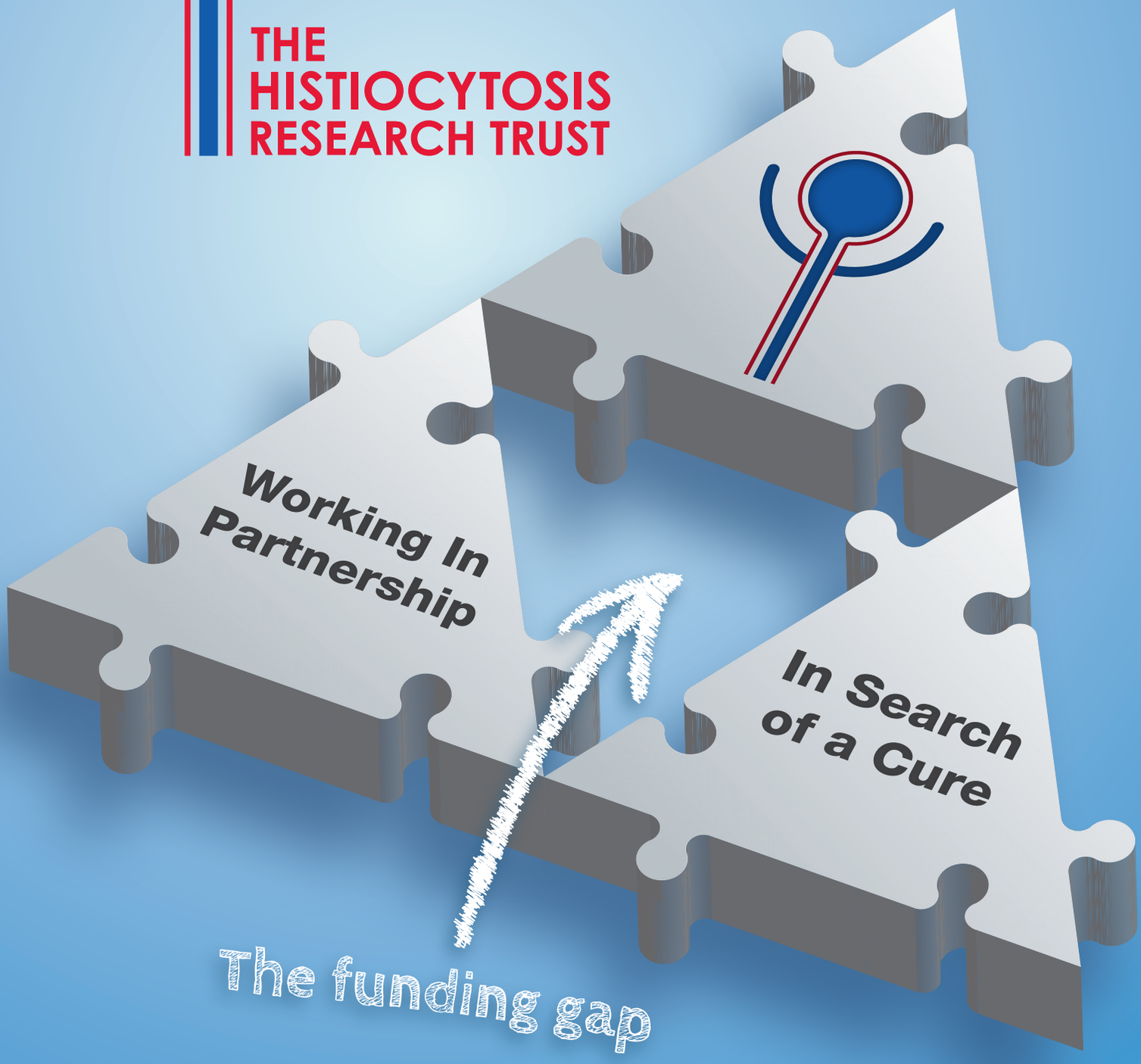
THE HISTIOCYTOSIS RESEARCH TRUST



We are dependent on your involvement and your generosity

Will you help us complete the puzzle?

