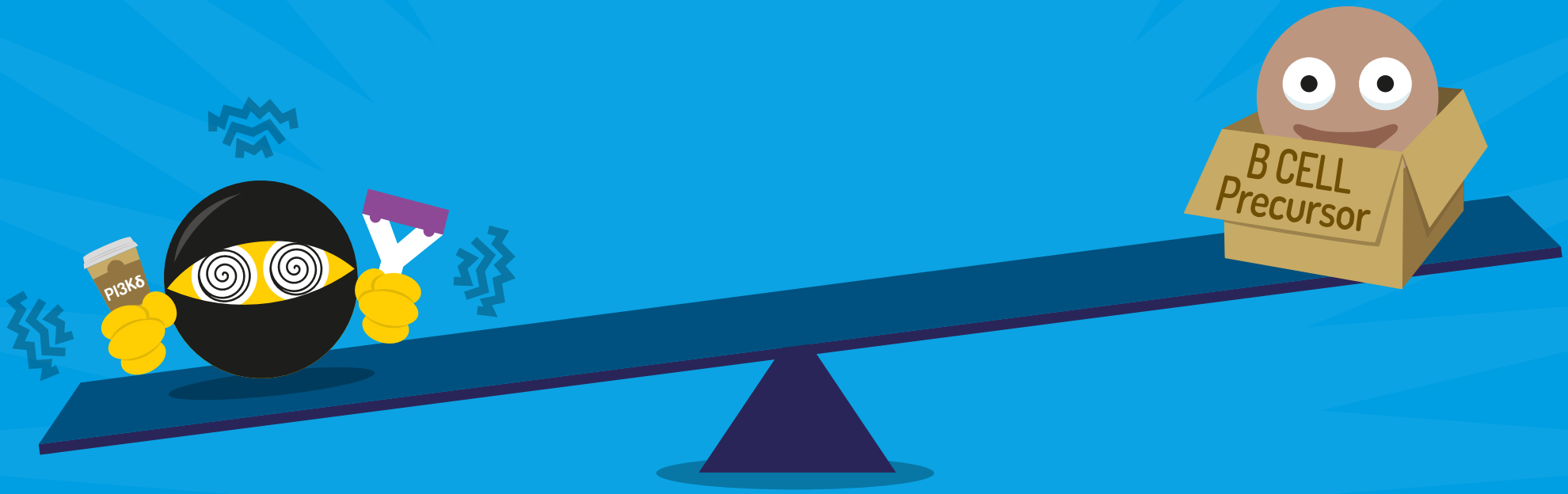
Because there are **drugs** that can be used to **inhibit PI3Kδ activity**, it is possible that APDS patients can be treated by taking such drugs.

This is something we are actively exploring, starting with a mouse model of the disease.

Summary

If you have too little, or too much, PI3K signalling in B Cells, the B Cells don't develop or function properly.

Much work at the Babraham Institute is therefore focussed on understanding precisely how PI3K activity is regulated in B Cells (and other cells) in health and disease.



Klaus Okkenhaug Laboratory

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Rafeah Alam
Daisy Luff
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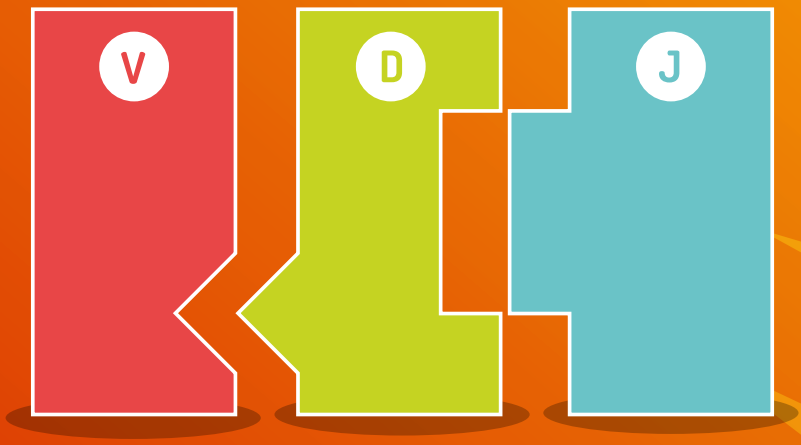
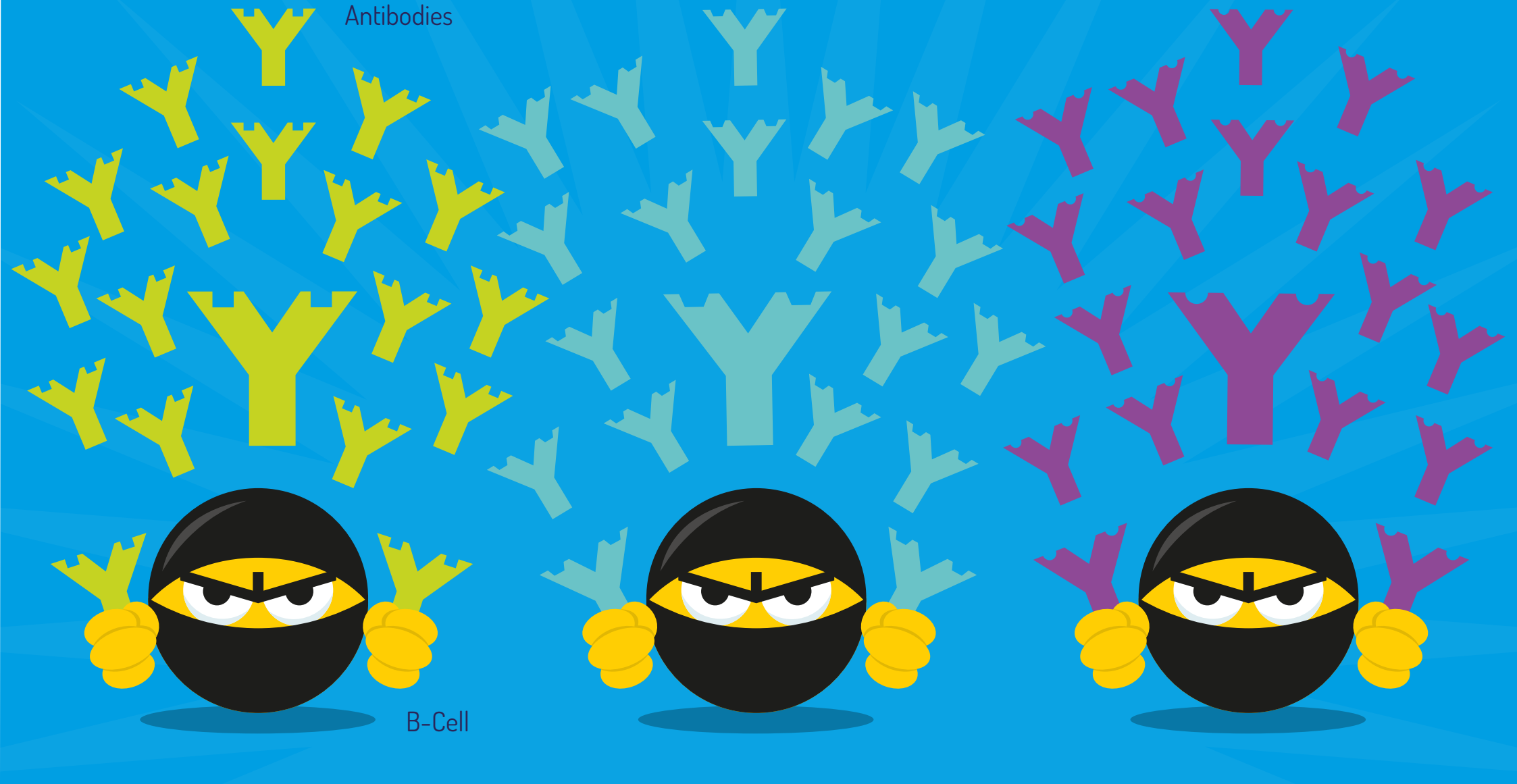
Research in the Okkenhaug Lab focuses on how a group of enzymes called PI3Ks are used by cells of the immune system.
www.babraham.ac.uk/our-research/lymphocyte/klaus-okkenhaug

