Project achievements

For the best chance of success, in any rare disease, and Batten disease is no exception, the basis for any future treatment must be based on science driven research of the highest quality. BATCure was designed to work in this way - to bring together a talented, diverse group with the necessary skills and expertise to offer a novel strategic and integrated approach to a set of very complex diseases.

"I truly enjoy working with the top researchers from all around Europe who are devoted to developing treatments for Batten disease. My role within the project is to provide financial, contractual and administrative support and to ensure the timely delivery of all the results. Significant progress has been achieved.

Evghenia Scripnic, European Project Manager, UCL

Young scientists have participated contributing to their continued involvement in rare disease research. One of the highlights was hosting NCL2018, the biennial international scientific meeting.

"Cooperation, discussions and exchange of ideas, during the regular meetings and at international conferences between partners were inspiring."

Dr. Stephan Storch, UKE, Hamburg

"My laboratory was new to Batten disease research. Joining BATCure was challenging and at the same time encouraging, as metabolism was never previously associated with Batten disease. The opportunity to collaborate with widely reputed Batten disease experts within the UK and the rest of Europe brought to our group the new dimension of translational research. Thanks to this experience, we have now secured further funding to investigate other metabolic aspects of Batten disease. This has now become a new research line within my laboratory."

Dr. Juan Bolaños, USAL

Progress has been made in the areas of drug discovery and the development of gene therapy approaches for CLN3, CLN6 and CLN7 disease. The group have utilised new technologies in science and diagnosis to great effect. These results are already emerging in scientific publications and will continue to do so over the next few years.

"As a charity, being part of BATCure has allowed us to bring the family voice to a major research project. It has provided vital resources for us to strengthen our links with other Patient Organisations in Europe and worldwide, patients, their families and the professionals who care for them."

Heather Band, Scientific Officer, BDFA

"At BATCure we believe that we have taken science driven research forward for the benefit of all those affected by Batten disease. Our work on CLN3, CLN6 and CLN7 disease has improved our understanding of all aspects of the disease from basic research to improved diagnosis and clinical outcomes. We have worked efficiently together and have long-term ambitions for NCL research."

Professor Sara Mole, Project Coordinator, UCL

Please visit **www.batcure.eu** for a copy of the full project report.

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www.batcure.eu **BATCure** **BAT_Cure**

BATCure has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 666918

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BATCure

Developing new therapies for Neuronal Ceroid Lipofuscinoses (NCL) commonly known as Batten disease

BATCure Executive Summary

Batten disease

The Neuronal Ceroid Lipofuscinoses (NCL), commonly known as Batten disease, are a group of devastating life-limiting neurodegenerative diseases affecting children and young people for which, at present, there is no cure.

This disease encompasses a progressive loss of physical and mental abilities that includes visual impairment and blindness, severe epileptic seizures that are difficult to control, involuntary muscle spasms, speech loss and the deterioration of motor skills.

Changing the outcomes for those affected by Batten disease

Batten disease is a rare neurological disease with only 1-2 thousand new cases being diagnosed worldwide each year. This presents a particular set of challenges when working towards finding successful treatments and ultimately a cure. As with many rare diseases the disease is not well known from a general clinical or public perspective. It is a complex disease and in order to develop treatments requires a multidisciplinary approach to maximise the chances of success.

BATCure focused on developing therapeutic options for three types of the disease CLN3, CLN6 and CLN7 disease. The BATCure consortium led by Professor Sara Mole, UCL, followed a clear path with a multifaceted integrated approach to the problem.

"I put together the BATCure project consortium and acted as the overall Coordinator. In this role I ensured that the project proceeded as planned to achieve its aims. We have exceeded expectations with some exciting new science discovered along the way. All partners met regularly to share and discuss progress. Over the 3 years we have developed excellent working relationships and I know that collaborations will continue beyond the end of this award. It has been a lot of hard work but something that we will be drawing on in our research for many years to come."

Professor Sara E. Mole, BATCure Coordinator and Professor in Molecular Cell Biology at UCL

Patient involvement

A ground-breaking addition to this project was including the patient voice as central to all the work of the consortium, and the UK Batten Disease Family Association (BDFA) was invited to participate to represent all those affected by this devastating disease.

BATCure brought together ten leading scientific research groups, three companies and one patient organisation from across Europe, with half of the researchers applying their expertise and skills to Batten disease for the first time.

