Haematology: Research into T-cell prolymphocytic leukaemia and other blood cancers

Proposal for The Paul Lee Davis Fun Fund

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Written in conjunction with Dr Claire Dearden, Consultant Haematologist

Summary

Cancer's pervasiveness and traumatic impact drive The Institute of Cancer Research (ICR) in its mission to make the discoveries that defeat cancer.

Cancer research remains crucial, as 1 in 3 of us will develop the disease in our lifetimes. The ICR is one of the world's most influential cancer research institutes and is engaged in a wide range of research across many cancer types to develop new treatments for cancer patients. These treatments are based on an understanding of the genes that cause the disease and then designing and developing drugs that counteract the effects of the faulty genes.

Dr Claire Dearden of the ICR and our clinical partner The Royal Marsden Hospital leads research specifically on developing new treatments for blood cancers. Within this research programme we are hoping to learn more about T-cell prolymphocytic leukaemia (T-PLL). Currently little is known about T-PLL and we aim to find genetic faults associated with T-PLL to help develop new targeted treatments.

We hope the Paul Lee-Davis Fun Fund will consider supporting research under at the ICR to increase our understanding of the rare blood cancer T-PLL, leading to better treatment options for cancer patients.

Making the discoveries that defeat cancer

Scientists' current understanding

T-lymphocytes are specialist white blood cells that constantly patrol our bodies scanning for abnormal cells (including cancer cells) and infections. These cells are produced in the bone marrow and then spend time maturing in a gland called the thymus, after which they begin their patrol duties. T-cell prolymphocytic leukaemia (T-PLL) is a rare cancer of mature post-thymic T-cells. Clinicians will often only see a case of T-PLL once every 5-10 years which makes recognition and management of the disorder difficult.

T-PLL is a disease of adults and typically follows an aggressive clinical course from presentation. A minority of patients, about 15%, may be asymptomatic (showing no symptoms) at diagnosis and this 'indolent' phase can persist for several years. However, progression is inevitable and may be very rapid when it occurs. Confirmation of the diagnosis requires a systematic approach and careful integration of the results of morphology (structural appearance of the tumour cells) with specialised diagnostic tests including immunophenotyping (to detect distinct protein tumour markers on the tumour cells surface) and cytogenetics (to analyse the microscopic structure of the tumour cells chromosomes).

The disease is usually resistant to conventional chemotherapy and can be rapidly fatal. Currently the best treatment is with a drug called alemtuzumab followed by a haematopoietic stem cell transplant (HSCT – a transfusion of specialist cells, obtained from another person, that are able to divide and form new white blood cells in the recipient) where possible. This approach has led to an extension of the median survival from 7 months in patients treated with conventional chemotherapy (as shown in our historic series of over 70 patients treated with conventional chemotherapy) to over 4 years for those patients receiving alemtuzumab followed by HSCT (as shown in Dr Dearden's study of more than 80 patients receiving either alemtuzumab alone or alemtuzumab followed by HSCT - this is one of the largest studies ever conducted in patients with this disease). A number of our patients remain in remission more than 5 years following HSCT. However, new treatments are needed in order to ensure that more patients survive for prolonged periods.

At the ICR and in partnership with the Royal Marsden Hospital, we have had a research interest in T-PLL, and other mature lymphoid leukaemias, for several decades. This has included investigation into the biology, clinical and laboratory features and treatment of these diseases. We were the first to describe some of the unique genetic defects in T-PLL and the first to develop treatment trials specifically for patients with this disease; firstly with pentostatin and subsequently with alemtuzumab and stem cell transplantation. We have also been involved in similar research into chronic lymphocytic leukaemia and two other rare lymphoid disorders; T-cell large granular lymphocyte leukaemia and hairy cell leukaemia.

What the researchers will be investigating next

Our current and future research is directed in the same disease areas where we continue to participate in clinical trials of novel therapies and to undertake innovative laboratory research. The latter is focussed on whole gene sequencing to discover novel genetic defects which may be important in our investigations into:

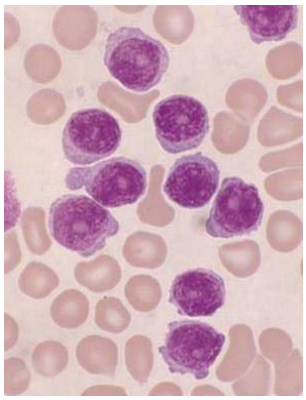
- the cause of the disease and/or present potential therapeutic targets,
- examination of biological factors which may have prognostic significance (for example, the expression of TCL1)
- investigation of critical cellular communication pathways

The Institute of Cancer Research – a unique environment

This research illustrates how the ICR's unique, integrated approach enables closely situated chemists, physicists, clinicians (at our on-site partner, the Royal Marsden Hospital) and basic scientists to work together to facilitate the process of academic drug discovery.