For more information on APDS, please see:
www.apdsyndrome.org/

Missing Antibody Puzzle Pieces – Danger to Older People



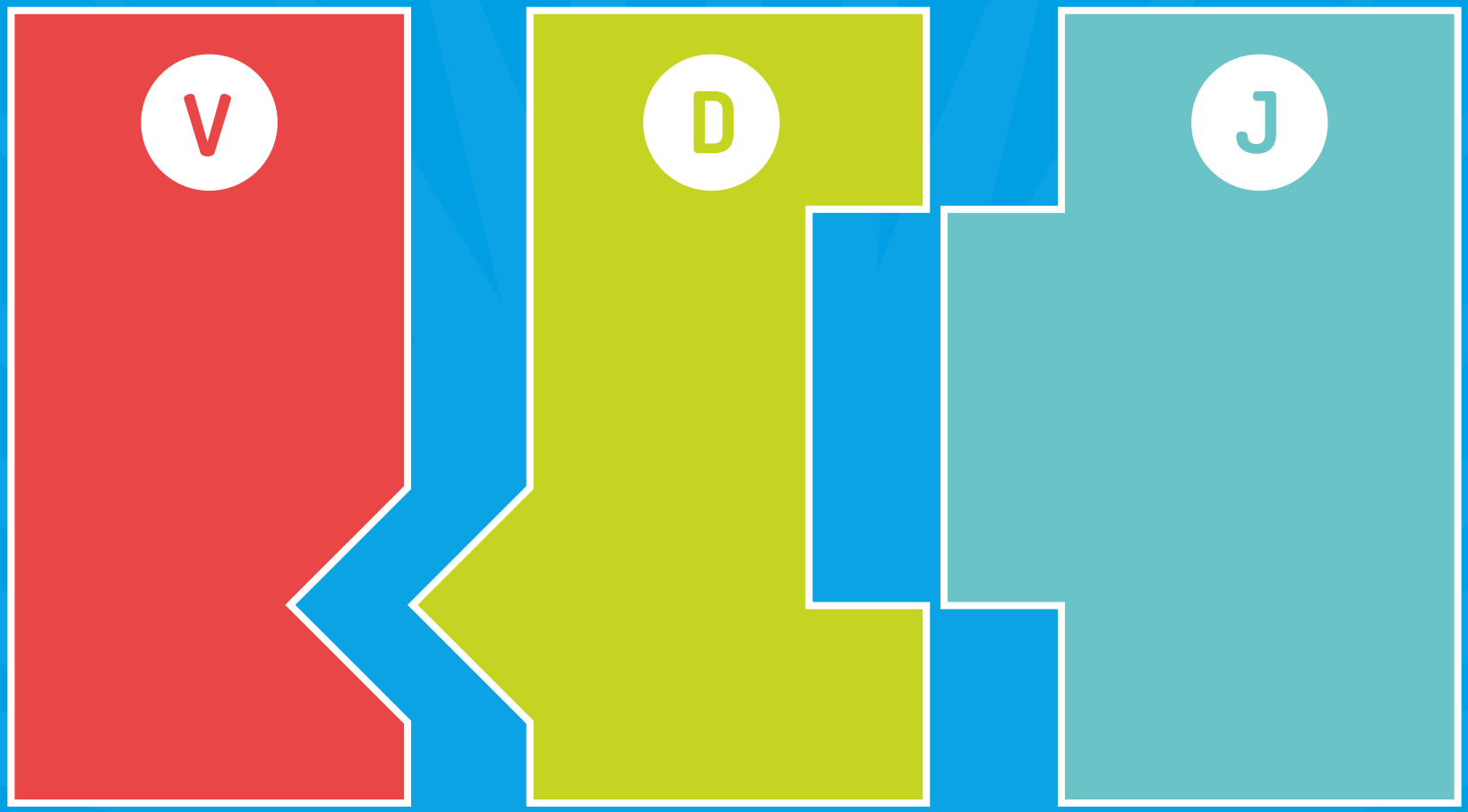
How do our B cells make enough **different antibodies** to catch all the different germs that could attack us?



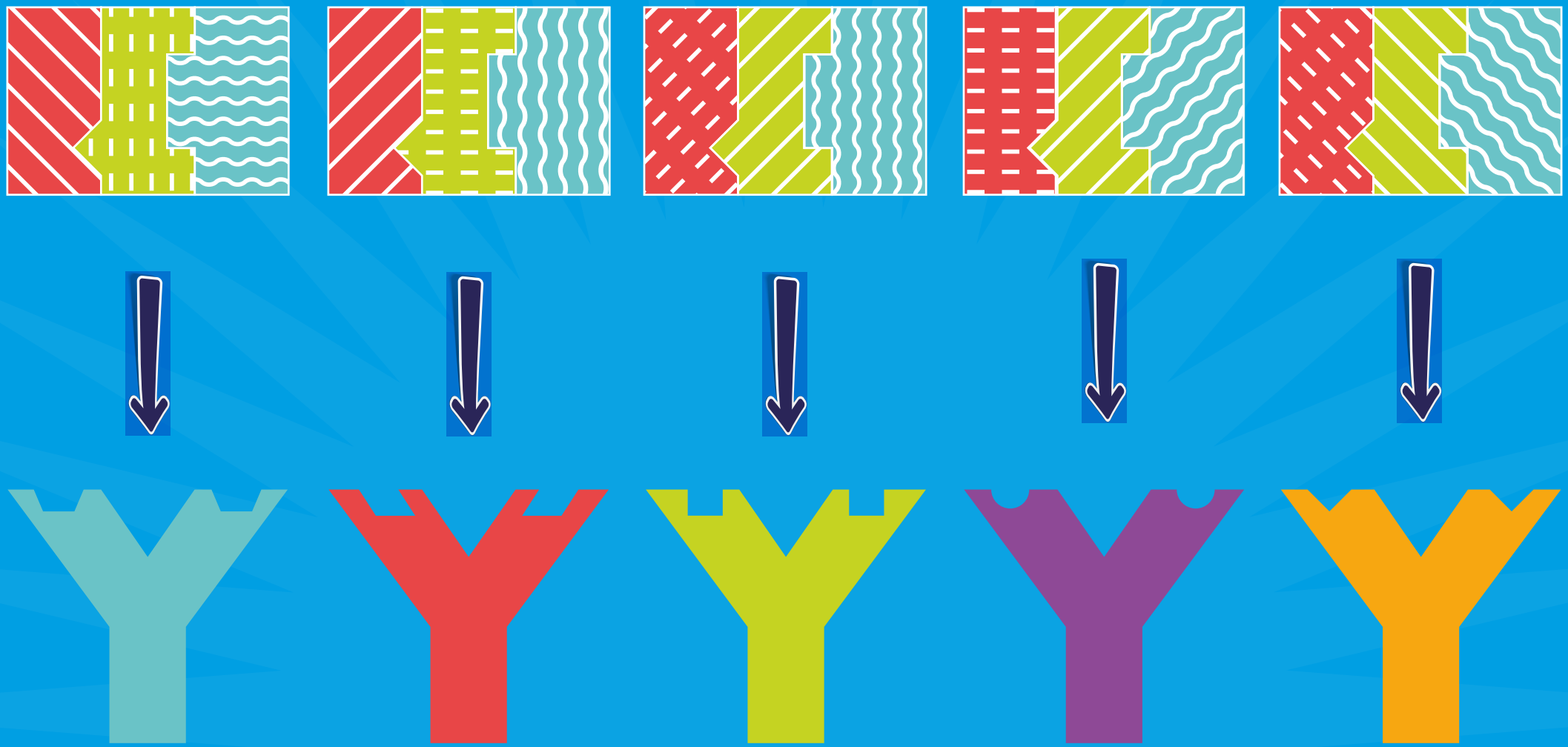
If we had a gene for every antibody we can make, our genome would be **over 1,000 times longer** than it already is...

...that's too much DNA to carry around!