The aim of BATCure was to investigate the natural history of three types of Batten disease, to provide new research models, to elucidate the function of key proteins, determine disease mechanisms, and to develop new therapies. The overall project was coordinated by Prof Sara Mole at UCL.


Professor Sara E. Mole

Prof. Sara Mole's Laboratory at UCL developed new yeast strains that carry mutations in their *'CLN3'* gene (called *btn1*) that works in the same way as CLN3 in humans. They used a genetic approach, to look at whether removing any of the other 5000 yeast genes makes the yeast grow better or worse. This gave an insight into what is happening in the cells and which pathways are most important. The lab at UCL carried out drug screens to identify promising compounds, supplementing other new compounds being taken forward by other partners for further testing.

In the UK, Prof. Tris McKay's group at the Manchester Metropolitan University (MMU) were tasked with generating stem cells from NCL patient cells, to "reprogramme" them into induced pluripotent stem cells (iPSC). In the lab, these cell lines can be stimulated to become brain neurons, cells that protect neurons in the brain (glial cells) or even heart cells. These cell lines provided a vital resource for the work of BATCure. They are now the largest repository of NCL disease iPSC lines in the world and are available to all academic researchers worldwide working to understand or find a cure for all forms of NCL. The group themselves focused on the CLN7 neurons they produced to find ways to prevent the cells from self-inflicted damage when under disease induced stress.

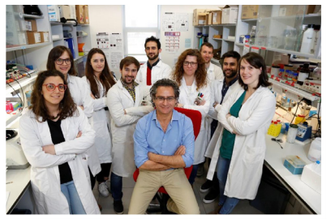
Dr Emyr Lloyd-Evans at the School of Biosciences, Cardiff University provided expertise in how cells with Batten disease communicate with each other compared to healthy cells. Using model cell lines produced within BATCure, they discovered a key finding, that CLN3 is providing an important role in maintaining the ionic balance in cells to keep them healthy.

Dr. Claire Russell at the Royal Veterinary College (RVC) in London worked to produce new zebrafish models for CLN3, CLN6 and CLN7 as these are ideal models to test the most promising compounds, identified from work with cellular models of the disease. They worked closely with UCL, TIGEM and Cardiff University to identify the best candidate compounds. Three compounds were tested in zebrafish with NCL and two of these look promising as potential treatments. They expect to test further compounds, continuing the collaboration beyond BATCure.

Dr Diego L. Medina is head of the high content screening facility at the Telethon Institute of Genetics and Medicine (TIGEM) in Italy. Together with other partners their laboratory developed assays in a variety of cellular models of the NCLs, enabling them to screen thousands of existing drugs, to find compounds with the potential to treat Batten disease. They identified several that can reduce a key disease marker.

Marc Masa at the Leitat Technological Centre in Spain has contributed towards the goals of the project through two main activities. They developed new research tools, such as special antibodies, provided to other consortium members for their research, and ultimately to gain more knowledge on the functional changes that are occurring within an individual due to a disease (pathophysiology). Their research effort was focused towards the discovery of new disease biomarkers by analysing urine samples from patients. Among the results, differences in the urine metabolites have been observed which require further study.

Prof. Juan Bolanos laboratory, at the University of Salamanca in Spain, was new to the world of Batten disease research bringing much needed expertise in the field of cellular energy metabolism. Metabolism comprises all chemical changes occurring within cells in a finely balanced and coordinated manner. An energy supply is required by cells to make tissues and organs to work properly. Neurons are brain cells requiring a vast and continuous amount of energy to sustain the work that neurons do to keep the brain alive.


Professor Juan Bolaños (seated) and his team. Dr. Irene Lopez-Fabuel (first on the right) is the BATCure postdoc.

In essence, they found that neurons affected by Batten disease undergo profound changes in metabolism strongly influencing energy supply. Importantly they found a specific target, in CLN7 Batten disease mice, that may account for many of the metabolic problems that take place within damaged neurons. They are currently looking for ways to try to rescue this effect.

Dr. Stephan Storch and his colleagues at The Universitätsklinikum Hamburg-Eppendorf (UKE) produced a mouse model of CLN7 disease for the benefit of all partners providing a vital resource for many studies. The group focused on the main question why the loss of the CLN7 protein leads to lysosomal dysfunction and subsequent damage of neurons, especially in the brain and in the eye. Their work revealed that many other proteins were also depleted in the absence of functional CLN7 and that specific lipids accumulate in the brain.