Over our 100-year history, notable successes include identifying the potential link between smoking and lung cancer which was subsequently confirmed, discovering that DNA damage is the basic cause of cancer and isolating more cancer-related genes than any other organisation in the world.

The ICR has the largest academic drug discovery unit in the world, the award-winning Cancer Therapeutics Unit, which in the last six years has discovered 16 innovative drug candidates and progressed six of these drugs into Phase I clinical trials and one into the clinic: a feat unmatched anywhere else in the world. Unique to academic centres worldwide, the ICR has an on-site medicinal chemistry unit, with the capability to invent and chemically synthesise (produce) cancer drugs, in collaboration with biological scientists and medical doctors. It is very uncommon that a single centre possesses all the combined expertise to move from concept through the laboratory and into the cancer clinic.




Blood cancer research remains a key priority for the ICR which has a rich history of success in this area. For example, ICR discovered that cancer stem cells in the most common childhood leukaemia have complex and diverse combinations of mutations, even within individual patients. This research may help explain why advanced cancers remain so difficult to eradicate. Many companies are developing new drugs for advanced cancer that target the tumours' specific genetic mutations, ICR research has shown that these genetic mutations are constantly evolving, which has the potential to create lethal resistance to treatment.

Together with our clinical partner, the Royal Marsden Hospital, specific on-going achievements in blood cancer research include:

- We have expanded and improved the number of molecular diagnostic tests available in the 'Molecular Diagnostic' laboratory and continue to expand the diagnostic repertoire and clinical relevance of the tests. This facility is now in a purpose built 'Centre for Molecular Pathology' and we have set up a number of strategic alliances aimed at putting the laboratory at the cutting edge of modern developments.
- We have continued to study the role of chromosomal rearrangement in the pathogenesis of myeloma, paediatric leukaemia and acute myeloid leukaemia.
- In chronic lympho-proliferative disorders, we have successfully studied the relationship between hairy cell leukaemia, its variant and splenic marginal zone lymphomas. In addition we continue to characterise the biology and genetics of Chronic Lymphocytic Leukaemia.
- We have continued to develop the transplant programme for adults and children, after being competitively selected as a 'cord blood transplant centre', with a particular focus of using the graft-versus-leukaemia effect and of alternate donor strategies such as cord blood stem cells which will make the therapy not only more effective but also available for more people.

- We have completed a number of studies studying the molecular characterisation of myeloma at the mutation level, including studies using mapping techniques to study the impact on classifications and clinical outcomes of regions of chromosomal gain and loss, as well as studying the methylome of myeloma.

- In myeloma, we reported results from the Medical Research Council (MRC) Myeloma IX, the largest trial ever in myeloma in 1,960 patients. The results showed that zoledronic acid plus chemotherapy gave a 26% reduction in skeletal related events and a significant improved survival compared with clodronate plus chemotherapy. This is set to become a new standard of care for these patients.

How you can help

It is an exciting time to be investing in cancer research. New therapies and treatments mean our scientists continue to work to improve cure rates, reduce side effects and improve function and quality of life for cancer patients.

One of the ways in which the Paul Lee-Davis Fun Fund could support the ICR to take forward and sustain our research into T-PLL over the next 2-3 years would be to contribute to the costs of whole genome sequencing to discover novel genetic defects which may be important in this disease. Such a donation might go towards:

- £15,000 for laboratory work to pay for the cost of sequencing around 5 T-PLL genomes;
- £10,000 for storage costs of samples from T-PLL patients;
  or
- A researcher to specifically study T-PLL, carry out data collection and preparing the patient samples for further analysis would cost:

	Year 1	Year 2	Year 3
Scientific Officer (inc. NI, pension etc.)	£31,878	£33,090	£34,347
Lab Consumables	£18,000	£18,000	£18,000
Lab costs (inc. equipment maintenance)	£12,500	£12,750	£13,000
Total	**£62,378**	**£63,840**	**£65,347**

By supporting this research the Paul Lee-Davis Fun Fund will help keep the ICR's research at the heart of delivering better treatments and improving the outlook for patients with T-PLL and other blood cancers.

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