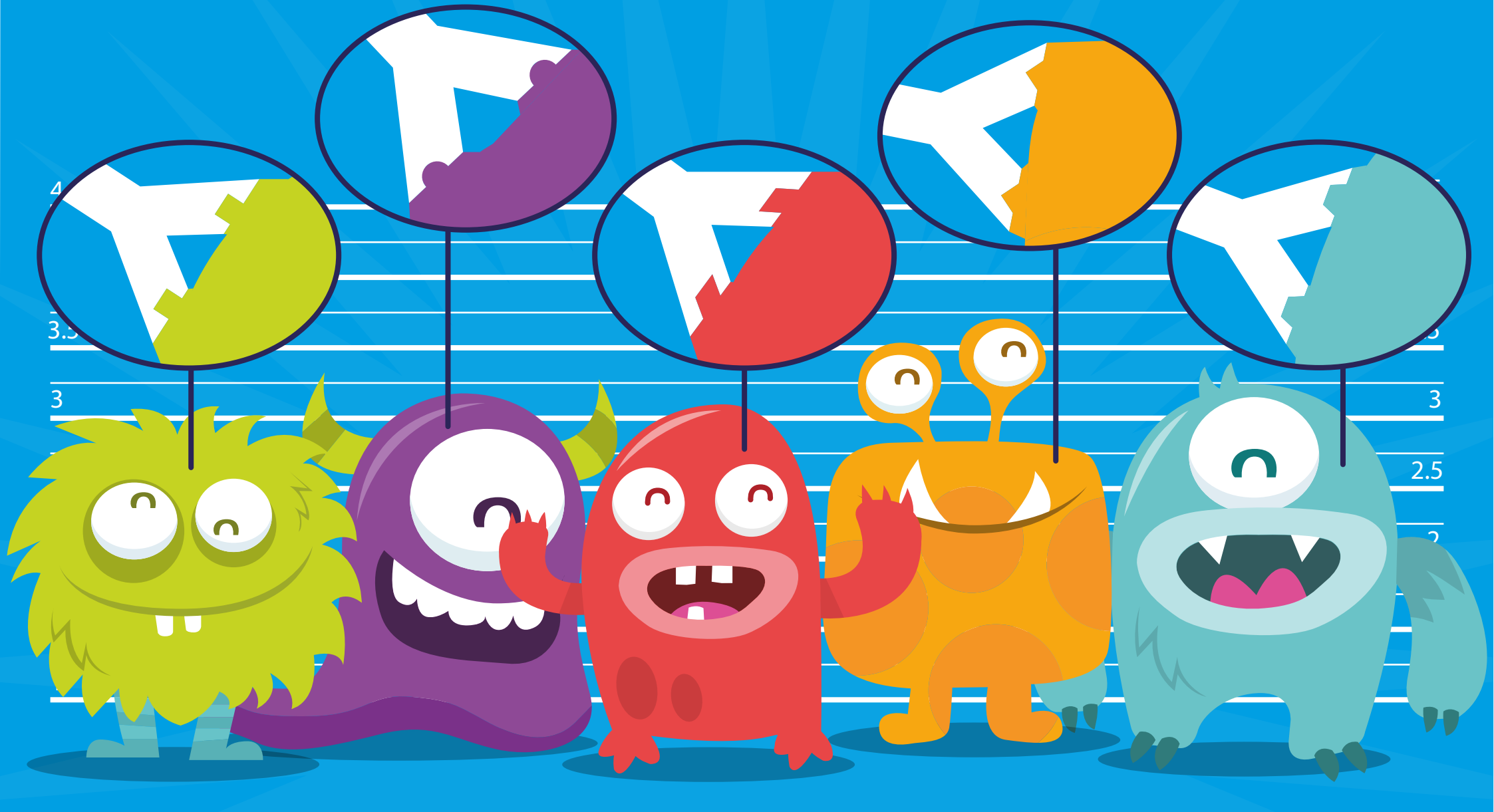
Instead, every B-Cell makes its own **unique antibody** out of a small set of components – **V**, **D** and **J** gene segments:



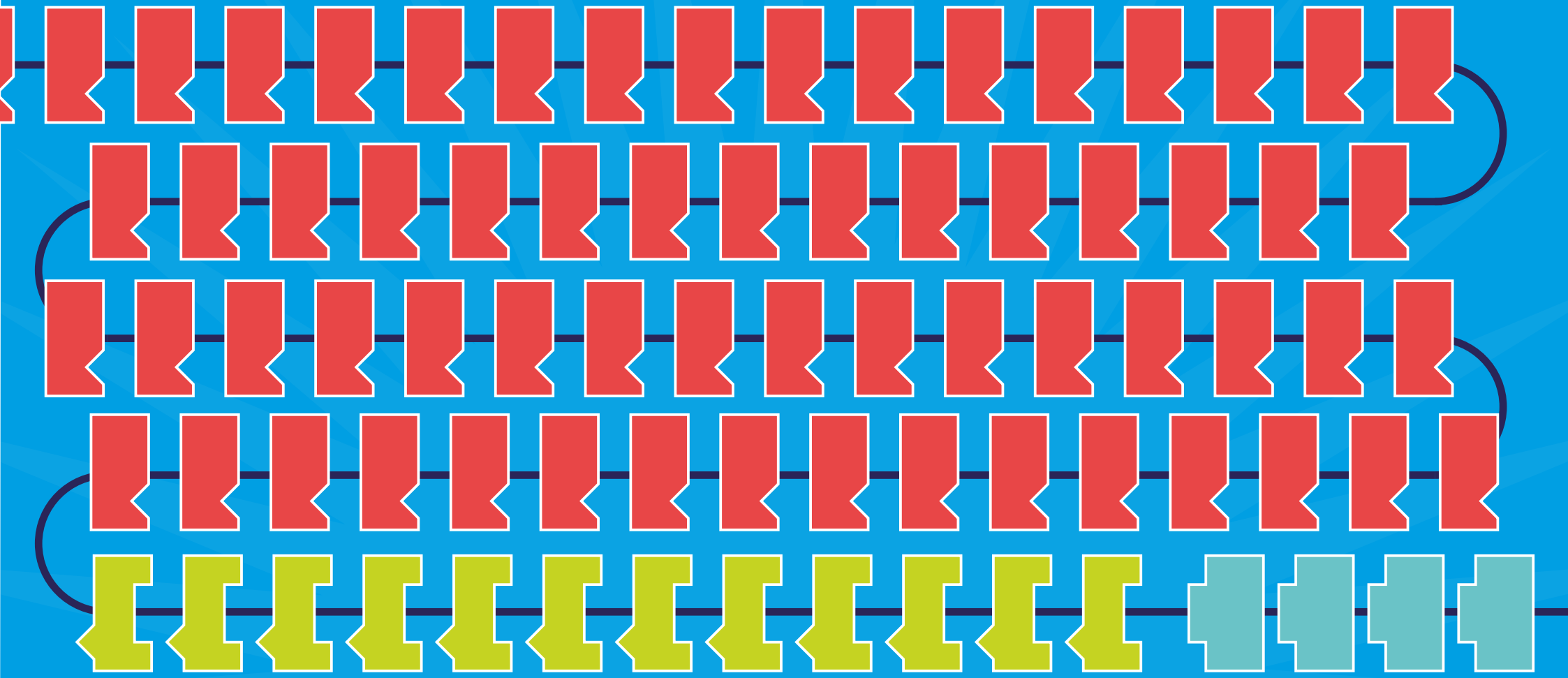
Different combinations of gene segments connect to each other to make the antibodies.