There is just one piece of the puzzle missing!

Despite the misery it causes, Histiocytosis is too rare a disease to have generated substantial research in medical circles. Unfortunately, for every child or adult fighting for his or her life, the pain and suffering are just as severe for children and adults afflicted with other better known disorders receiving funding.

For the children and adults battling these illnesses, there is now reason to hope. To ensure the research continues, we ask for your help, to complete the funding puzzle.

Our research programmes provide a beacon of hope for the many children and adults battling Histiocytosis, to ensure this research continues we ask you to pledge your support.

Our Research Goals

- **To facilitate the development of gene therapy for HLH patients**
- **To further research on genetic changes in LCH**
- **To proceed to clinical trials of drugs targeted to the BRAF mutation**

The Histiocytosis Research Trust - Who we are

The Histiocytosis Research Trust was set up as a registered charity in 1991 and is dedicated to promoting and funding scientific research into uncovering not only the causes of all histiocytic diseases, which include Langerhan's Cell Histiocytosis and Haemophagocytic Lymphohistiocytosis, but also ensuring early diagnosis, effective treatment and a cure.

The Trust also aims to support patients and their families as well as raise public and professional awareness of histiocytic disorders. Its team of Trustees include the UK's leading paediatric LCH and HLH specialists.

Our Objectives

- The promotion and furtherance of scientific research into the physiology and pathology of histiocytes and the aetiology of histiocytocytic diseases.
- The development of more accurate means of diagnosis, improved protocols for management of patients and ultimately measures for prevention of histiocytic diseases.
- The provision of information in support of patients and families affected by histiocytosis.

What is Histiocytosis?

Histiocytosis is an umbrella term applied to a group of rare diseases, characterised by increased numbers of white blood cells called histiocytes in the blood and tissues. In all forms of histiocytosis, these cells, which are part of the protective immune system, begin to attack the body, targeting many organs of the body including the bone marrow, liver, spleen, lungs, skin, bone and brain. The prognosis for patients varies greatly depending on the form of histiocytosis.

There are two main types.

Langerhans Cell Histiocytosis, LCH for short, histiocytes called Langerhans cells, which are normally found in the skin, may spread to many organs and damage them, so that the symptoms vary depending on which organs are affected, but skin rashes, destruction of bone, breathing problems and damage to the brain are common.

LCH occurs in children, often during infancy but also in adults. It is usually a chronic disease and may cause severe disabilities due to brain damage. The diagnosis is made by microscopic examination of a tissue specimen obtained by biopsy. The prognosis depends very much on the extent of disease and organs affected, which can be assessed by imaging studies. LCH is thought to be caused by alterations in the DNA of Langerhans cells.

Haemophagocytic Lymphohistiocytosis HLH for short. In this disease a virus infection triggers another type of histiocyte, the macrophage, to become over active and attack the body. Red blood cells and other white blood cells are engulfed and destroyed by the macrophages, so that the patient is unable to fight infections.

Patients therefore suffer from high fevers, may become anaemic and often have skin rashes, as well as symptoms due to the infecting virus. HLH is an acute and life threatening disease. It frequently occurs in childhood but may occur at any age.

Diagnosis depends on detection of the infecting organism and demonstration of macrophages engulfing other cells as well as other abnormalities of white blood cells, usually in sample of bone marrow. In familial forms of HLH, abnormal genes, which alter white blood cell function, are passed from the parents to children.

Rarer Forms - there are other even rarer forms of histocytosis related to both LCH and HLH and very rarely malignant histiocytosis occurs, which is a leukaemia-like disease of histiocytes.

The Impact - regardless of the form of histiocytosis, children and adult patients suffer from the physical pain associated with the disease and the emotional trauma of long hospital admissions or travel away from home, as well as the fear of not knowing what will happen to them. Because these diseases are so rare, diagnosis is often delayed and misdiagnosis common, so that treatment may not be started promptly.

The stress devastating parents and family members.