Prof. Maija Dambrova, Head of the Laboratory of Pharmaceutical Pharmacology and the OSI researchers.

The Latvian Institute of Organic Synthesis, (OSI) has many years' experience and expertise in making new compounds specifically designed to treat a variety of diseases. Under the leadership of **Prof. Maija Dambrova** they took the most promising compounds from the drug screens by TIGEM and UCL and redesigned them, using a medicinal chemistry approach, with the aim to improve their properties. As a result, 121 new compounds were synthesised and further tested by BATCure partners. In Batten disease, it is important to know how well these new compounds can enter the brain (bioavailability) and if they may be toxic, so they were first tested in wild type mice. That way the best candidate drugs can be chosen for further testing in the mouse models of Batten disease.

AcureOmics is a company based in Sweden specialising in using metabolomics to identify disturbed biochemical pathways diseases. The knowledge gained for CLN3, CLN6 and CLN7 disease is being used to both help assess and design novel treatments and will contribute to improve how the effect of ongoing treatment is monitored.

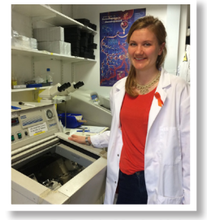

The team at AcureOmics.

Orphazyme is based in Copenhagen, Denmark, and specialises in novel therapies for rare degenerative diseases. They looked at stress responses in cell lines provided by BATCure partners. The results generated data indicating a similar responsiveness to previous work in other rare lysosomal storage diseases. Whilst it is too early to tell whether this new knowledge has any potential in the treatment of NCL patients the work has generated new scientific insight that will aid future research.

Pronexus are a preclinical contract research organization (CRO) offering advanced services and collaborative projects in studies on the Central Nervous System (CNS). Their role was to evaluate whether the selected potential therapeutic compound, developed by BATCure would be able to alter the biomarker molecules identified as important in the disease progression. **Dr. Jan Kehr** and the team tested the best candidate compound in the brains of the CLN7 mouse model and compared its effect on the levels of the biomarkers in wild type mice. No detectable differences were observed. Further work can examine the dose and timing of giving the drug.

UKE is a clinical centre with long-standing expertise in the diagnosis and management of Batten disease involved in regular and holistic assessment of patients including by MRI and psychiatric assessments. **Dr Angela Schulz**, a paediatrician, has run the NCL clinic at the UKE Children's Hospital for more than 10 years and coordinates the recruitment of NCL patients, collection of patient data for natural history studies for the project. She also coordinates the international DEM-CHILD NCL patient database.

Drs. Sander Smith & Sophia Kleine Holthaus, from the Institute of Ophthalmology in London, led the gene therapy work with **Dr Ahad Rahim at the School of Pharmacy, UCL** with the aim to develop new treatments for the brain and for the eye in all three forms of Batten disease investigated by BATCure.


Dr Sophia-Martha kleine Holthaus at UCL

Building on previous work on CLN6 gene therapy, they developed effective methods to restore CLN6 to the brain and to the eye of CLN6-deficient mice, to normalise their lifespan and improve their mobility and their vision.

As the mouse model of CLN3 disease does not have brain disease, only eye therapy was feasible in this part of the project. By treating the retina (the layer of nerve cells lining the back wall inside the eye that senses light and sends signals to the brain) loss of nerve cells and the concomitant blindness was prevented. The combined evidence that CLN3 gene therapy can preserve nerve cells in the eye and that CLN6 gene delivery is effective, in the brains of CLN6 mice, gives the group confidence that CLN3 gene therapy for the brain is also a realistic prospect.

Working on the CLN7 mouse model, they showed that gene therapy can preserve vision and mobility and prolong the animals' survival. There is an indication that there may be a risk of toxicity associated with CLN7 gene therapy. It is important that the underlying cause of this toxicity is identified before the treatment is tested in the clinic, and they will continue to work with other members of the consortium to discover what is happening in this model.

The team at the BDFA led by Heather Band and Laura Codd, developed resources, raised awareness and disseminated the progress of the project to affected families, professionals and the wider public. It was also an opportunity to bring, to a wider audience, the impact of living day-to-day with a diagnosis of Batten disease.


Heather Band and Laura Codd

The BDFA conducted an online survey for affected families across the European Union and the results are available on the BATcure website, **www.batcure.eu**

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