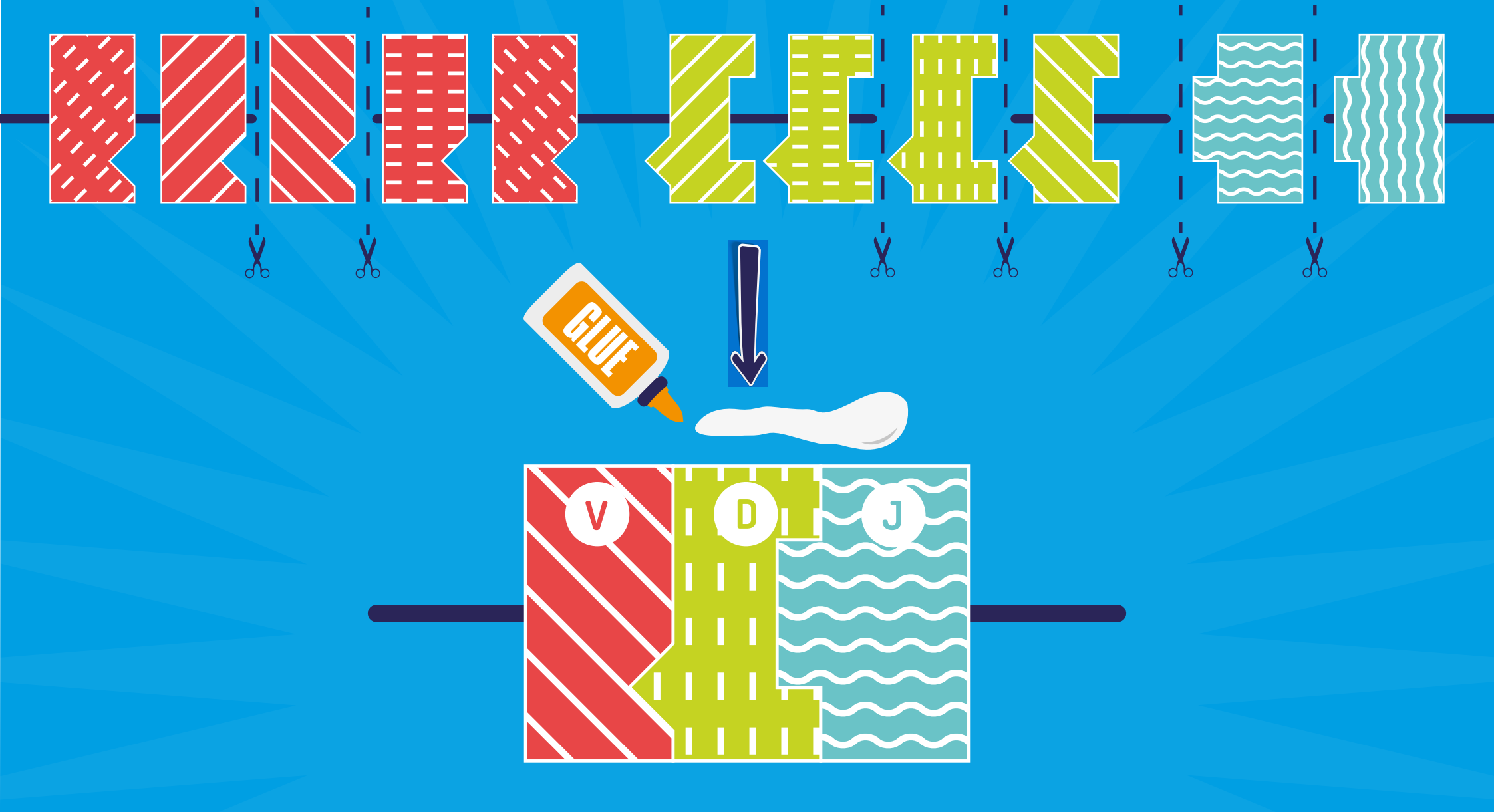
The antibodies are then able to **recognise and stick** to markers on pathogens (germs), known as antigens.



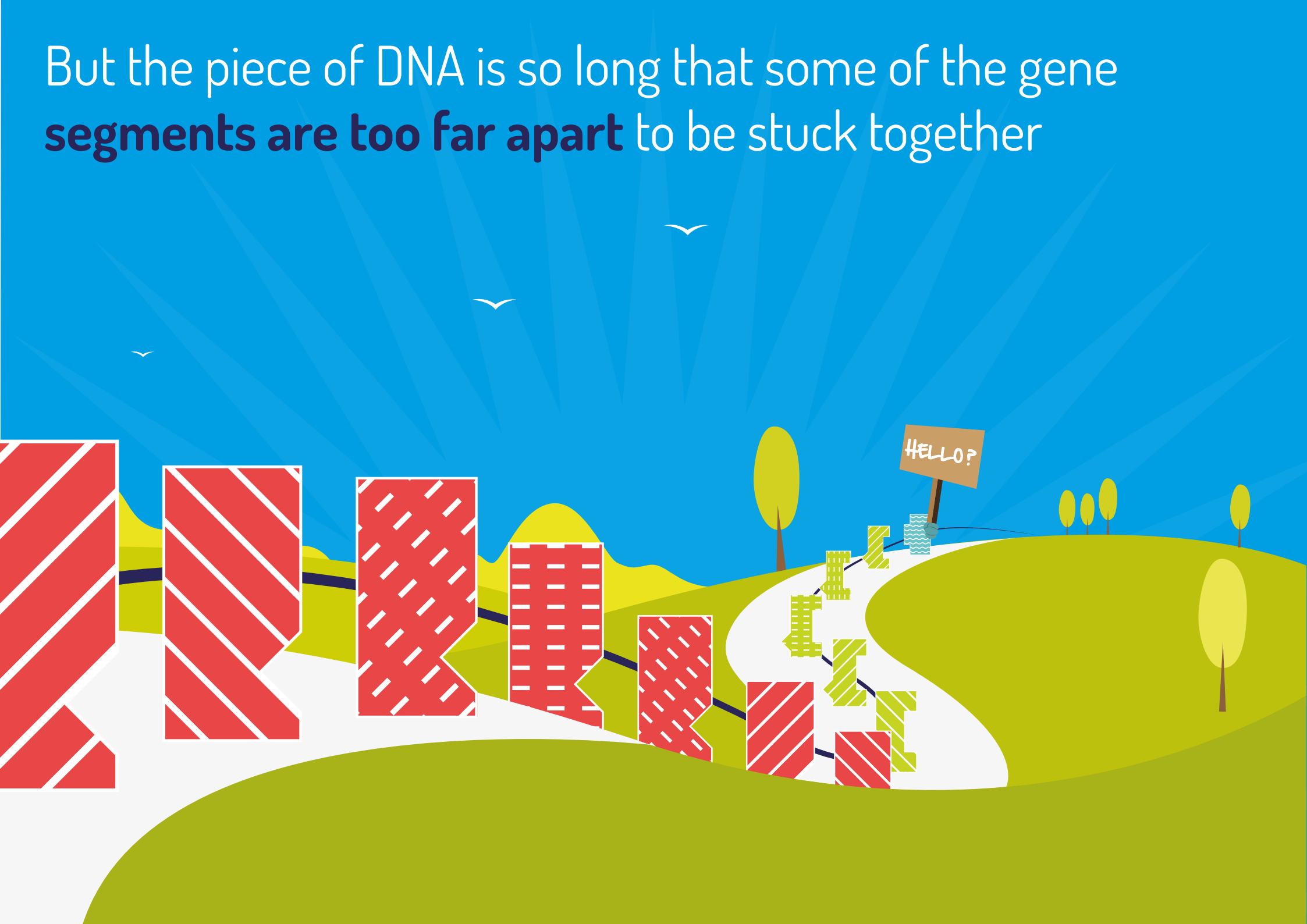
The V's, D's and J's are all on **one long piece of DNA**.



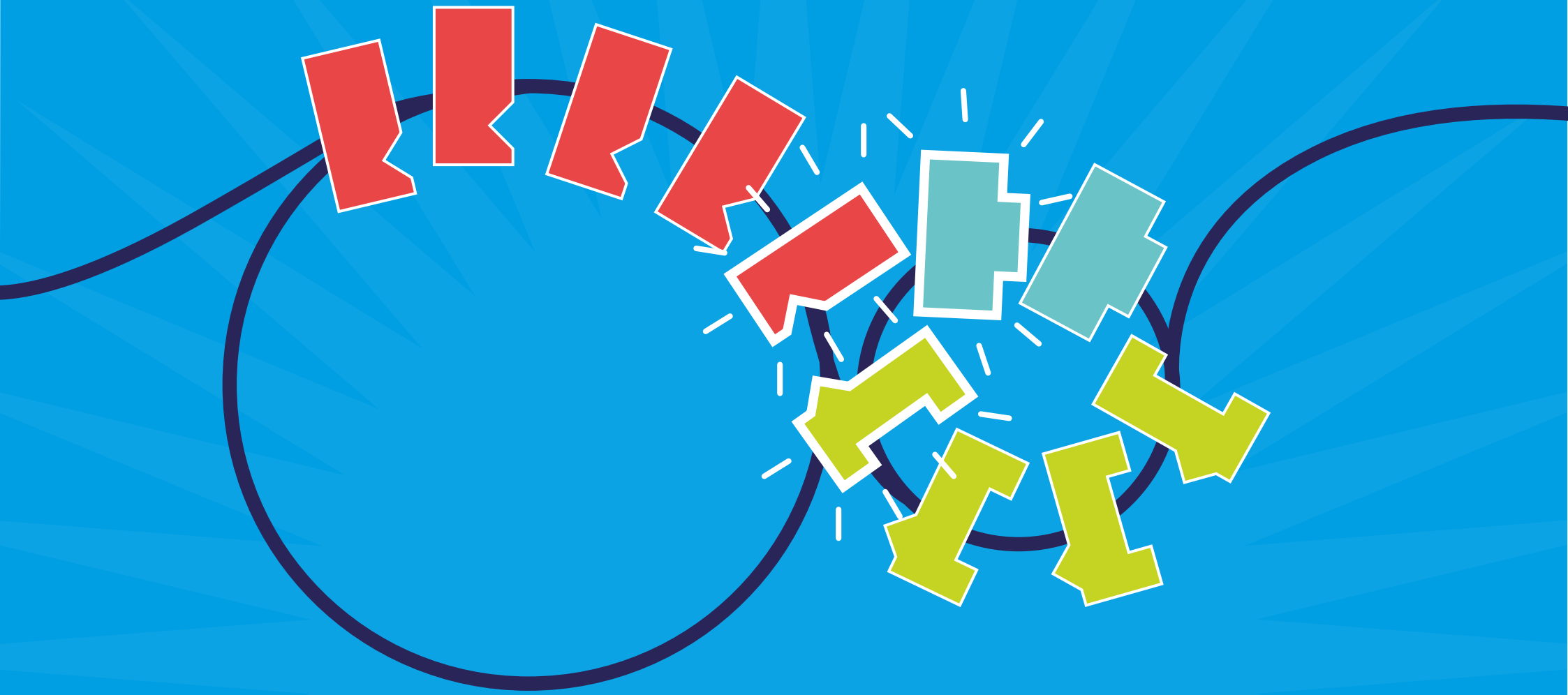
The DNA has to be **cut up and stuck back together** again to make an antibody.



