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

Lead researcher: Dr Lisa Russell, Newcastle University

Project Stage: Ongoing (started June 2022, planned end September 2025)

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

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 of this research 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 targets the leukaemia cells and not normal body cells.

CCLG RESEARCH PROJECT UPDATE

PROGRESS

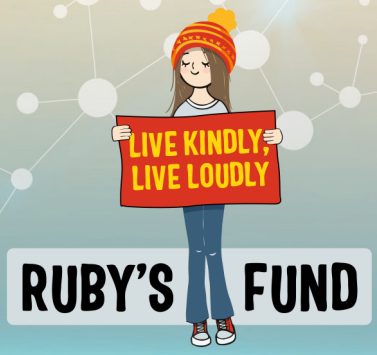
Dr Russell's team have been trying to shut down important parts of enhancers in cells that have T-cell acute lymphoblastic leukaemia (T-ALL). First, they had to genetically edit the cells to make them produce proteins that would shut the enhancer down. They used these proteins to target four areas in one large enhancer region.

Whilst they did manage to switch off a cancer causing gene in initial experiments, further research showed that it was being turned off in the wrong cells. Since then, the team have designed viruses ensure the gene editing proteins go to the right place. These 'guides' take the gene editing machinery to the four small enhancer regions, where it can use the proteins to turn off the gene. Designing this approach has taken many months, and the team hope to start testing it more fully soon. There has been a 16 month extension to the project, due to staffing changes, which will allow more time for this work.

WHAT'S NEXT?

The team will continue to test the new approach. Once they can successfully and reliably turn off the enhancers, they will generate data for publication that will enable further research into enhancers in T-ALL. The researchers also plan to look for drugs that can turn off enhancers, in order to start developing or repurposing new medicines for childhood leukaemia.

Dr Russell has combined the preliminary data from this and related grants and applied for Cancer Research UK funding. She hopes to receive the outcome of this soon.



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