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ANIMATION SCRIPT

WHAT HAPPENS WHEN OUR BLOOD PRODUCTION SYSTEM FAILS?

DR KRISTINA AMES

TO MAKE THE MOST OUT OF THIS SCRIPT, YOU COULD:

- Stick it in your book as a record of watching Kristina's animation
- Pause the animation and make notes as you go
- Add your own illustrations to the sheet
- Create your own animation to accompany it
- Add notes from classroom discussions
- Make notes of areas you will investigate further
- Make notes of key words and definitions
- Add questions you would like answered – you can message Kristina through the comments box at the bottom of her article: **www.futurumcareers.com/what-happens-when-our-blood-production-system-fails**

SCRIPT:

An adult human body contains approximately 5 litres of blood, forming about 10% of the body's weight, and produces billions of new blood cells every day.

At the Albert Einstein College of Medicine in New York, USA, Dr Kristina Ames investigates why blood production problems occur.

The production of blood cells is called haematopoiesis, which occurs through haematopoietic stem cells (HSCs) that exist in bone marrow.

HSCs self-renew, meaning the supply never runs out.

HSCs can also differentiate, meaning they can turn into other types of blood cell, such as red blood cells, platelets and T cells.

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Once the blood cells are mature, they move out of the bone marrow and into the blood system, where they circulate around the body.

If the balance between HSC self-renewal and differentiation is disturbed, improperly undifferentiated blood cells remain in their immature form, known as 'blasts', which can lead to cancer.

Myelodysplastic syndrome (MDS) is a type of cancer that occurs when HSCs do not differentiate into mature blood cells, resulting in presence of blasts in the bloodstream.

If too many blasts are formed, MDS can progress into acute myeloid leukaemia (AML).

About 20,000 people are diagnosed with MDS every year in the US, and up to 40% of MDS patients progress to AML.

To maintain proper haematopoiesis, molecules in the body send signals to HSCs in the bone marrow to convey whether they need to produce new blood cells.

Kristina is interested in the role of the phosphoinositide 3-kinase, or PI3K, pathway in haematopoiesis. This pathway is activated during several types of cancer, but the role of PI3K in regulating HSC function is poorly understood.

Because the PI3K pathway regulates multiple cellular processes, but Kristina only wants to study its influence on HSCs, she used a mouse model that allowed her to delete the three redundant isoforms of PI3K in the mouse's haematopoietic system.

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Kristina used this Triple Knock Out (TKO) mouse model to investigate whether the TKO mice had normal blood production. She discovered that removing the three isoforms from a mouse led to a significant decrease in the populations of all types of blood cells.

Kristina then performed bone marrow transplants on the TKO mice and saw that the bone marrow cells of these mice showed signs of abnormal differentiation, similar to those seen in patients with MDS.

In TKO mice, HSCs are unable to regulate the process of autophagy, in which cells recycle unnecessary organelles and clean themselves. This is because mice without PI3K isoforms displayed decreased expression of several autophagy genes.

Kristina's research has shown that a lack of PI3K signalling disrupts autophagy in HSCs, and this causes defective differentiation. Impaired autophagy is a key mechanism for disrupted HSC differentiation in patients with MDS, so autophagy-inducing drugs could help to restore HSC function.

What discoveries could you make as a cell biologist?