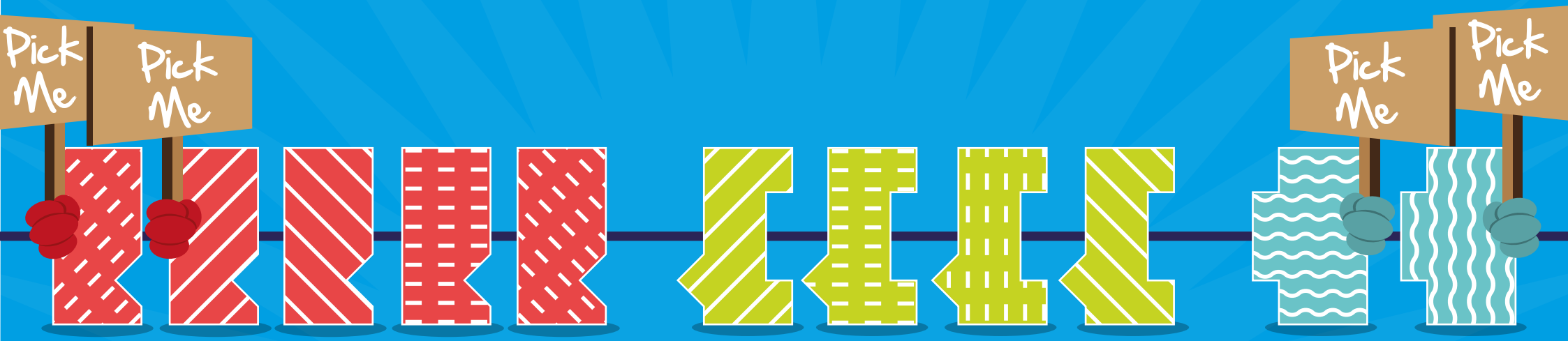
But the piece of DNA is so long that some of the gene **segments are too far apart** to be stuck together



B-Cells get around this problem by making loops in the DNA, pulling **far apart** gene segments **closer together**.

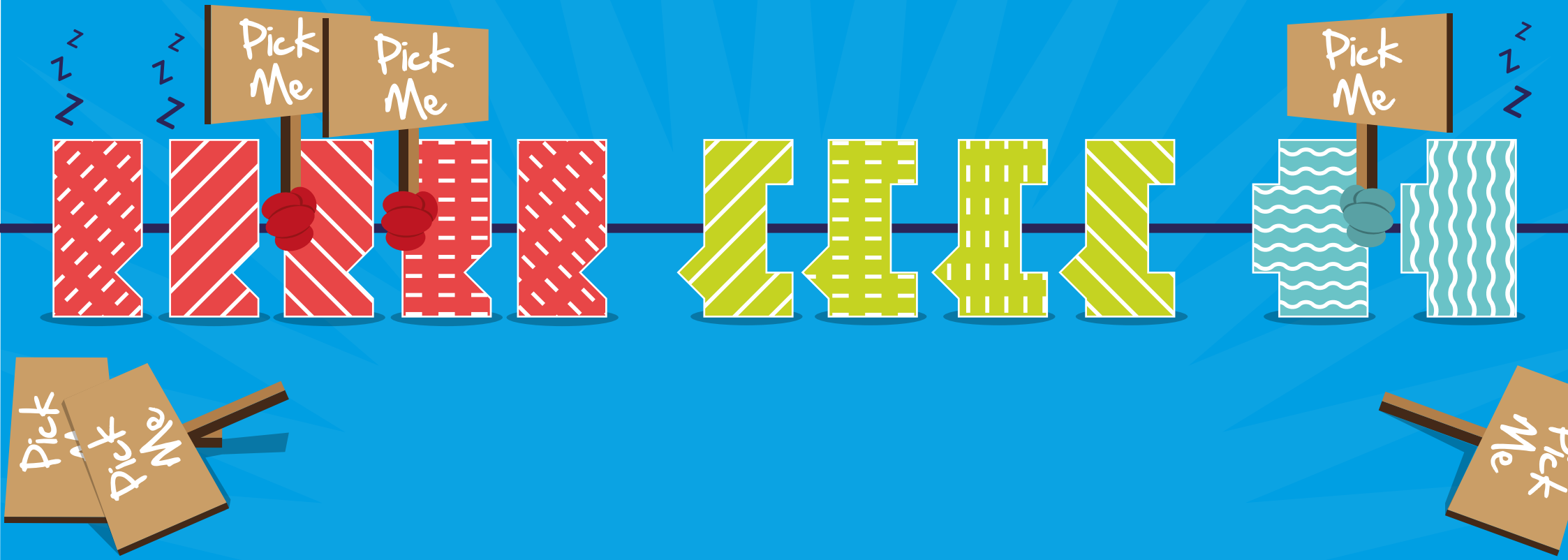


They also give special help to far away segments by giving them **epigenetic marks** to help them get chosen.



