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

Understanding why some childhood blood cancers are incurable

Project title: Understanding molecular mechanisms that drive high-risk childhood acute lymphoblastic leukaemia

Project stage: Ongoing (started August 2023, planned end July 2026)

Funded by: CCLG and CCLG Special Named Funds including Ruby's 'Live Kindly, Live Loudly' Fund, Fred Bennett's 'Don't Look Down' Fund, Toti Worboys Fund, Harley James Reynolds Fund, Josh's Gold Star Fund, Seren's ALL Stars, Thomas Fight Tall, and Ariana's Rainbow Friends.

Led by: Professor Anindita Roy, University of Oxford

About the project

Although we can now cure nine out of 10 children with leukaemia, there are still some children who can't be treated successfully. These children have 'high-risk' types of leukaemia that are usually caused by errors in specific genes. These patients often don't respond to treatment and their cancer can return after treatment. We urgently need a better understanding of these treatment resistant subtypes, so that we can cure every child with leukaemia.

Professor Anindita Roy and her team at the University of Oxford have developed a way to create models which behave like cancer, by giving leukaemia genes to normal cells. They will use these models to understand how high-risk leukaemias develop, the pathways that drive this aggressive disease and to test new drugs for treatment. Previous research by their lab has shown that leukaemia cells can need certain genes to be mistakenly turned on or off in order to survive.

In this project, Professor Anindita Roy will use leukaemia cells from these models, and from patients, to understand how these leukaemia survival genes cause the cancer cells to develop and resist treatment. To do this, her team will analyse how different types of healthy cells change when given leukaemia genes, and see whether preventing these changes can make the leukaemia less aggressive. The results of these experiments will show suggest new targets for treatment - especially if the researchers can find a preventable change that is only found in treatment-resistant leukaemia cells.

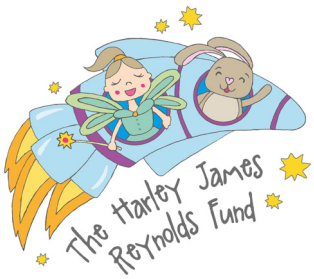
Progress

The team have been working on creating a model with a genetic error called MLL::AF4 (more recently known as KMT2A::AFF1) translocation. This error can be formed in a few different ways, which causes distinct differences in the leukaemia. After their work to introduce this genetic error to cells, the researchers have created three stable leukaemia models that can be reproduced and worked on in the

lab. These models are now being used to understand more about the effects of different leukaemia mutations. The researchers have continued their work into how these errors lead to leukaemia. They had already shown that different types of leukaemia can develop, depending on how the translocation formed. Now, they are doing a deep dive into these leukaemias, looking at which cells are present and how the cancer behaves.

What's next?

Over the next year, the team will continue investigating high-risk leukaemia development through their new models. They plan to look at which genes are active in cancer cells and how DNA is used. They hope to identify what the cancer needs to grow and survive in order to suggest new methods of killing leukaemia cells. Prof Roy will also look at how the leukaemia cells change over time, hoping to identify whether the high-risk leukaemias are more likely to develop into a second type of leukaemia. This is often especially difficult to treat.



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