

Annual Report 2008

of the charitable NCL-Foundation

FUNDING



FUNDRAISING



TRAINING



RESEARCH



FOCUSSES in 2008:

NCL-Congress

(Co-)Financing of research projects in Berlin, Würzburg / London and the USA

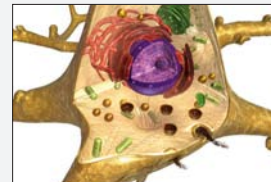
Teachers' training and school project *Biologie-up-to-date*

NCL: The nerve cell is polluted. The brain degenerates.

The NCL-Foundation was founded in 2002 and has made it its aim to develop a therapy to combat the **lethal children's disease NCL** (Neuronal Ceroid Lipofuscinosis) or Batten Disease.

NCL is a genetic metabolic disease that breaks out in children of pre-school age and after an agonizing degeneration process leads to death at the latest at 30 years of age. After an initially normal development the children become blind at about 6-9 years of age within a very short time and gradually lose their ability to speak, think and act.

The disease is caused by a mutation in the genetic material. The gene concerned is located on chromosome 16. The defect causes lipid substances to collect in the nerve cells – the „recycling centre“ of the cell no longer functions. As a result the cell cannot be cleansed of the pollutants caused by the daily production of energy, it becomes soiled and dies off. The brain in the affected children shrinks.



Healthy nerve cell



Nerve cell in NCL patients

In order to reduce the rate of false diagnoses, we informed the following target groups about NCL in the course of 2008:

Eye specialists: Ophthalmologists are usually the initial diagnosticians of NCL. The NCL-Foundation therefore developed a special **NCL informative brochure** especially designed to fulfil their requirements.

This NCL information sheet was enclosed free of charge with the information in the congress folders at the Annual Ophthalmologists Congress (DOG) in Berlin (**3,500 copies**).

Dr. Frank Stehr gave **NCL seminars** at eye clinics in Essen, Jena and Schwerin.

Neurologists: The established NCL leaflet was distributed at the Annual Conference of **Neurologists** to all participants (**5,000 copies**). Thanks to the improved parenteral feeding the juvenile NCL patients usually reach adult age and therefore fall under the field of responsibility of the neurologists. NCL represents a completely new clinical picture for the neurologists.

(Neuro)pediatricians: A further emphasis of the work of the foundation lay in the advanced **education** of neuro-pediatricians, a highly specialised professional medical group that is concerned with the development and disorders of the nervous system in children. The NCL-Foundation offered a separate **NCL Workshop** at the Annual Conference in Jena. All congress participants (6,000) received the **NCL leaflet** designed for doctors. The NCL-Foundation was represented with an information stand at the Congress. Dr. Stehr also gave a lecture to pediatricians at the "European Research Conference on Paediatric Neurology" in Tübingen.

Teachers: For a biology teachers' further **education seminar** in September the human genetics specialist, Dr. Marschner-Schäfer, the molecular biologist Dr. Kutsche and the NCL doctor at the University Hospital Hamburg-Eppendorf (UKE), Dr. Schulz gave lectures. Another further education measure with 25 biology teachers took place in November.

Schoolchildren: Altogether we reached **200 schoolchildren** with the NCL biology lesson "**Biologie up-to-date**" in which we informed 12 grammar and comprehensive schools in Hamburg about rare inherited diseases, taking NCL as an example.



Children's neurologists during the NCL Workshop in Jena.

Juvenile NCL (JNCL) is caused by a genetic defect in the CLN3 gene that can be found on Chromosome 16.

BASIC RESEARCH

New studies have shown that the CLN3 protein interacts with the cytoskeletal protein **Fodrin** and the **Na⁺-K⁺-ATPase** protein. Mutation of the DNA in the CLN3 gene disturbs the **endocytosis** of the ATPase. In addition, further **transport processes** are affected, such as the transport of certain receptors of the nerve cells or important enzymes from the Golgi apparatus to the lysosome. This could be a reason why certain metabolic enzymes show increased activity (**compensation**). Furthermore, the cell must cope with aggressive substances (**oxidative stress**) and auto-antibodies that might possibly contribute towards the inflammatory symptoms. However, the genetic information of humans also appears to possess **protective genetic factors**, which must still be identified for juvenile NCL.