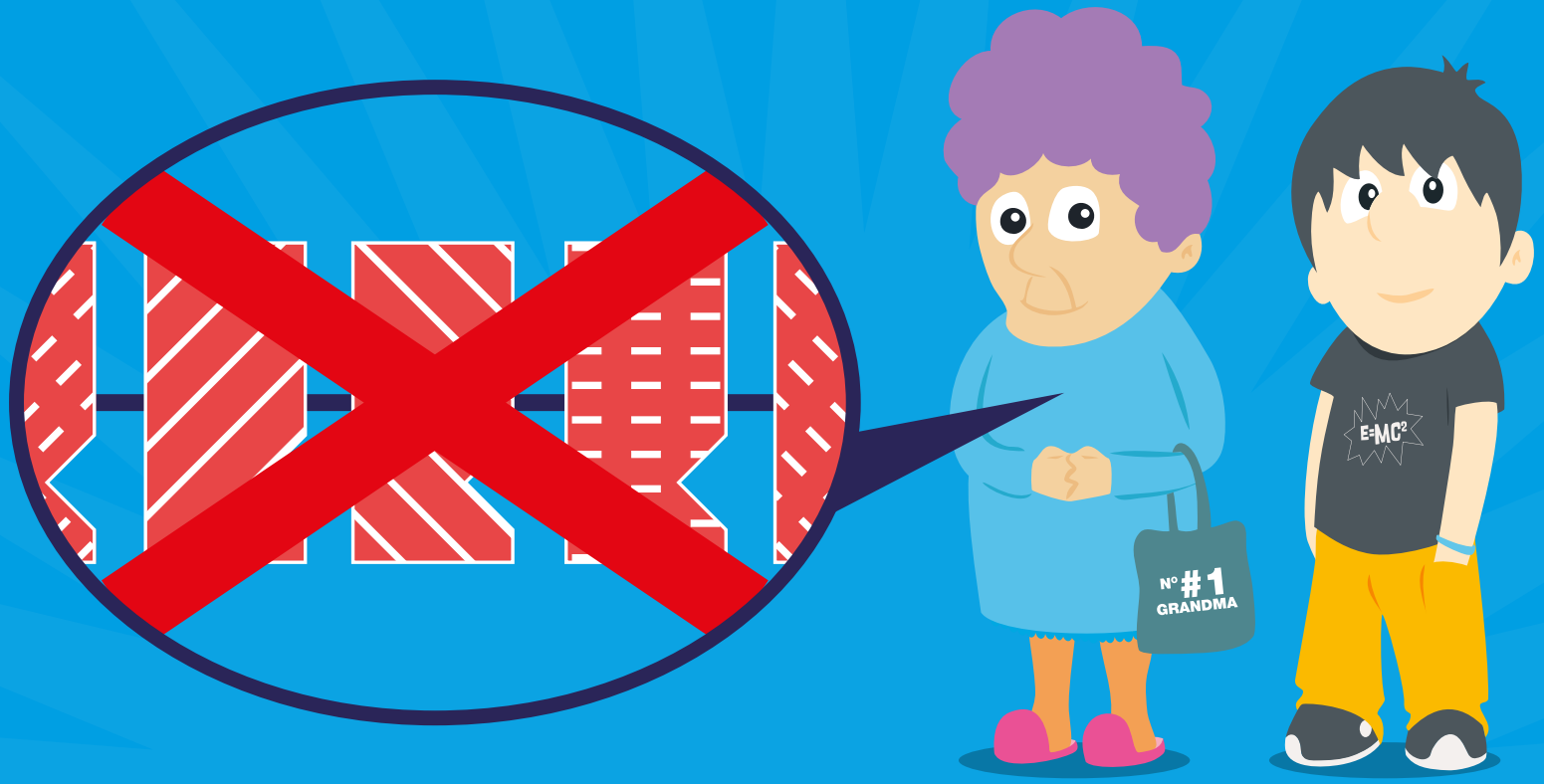
We have created a new technique called **VDJseq**. It lets us sequence the VDJ's in B-Cells so we know which V's, D's and J's were chosen in each cell.

This sequencing helps us find out **which genes are chosen and why**. It could also help find out what's wrong in people who have a weak immune response to infection.



Do some of their gene segments get ignored so they can't make as many antibodies?

Older people have a weakened immune response. VDJseq shows that **in older mice the far away V genes don't get chosen** as much as in younger mice.



We hope to understand whether problems with DNA looping or epigenetic marks cause this defect.

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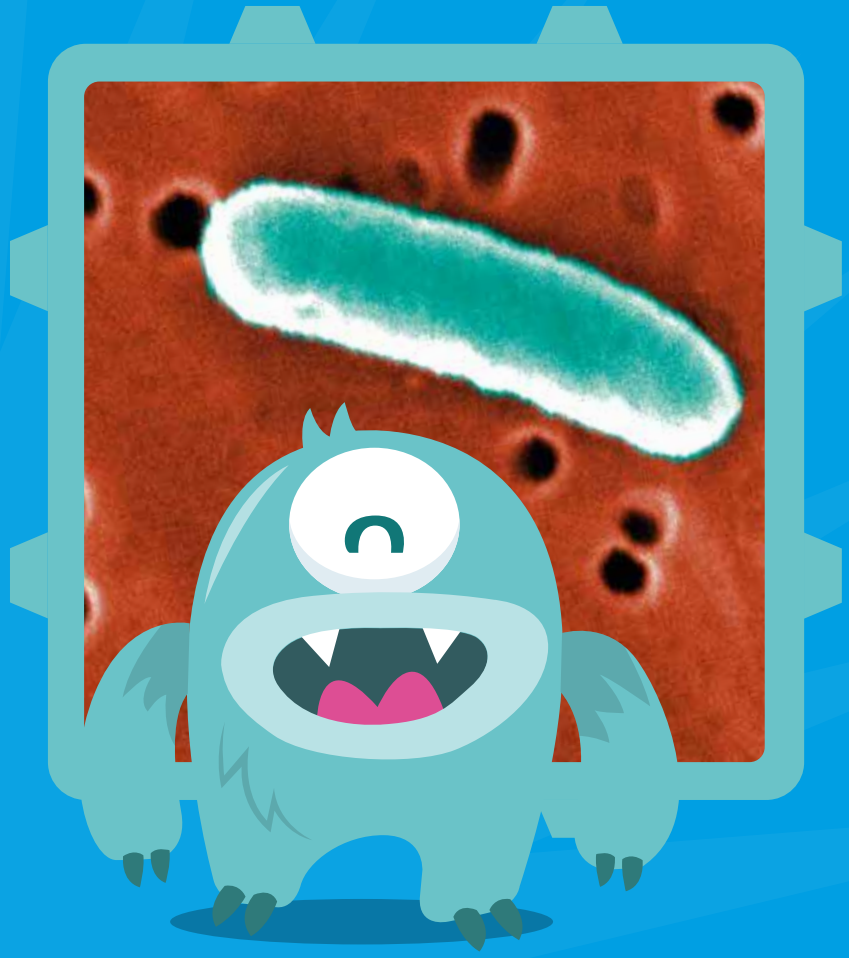
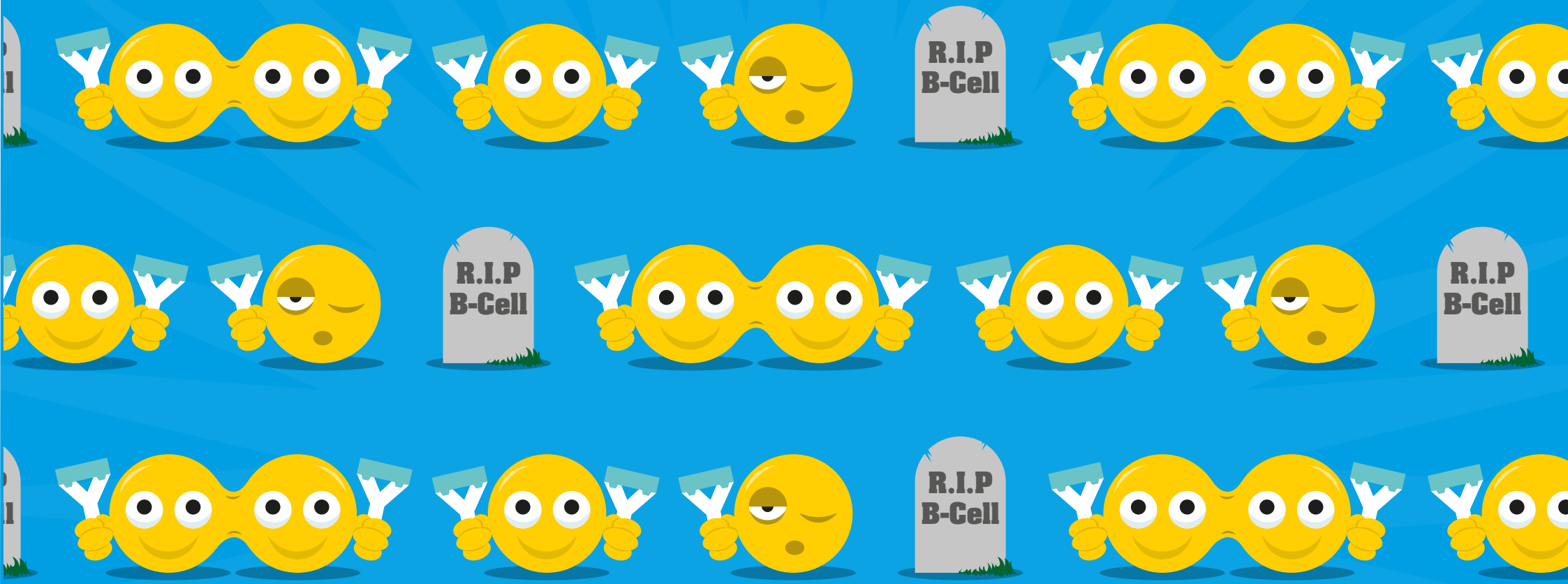
Research in the Corcoran Lab focuses on understanding the role of chromatin and nuclear organisation in controlling gene expression during the development of the immune system: www.babraham.ac.uk/our-research/nuclear-dynamics/anne-corcoran

What happens to B-Cells during an infection?

