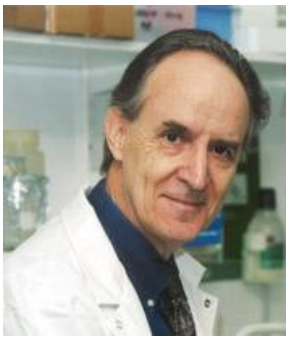

Tildy's Trust gave £25,000 to support Prof Mel Greaves' work at the Institute of Cancer Research in Sutton in 2012. Mel has already proven that the initial steps leading to childhood acute lymphoblastic leukaemia (ALL) occur as the child develops in the womb. Comparison of cells from identical twins Olivia, who was being treated for leukaemia, and Isabella who was healthy found the same genetically identical pre-leukaemic stem cells in both children.

Mel's on-going research aims now to understand how these stem cells are converted into full-blown leukaemia in some children and not others. Evidence suggests that the 'second trigger' is related to an unusual response to infection.

As yet the second 'trigger' or 'triggers' are still be defined but together with his colleague Prof Richard Houlston, Mel's work continues to deepen our understanding of ALL.

A study published by the team in April this year[1] used recently developed state of the art technology to sequence all the genes present in the cancer cells of two twin pairs that each developed ALL in both twins. This study provided a unique means of uncovering the timeline of mutations contributing to the clonal evolution of the disease in each case. The study identified a limited number of shared, mutations in each twin pair that must have arisen prenatally and then a greater number of mutations that most likely occurred after birth. The study also identified that the later mutations are likely to be mixture of 'driver' mutations that convert the pre-malignant cells into cancer cells and a significant number of other 'passenger' mutations that do not affect the cancerous nature of the cells. More studies of this type will in future inform what types of mutation do cooperate to cause ALL and which do not. In turn this will also inform us of those mutations that will provide valuable drug targets for developing less toxic therapies for children with ALL.

In another study[2] published in October 2012, the team have provided evidence about the genetic risk of contracting ALL. The team used a technology called genome-wide association studies (GWAS) to identify that although individual inherited genes do not greatly increase the risk of ALL, combinations of gene variants when inherited together may significantly increase the risk.

Mel's wider work in the field include studies of cellular and genetic origins of the more rarer form of childhood ALL which arises in T-lymphocytes rather than B-lymphocytes.

Mel reports that the work on defining the evolution of ALL from a premalignant state to full blown disease continues to go well. They have developed a technology to look at the genetics of leukaemia cells at the level of single cells.

The team have also completed a major 'genomics' project on ALL with The Sanger Centre. Mel reports that there are some striking findings. One is that the highly recurrent genetic changes are losses of genetic information rather than recoding of genetic information. They also have evidence of the mechanism leading to these mutations. Again a manuscript is submitted for publication.

Finally In June 20013 Mel also published together with eminent colleagues from St Judes Children's Research Hospital a landmark review[3] of our current understanding of ALL and its treatment. This review documented the seminal contributions made by Mel and his team and also his unique intellectual insight into the problem.

1. Developmental timing of mutations revealed by whole-genome sequencing of twins with acute lymphoblastic leukemia. Ma Y, Dobbins SE, Sherborne AL, Chubb D, Galbiati M, Cazzaniga G, Micalizzi C, Tearle R, Lloyd AL, Hain R, Greaves M, Houlston RS. Proc Natl Acad Sci U S A. 2013 Apr 30;110(18):7429-33.
2. Common genetic variation contributes significantly to the risk of childhood B-cell precursor acute lymphoblastic leukemia. Enciso-Mora V, Hosking FJ, Sheridan E, Kinsey SE, Lightfoot T, Roman E, Irving JA, Tomlinson IP, Allan JM, Taylor M, Greaves M, Houlston RS. Leukemia. 2012 Oct;26(10):2212-5
3. Acute lymphoblastic leukaemia. Inaba H, Greaves M, Mullighan CG. Lancet. 2013 Jun 1;381(9881):1943-55.