The fundamental question with regard to NCL is: what goes wrong and when? Scientists use different tools to answer this question. **Animal and cell culture models** simulate the course of the disease. Each individual model has its advantages and disadvantages. Therefore, new models must be established and those that already exist must be analysed in more detail with regard to both the „normal“ as well as pathological processes. Dr. J. Cooper presently has two models in the start-up phase: a fruit fly and a zebra fish model.

Together with the **R+W Foundation**, the NCL-Foundation is sponsoring a **cooperative project** between Dr. J. Cooper and Professor R. Martini (Würzburg) to analyse the neuro-immunologic complications more closely. A **new postgraduate position** will be set up in both laboratories.

Sponsored by the NCL-Foundation and BDSRA, the American NCL self-help group, Dr. C. Stein (Laboratory Prof. B. Davidson, USA) will be studying the influence of CLN3 on the characteristics of certain **ion channels**. These channels are expressed in the central nervous system and the cardiac tissue. These studies may possibly contribute to the development of an **activity assay**. In addition, a **biomarker** identified by biochemist S. Pohl - the lysosomal acid phosphatase (LAP/ACP2) - could be used.

PRECLINICAL

In order to influence the various effects that appear with JNCL, there are several approaches in the pre-clinical phase, i.e. these are already tested in cell cultures and/or mouse models. The following projects are supported or initiated by the NCL-Foundation.

A **retinal stem cell approach** in the mouse model led to negative results (Prof. K. Rüther, Berlin). Therefore, a genetic therapeutic approach has the potential to be more successful. **„Bild hilft – Ein Herz für Kinder“** (newspaper project to help children) supports the development of a **JNCL-gene therapy** in the laboratory of Prof. R. Crystal (USA). A **„Gentaxi“** is supposed to transport a healthy CLN3-gene to the nucleus of the sick cells. During a gene or stem cell therapy the patient has to be **immunosuppressed**. This could even be an advantage for JNCL patients, since an immunosuppressant led to an improvement of motor abilities in the mouse model. An **AMPA-receptor antagonist** also led to an improvement in motor skills. As a result of the involvement of the NCL-Foundation a new antagonist is being tested in the laboratory of Prof. D. Pearce (USA).

7th NCL CONGRESS

With an international participation, the Congress took place at the premises of our long-term sponsoring partner, the **Hamburg Marriott Hotel**. The lectures showed that the first steps are being taken in the preclinical areas of JNCL, such as, for example, the investigation of the influence of various substances on secondary effects such as disturbed **autophagocytosis**. CLN3 seems to be involved in many central processes. New evidence indicates a role in **clathrin-independent endocytosis**. The **immune cells** proven in the JNCL brain appear to be adversely affected in their morphological transformation.

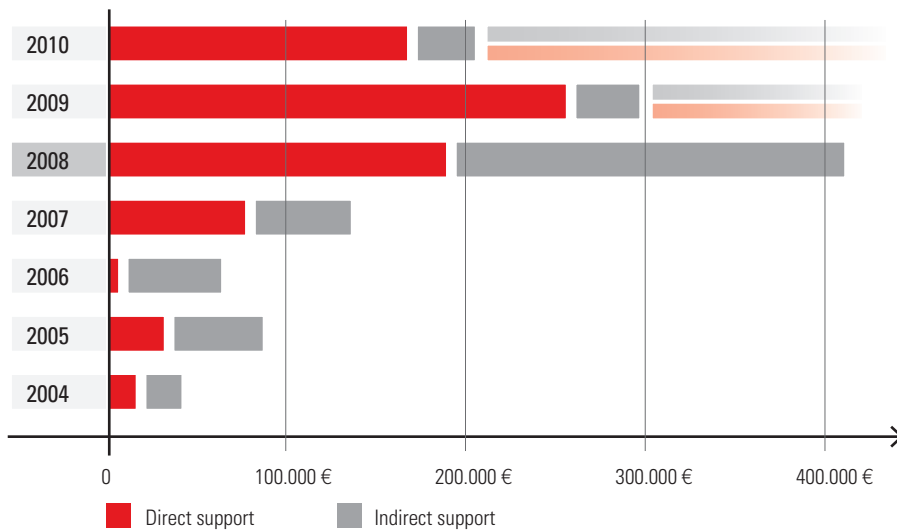


Dr. S. Cotman and Prof. R. Crystal at the 7th NCL Congress.