An infection activates naïve immune cells.

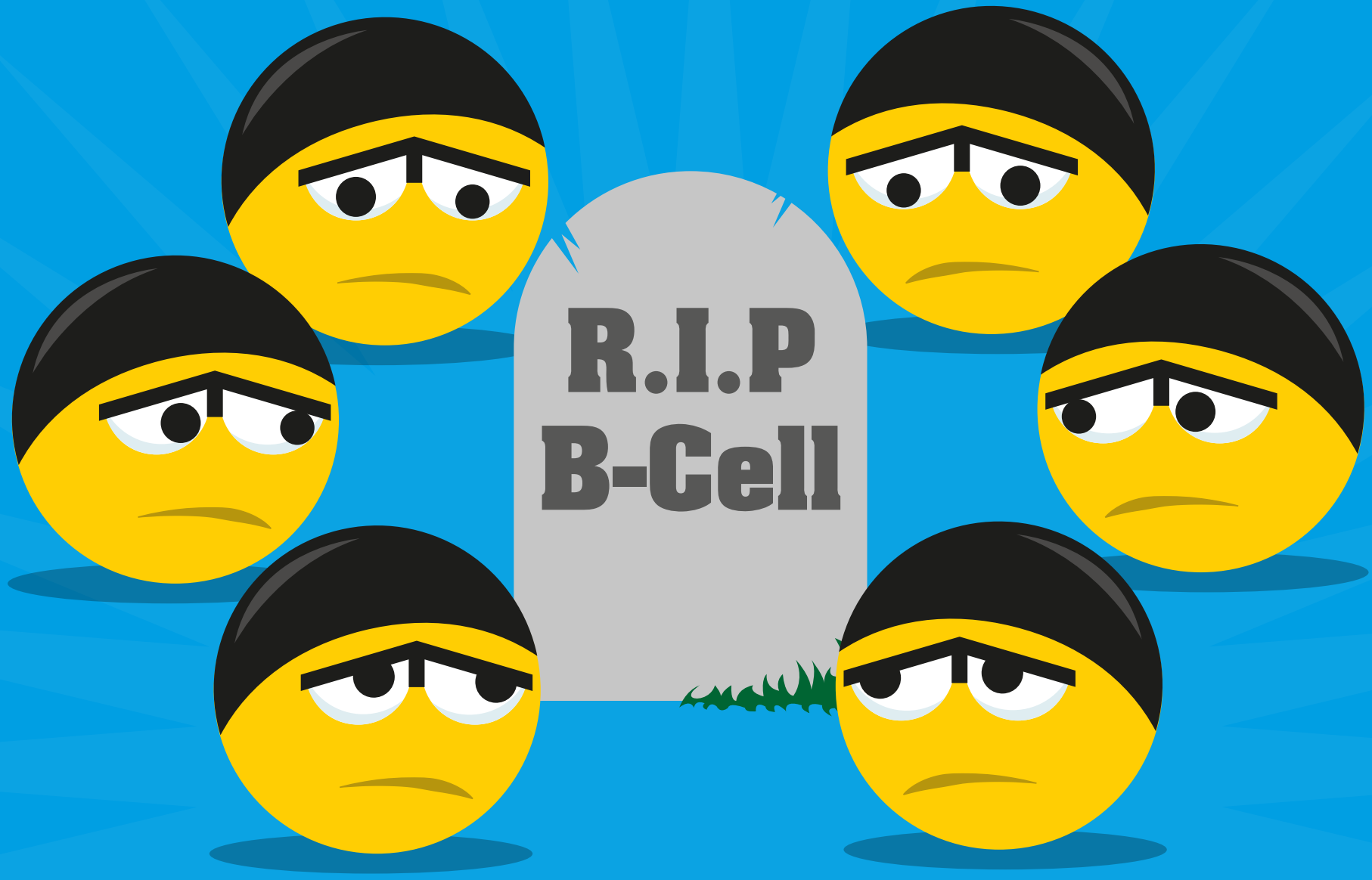


Initially some B cells are activated, they proliferate and make antibodies **(also called "immunoglobulins")** against the infection but these cells are short-lived and the antibodies **could be better at binding to the antigen**.

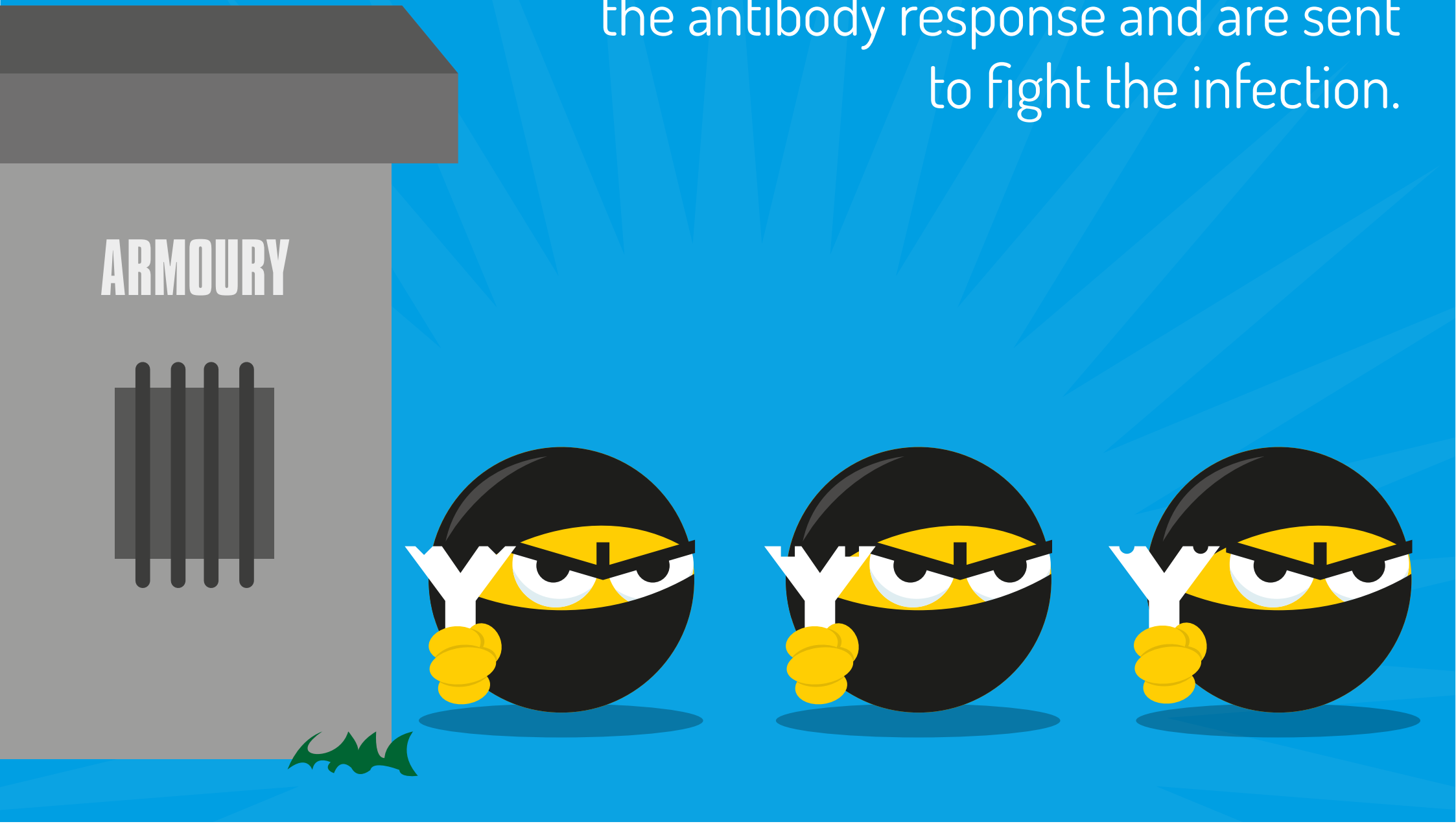


Whilst this initial response is happening, specialised areas form called **‘germinal centres’**, where B-cells can obtain the necessary weapons they need to further fight the infection.