Langerhan's Cell Histiocytosis (LCH)

It is estimated that 1 in 200,000 children will become ill with it each year and adults can also be affected. In the UK alone, there are 50 new cases each year. Doctors are often unable to diagnose it because it presents with many different symptoms and as a result, diagnosis and treatment is delayed.

People suffering from LCH have too many histiocytes – a type of white blood cell that normally helps to fight infection. However, in those suffering from LCH, the histiocytes gather together in large numbers causing damage to healthy parts of the body. LCH is similar to cancer because of the uncontrolled accumulation of histiocytes and more than half of patients have a specific change, or mutation, in the DNA of the histiocytes. Because LCH has similarities to cancer it is currently treated with chemotherapy, radiation and steroids.

Doctors call LCH an 'orphan' disease because it is so rare. As a result, research into why it happens, how it can be treated and even cured, has been limited. Nevertheless, although doctors and scientists do not know what causes LCH – it is not hereditary and it is not infectious.

LCH is divided into two main groups – single system and multi-system.

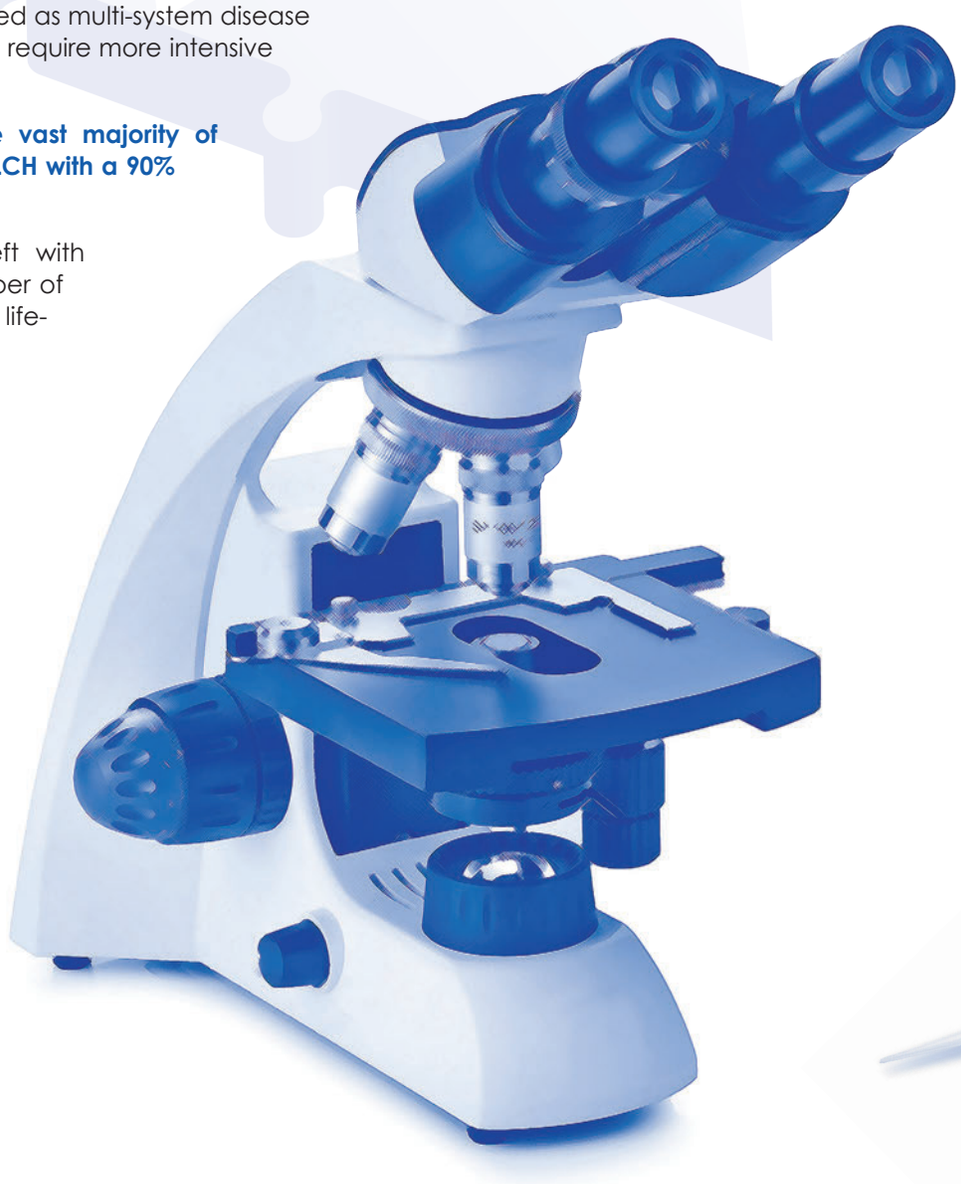
When LCH is described as a 'single-system' disease, it means that it only affects one system in the body – for example skin or bone or an organ. If it is only in one place in that particular system, it is single site and if in more than one, multi-site or multi-focal. So a child with several affected areas in the bones but no disease elsewhere is considered to have 'multi-focal, single-system' disease.