RESEARCH STEPS

Description		Diagnostic		Basic Research
First description of disease	Description of individual forms	Phenomenological disease description	Cause	Generating cell and animal models
1826 The Norwegian Stengel describes for the first time an NCL-case.	1903-09 Batten, Spielmeier and Vogt report on the juvenile NCL-form.	Physiological parameters, anamnesis, lymphocyte-vacuoles.	1995 the disease-causing mutation in the CLN3-gene was discovered on chromosome 16, which is molecular-biologically verifiable.	2002 CLN3-Knock in-mouse 1999 CLN3-Knock out-mouse 1998 Yeast-model

RESEARCH SUPPORT



The amount of research support has **risen steadily**. Since 2007 the NCL-Foundation has also been active in **international support**. Support is divided into direct and indirect support. Direct support includes, for example, **doctoral fellowships**. Within indirect support **co-operations** are formed where, for example the laboratory itself funds the consumables to be used. This also includes projects initiated by the foundation. Research support has already been guaranteed to researchers for the coming two years. In order to be able to continue to progress research long-term **we require your donation**.

SCIENTIFIC ADVISORY BOARD & RESEARCH PRIZE

The **scientific advisory board** of the NCL-Foundation was newly elected. We are pleased to welcome to the board: Prof. Ralf Baumeister (Freiburg), Prof. Beverly Davidson (USA) and PD Robert Steinfeld (Göttingen).

The NCL-Foundation awarded an **NCL Research Prize** this year for the first time. This prize money amounts to Euro 50,000 and will, in future, be available once a year worldwide. The prize money serves to **establish a doctoral position**. The first task of the scientific advisory board will be to evaluate the applications which will come in as a result of this prize being awarded.

RESEARCH PROJECTS SUPPORTED IN 2008



Project: „Pathogenetic impact of immune-related cells in two models of neuronal ceroid lipofuscinosis (Batten disease)**“

Researcher: Dr. Jon Cooper, King’s College London – GB

Co-operation partner: BDSRA



Project: „Translational Program for Adeno-associated Virus-mediated Treatment for the Eye and CNS Manifestations of Juvenile Neuronal Ceroid Lipofuscinosis. I. Animal Efficacy Studies“

Researcher: Prof. Ronald Crystal, Weill Cornell Medical College – USA

Co-operation partner: Bild Hilft – Ein Herz für Kinder e.V. (Newspaper project to help children)



Project: „Dissecting the Molecular Basis of JNCL“

Researcher: Prof. Beverly Davidson, University of Iowa – USA

Co-operation partner: BDSRA



Project: „Pathogenetic impact of immune-related cells in two models of neuronal ceroid lipofuscinosis (Batten disease)**“

Researcher: Prof. Rudolf Martini, Neurological Clinic of the University of Würzburg – Würzburg

Co-operation partner: R+W Foundation



Project: “Functional investigation of the retina and therapy of the CLN3-knock-in mouse model”

Researcher: Prof. Klaus Rütter, Charité – Berlin

Co-operation partner: Griebel Foundation

**Co-operation project

Basic Research		Preclinical stages			Clinic	Therapy	
Localization	Functional analysis / clarification of mechanisms	Therapy approach in cell culture and mouse model	Toxicity tests on rat	Functional- / toxicity test in large animal model	Clinical examination (Stages I–IV)	Palliation / Delay	Healing
2003 Lysosomal membrane	2003 CLN3 takes part in transport processes; function has not been conclusively clarified yet.	2008 Test of a therapy approach in disease models.	2011 Test of a therapy approach on healthy rats concerning side effects.	2012 Tests in larger animal models, GMP-active pharmaceutical drug production.	2016 Test on NCL-patients: safety, efficiency, effectiveness.	2018 Relief and delay respectively of NCL-symptoms.	>2025 The process of preclinical and clinical stages must be passed through several times until the healing of the disease.