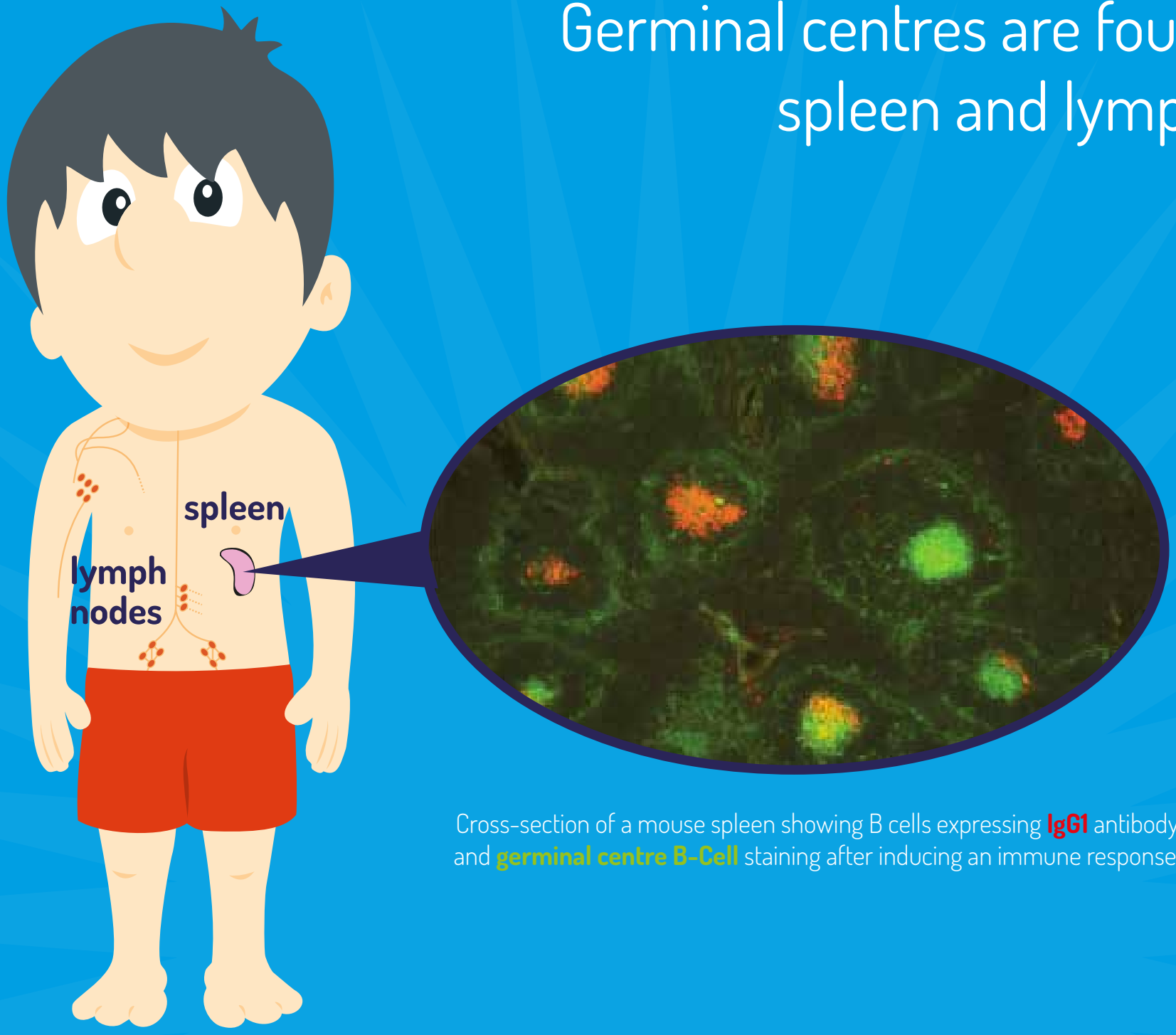
The cells that are unable to obtain the correct weapons to fight the infection **fail and die**...



...the B cells that do obtain the correct weapons by **"class switching"** are selected to improve the antibody response and are sent to fight the infection.

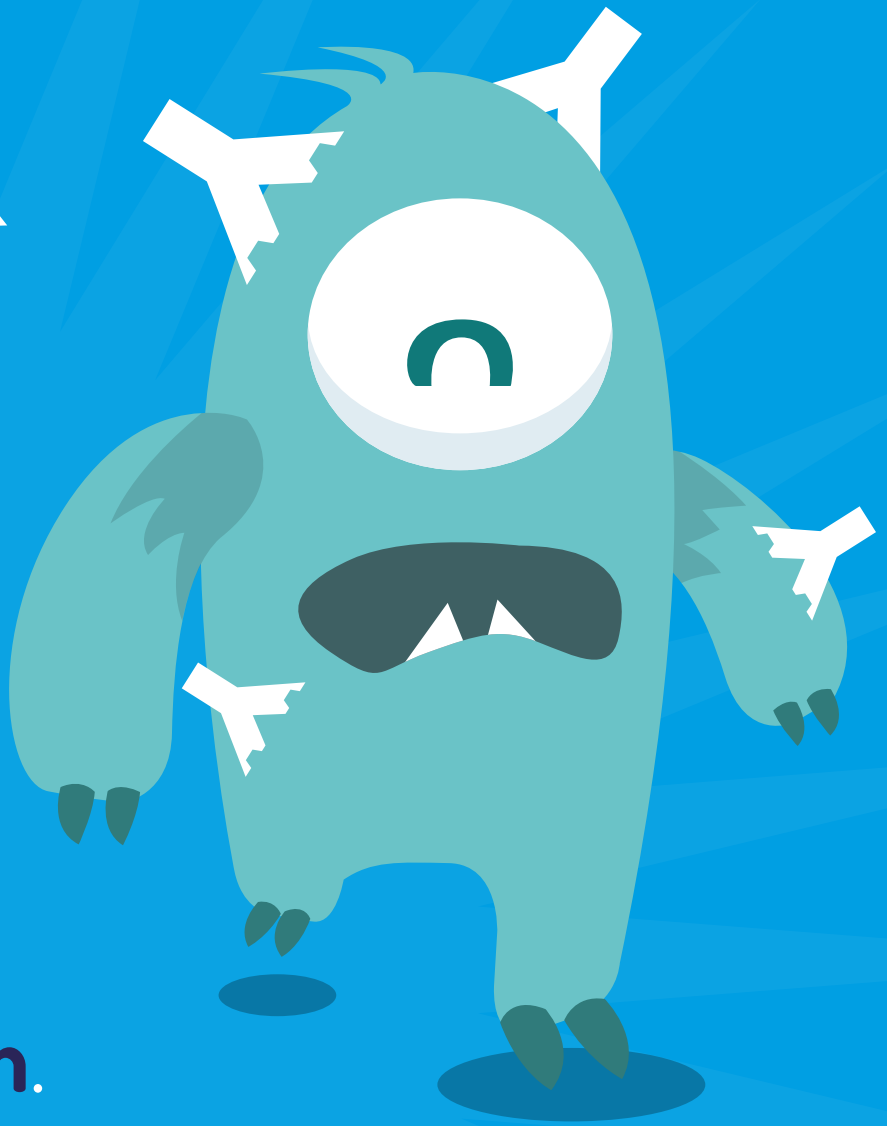


Germinal centres are found in the spleen and lymph nodes.



Cross-section of a mouse spleen showing B cells expressing **IgG1** antibody and **germinal centre B-Cell** staining after inducing an immune response.

One outcome is the formation of **specialised** B-cells called **plasma cells** which produce large amounts of antibodies...



...which **bind** strongly to the **antigen**.

'Memory B-cells' can remember encounters with infection in case the body needs to fight it again.

Why are the germinal centres so important?

A strong germinal centre response is critical for a successful response to infections and vaccinations (which are designed to simulate a weak infection).

What happens when an antibody response goes wrong?

Sometimes it can go wrong, for example the cancer called myeloma occurs when the plasma cells become abnormal, multiplying uncontrollably and releasing only one type of antibody.

We are investigating how programmes of gene regulation control antibody production.

Martin Turner Laboratory

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Research in the Turner Lab focuses on understanding the fundamental mechanisms that control immune cell development and function throughout the life-course.
www.babraham.ac.uk/our-research/lymphocyte/martin-turner