When LCH is found in more than one 'system', for example in both the skin and bones, it is described as 'multi-system' disease. Children with 'multi-system' disease affecting the liver, spleen, lung or bone marrow can have a more serious form of LCH. This is then described as multi-system disease with "risk organ" involvement and may require more intensive treatment.

It is important to remember that the vast majority of children will recover completely from LCH with a 90% survival rate.

Some children, however, may be left with life-long problems and in a small number of multi-system cases the disease can be life-threatening.

Sometimes the disease comes back, but unlike cancer, treatments for LCH that have worked before may be used again.



Haemophagocytic Lymphohistiocytosis (HLH)

A very rare and life-threatening disease that usually affects babies and children. In the United Kingdom, about 15 children are diagnosed each year with HLH and international studies have shown there is a survival rate of only 55%.

HLH is caused by an uncontrolled growth of activated white blood cells. It can be likened to a very severe form of inflammation that the body is not able to turn off. Unfortunately, the immune system is overwhelmed by this excessive activation and functions poorly, leaving the child susceptible to infection.

Because HLH often looks at first like a normal response to infection it can take time to realise that the child's immune system is not functioning properly.

Treatment includes chemotherapy and sometimes a bone marrow transplant.

Types of HLH

There are two types of HLH, genetic or familial, and acquired. The incidence of acquired HLH is unknown but it is thought to be more common than the genetic type.

Genetic HLH is also called Primary HLH and may be inherited in one of two ways:

Autosomal recessive - this is where the child has 2 copies of the abnormal gene, one from each parent.

X-linked - this is passed only to boys by one of the mother's X chromosomes which is abnormal.

Genetic or Familial HLH may occur alone, but very rare cases can be associated with other immune deficiencies such as Chediak-Higashi Syndrome 1 (CHS-1), Griscelli Syndrome 2 (gs-2) and X-linked lympho-proliferative syndrome (XLP).

Familial HLH

Most familial cases of HLH around 70-80%, develop symptoms before the age of 1 and a few, approximately 10%, experience symptoms within the first 4 weeks of life. In the same family, children with familial HLH usually develop symptoms around the same age. Several different inherited changes, or mutations, in DNA are associated with HLH.

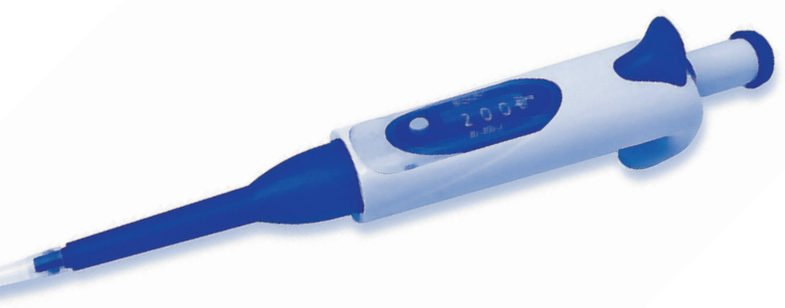
Acquired Haemophagocytic Lymphohistiocytosis

Acquired HLH is also called secondary HLH and can occur at any age. The frequency is unknown but it is thought to be more common than the genetic type. Like the genetic types of HLH, acquired HLH is usually triggered by an infection, often a virus. HLH can also occur in children with some cancers.

