CCLG: The Children & Young People's Cancer Association research:

Investigating how regulatory regions of the genome communicate with cancer causing genes

Project title: Identifying critical interactions between super-enhancers and proto-oncogenes: driver events in T-cell acute lymphoblastic leukaemia

Project stage: Ongoing (started June 2022, ending September 2025)

Funded by: Ruby's 'Live Kindly, Live Loudly' Fund

Led by: Dr Lisa Russell, Newcastle University

About the project

Acute lymphoblastic leukaemia is the most common childhood cancer, affecting over 650 children and young adults in the UK each year. Current treatments cure around 90% of children, but this comes at a significant cost: side-effects include heart, thyroid, lung and fertility problems. In addition to this, the outlook for children whose leukaemia returns remains poor.

Regulatory regions of our DNA are responsible for interacting with genes and switching them on and off. In healthy cells, regulatory regions called 'enhancers' carefully control important genes at the correct time to allow cells to complete their job. Some patients with leukaemia have errors in their DNA that lead to these enhancers switching on the wrong gene. Because there are a lot of genes involved in these errors, it is hard to develop ways of killing the cancer cells and most of these errors cannot be specifically blocked by current medicines.

Recently the research team at the University of Newcastle, led by Dr Lisa Russell, have proposed a new model that helps to understand how these regulatory regions switch on the wrong gene. Now they want to investigate how the enhancers and the genes they switch on are communicating with each other, so that they can develop new treatments targeting their interaction in cancer cells. Although many of the genes that are incorrectly turned on or off are involved, there are only a few regulatory regions controlling them. If there was a way to switch these misplaced enhancers off, it could stop the cancer cells growing.

Dr Lisa Russell hopes that this could benefit many children with a wide range of blood cancers. The final goal is to design drugs that stop the enhancers communicating with the wrong genes. Treatment targeting this communication should have reduced side effects, as it only wouldn't target normal body cells.

Progress

So far, the team have had some success in reducing the activity of a cancer-causing gene, but are still refining the process and ensuring that it is repeatable. They have done this by genetically editing cancer

cells so they produce proteins that can block the enhancer region. Blocking the enhancer reduces the activation of the cancer-causing gene.

As their previous method of introducing the gene editing machinery caused experimental problems, the team changed to an approach where viruses deliver the gene editing machinery and guides together. Once in the cancer cell, the guides take the gene editing machinery to the enhancer. They have now developed and validated viruses that can do this and have tested them on cancer cells in the lab.

They found that this method could reduce the cancer-causing gene's activity, but not turn it fully 'off' as they had hoped. The researchers are currently planning their next steps, and believe that more guides could help more of the gene editing machinery get to the right place in the DNA.

What's next?

Dr Russell has been awarded six years of funding from a new Cancer Research UK grant, and also hopes to use the results from this project to apply for further grants.

Together, this will enable the researchers to continue working on turning off enhancers, whilst also finding ways to identify proteins to inhibit which control cancer-causing genes.

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