

Investigating the shape of fusion genes in rhabdomyosarcoma



Project title: Investigating the RNA structurome of fusion-positive rhabdomyosarcoma

Lead researcher: Dr Darrell Green, University of East Anglia

Project Stage: Starting soon (October 2024)

Funded by: Funded by CCLG and CCLG Special Named Funds including Pass The Smile For Ben, Be More Ruby, Just George, Team Jake, Jacob's Join, Hattie's Rainbow of Hope, Cohen's Fight and The Jenni Clarke Fund

ABOUT THE PROJECT

Around 55 children are diagnosed with rhabdomyosarcoma each year in the UK. But unlike adult cancers, which are caused by an accumulation of genetic errors (DNA) acquired over decades, some types of rhabdomyosarcoma are caused by a single genetic fault.

Around 25% of patients with rhabdomyosarcoma have a genetic error where two normal genes have fused together to become one abnormal gene. This fusion causes the cancer. This is known as the 'fusion-positive' subtype and has the worst survival rates. Fusion-positive rhabdomyosarcoma patients have one of two fusion genes, PAX3::FOXO1 or PAX7::FOXO1.

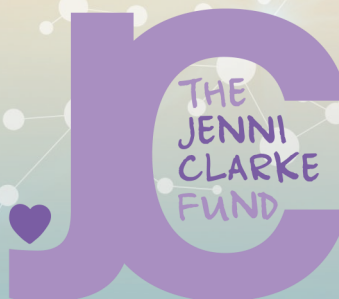
These fusion gene errors make abnormal instructions for proteins. More than just sequences of the genetic code, these instructions also fold into complex 3D shapes. The correct shapes are critical for producing the protein.

Dr Darrell Green at the University of East Anglia has recently discovered that the 3D shapes of these fusion genes are a central driver of fusion-positive rhabdomyosarcoma. He believes this could be critical in understanding how the cancer develops, spreads around the body, and responds to treatment. In the future, he hopes to create targeted medicines that can affect the 3D shapes of the fusion gene so that they no longer produce the cancer-causing protein.

In this project, Dr Green hopes to confirm the importance of 3D shape and discover what changes between different fusion genes and in different patients. His research team will:

1. Create the world's first 3D computer models of the shape of the two fusion genes.
2. Compare the tumours of each variant in lab models and patient samples to see how the 3D shape affects the spread around the body.
3. Look at whether shape-modifying medicines can stop the tumours from spreading.

The 3D models will be invaluable for companies developing and testing new shape-modifying drugs to treat gene mutations. Because the drugs would target fusion genes, which only the cancer cells have, Dr Green hopes that there would be no damage to healthy cells. The long-term goal for this project is to deliver a Phase 1 clinical trial of a new fusion gene targeting drug within five years.



This project was funded by Special Named Funds at Children's Cancer and Leukaemia Group raising funds for research into rhabdomyosarcoma.