Macrophage Activation Syndrome

Macrophage Activation Syndrome (MAS) is an extremely rare condition that occurs in both children and adults with auto-immune diseases, such as rheumatoid arthritis. It has the same features as HLH but some of the initial blood changes may be less severe and problems with clotting and the function of the heart may be worse.

Like other forms of HLH, viruses have been shown to trigger MAS, but also some medications. Those suffering from MAS have a better outcome than HLH, with a survival rate of 80-90%. Treatment is similar to HLH, but less intensive.



Working In Partnership

2005

In 2005 we committed £150,000 funding a major three year research project at the University of Lausanne, Switzerland, led by Professor Hans Acha-Orbea. The aim of the project was to identify genes that are switched on when normal dendritic cells, which are closely related to Langerhans' Cells, become tumours.

Outcomes

Professor Acha-Orbea used a virus to carry a tumour forming gene into mouse dendritic cells which went on to become dendritic cell tumours. He identified genes that are switched on or off as normal dendritic cells become dendritic cell tumours, and that might be targeted to kill abnormal dendritic cells. He plans to go on to search for these genes in human Langerhans Cell Histiocytosis samples. The cell lines continue to provide a resource for understanding normal and abnormal dendritic cells.

Steiner QG, Otten LA, Hicks MJ, Kaya G, Grosjean F, Saeuberli E, Lavanchy C, Beermann F, McClain KL, Acha-Orbea H. In vivo transformation of mouse conventional CD8alpha+ dendritic cells leads to progressive multisystem histiocytosis. Blood. 2008; 111: 2073-82.

Fuertes Marraco SA, Grosjean F, Duval A, Rosa M, Lavanchy C, Ashok D, Haller S, Otten LA, Steiner QG, Descombes P, Luber CA, Meissner F, Mann M, Szeles L, Reith W, Acha-Orbea H. Novel murine dendritic cell lines: a powerful auxiliary tool for dendritic cell research. Front Immunol. 2012; 3: 331.

2009

In 2009 we allocated £220,954 to fund a ground-breaking project with the Institute of Child Health at University College London. The project model investigated ways of introducing a normal Perforin gene – the gene most commonly affected inherited HLH – into white blood cells.

Outcomes

Professors Bobby Gaspar and Adrian Thrasher together with Dr. Marlene Carmo, who was funded by the grant, demonstrated that they can successfully introduce a normal perforin gene into mouse stem cells. These stem cells restore normal lymphocyte function when introduced into mice that have an abnormal perforin gene and usually develop HLH. Professors Caspar and Thrasher are now planning to develop this form of gene therapy to restore normal immune function in patients suffering from HLH.

2012

In 2012 we committed £327,000 over three years to a collaborative project at the Centre for Molecular and Cellular Biology of Inflammation, Kings College London and the Institute of Cellular Medicine, Newcastle, led by Professor Frederic Geissmann and Dr Matthew Collin.

The project will build on the recent important discovery of a genetic mutation in half of LCH samples tested.

This mutation (called BRAF V600E) is found in several human tumour types and alters the transmission of signals from the cell surface to the nucleus. In their project, Professors Geissmann and Collin are exploring how the mutation affects the behaviour of Langerhans cells and whether it is found in other cell types in LCH patients.

Interim Update

Professor Geissmann and Dr Collin have made good progress in setting up the model system they will use to study signalling in BRAF V600E positive cells and this work is expected to identify additional molecules that may be drug targets. They have already identified new mutations in BRAF itself.

Satoh T, Smith A, Sarde A, Lu HC, Mian S, Trouillet C, Mufti G, Emile JF, Fraternali F, Donadieu J, Geissmann F. Apr 10B-RAF mutant alleles associated with Langerhans cell histiocytosis, a granulomatous pediatric disease. PLoS One. 2012; 7: e33891.

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Together we will find a cure

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