Research costs money. In order to generate the funds for promising NCL research projects a number of charity events in aid of the NCL-Foundation took place in 2008:

JANUARY 2008

John Neumeier – donated the proceeds of the “Ballet Workshop” held by the **Hamburg State Opera Ballet Company** to the NCL-Foundation.

FEBRUARY 2008

2nd ‘LebensKünstler’ Art Auction – over **50 artists and galleries**, including Christian Brinkmann, Jonathan Meese and Daniel Richter, Annette Streyll, Galerie Herold, Galerie Hilaneh von Kories and many others contributed work for the auction at the Hamburg Marriott Hotel.



Ivo Hauptmann: Sailing boats on the Alster Lake; ca. 1950.

MAY 2008



Roland Ulmer (Marriott) in conversation with Sandra Maahn.

Summer festival at the Hamburg Marriott Hotel – large **Charity BBQ** with fashion shows and live music. NDR presenter Sandra Maahn acted as compere for the day.

JUNE/JULY 2008



Christa Kubsch (Wempe), Frank Stehr, Martin Wilhelmi and Marion groß Osterhues (Adendorf GC) at the wheel of fortune.

3rd NCL Golf Trophy – the fundraising event at **Adendorf Golf Club** offered golfers the opportunity to improve their handicap – and to win valuable prizes provided by jewellers Wempe and holiday company Hapimag.

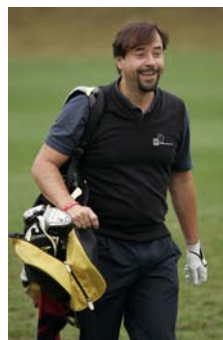
NCL summer events – a boat at the Duisburg **Dragon boat Fun Regatta** entered the fight against NCL; 12,000 tombola tickets in aid of the NCL Foundation were sold at the Hamburg **HarleyDays**; the **Mirbach Summer Festival**; the **Hamburg Channel Member Party** and at the **Arizona Kitchen** restaurant.

British Day Charity Spring Soirée – the British Chamber of Commerce organised a charity evening in aid of the NCL-Foundation.

AUGUST 2008

6th anniversary of the Foundation’s establishment – tour of Hamburg harbour with **Barkassen-Meyer** and many long-standing sponsors.

10th BILD-metro-press Golf Cup – many celebrities, including actors **Jan Josef Liefers** and **Günter Maria Halmer**, took part in the charity golf event in aid of the NCL-Foundation.



NCL ambassador Jan Josef Liefers after teeing-off.

British Day – the NCL-Foundation was one of the charities supported at this year’s **British cultural festival** held in the grounds of Hamburg Polo Club.

SEPTEMBER 2008

Benefit concert – the **German Doctors’ Orchestra** played at the Church of St. Nikolai in Hamburg. The proceeds were donated to the Alzheimer Society and the NCL-Foundation.

5th “Cooking for Kids” Charity Dinner – celebrity chef **Tim Mälzer** and catering company “Der Blaue Hummer” prepared earthly pleasures at the traditional NCL-Foundation charity dinner held in St. Johannis Church in Hamburg; soul singer **Regy Clasen** entertained diners with her velvety tones at the piano. Thalia Theatre actor **Peter Jordan** proved to be a very successful auctioneer.



Tim Mälzer live in action in support of NCL.

Taxi trips in classic cars – service organisation “**Old Table 300**” spent a Sunday driving for a good cause; owners of the historic dream cars provided their services as taxi drivers.



Classic cars in the grounds of Restaurant Randel.

Pedalo marathon – extreme athletes from the “Cabanauten” organisation pedalled their boats 42.195 km around the Aasee Lake in Münster in support of the NCL-Foundation.

DECEMBER 2008

“3 stars & Co. for NCL” fundraiser – restaurants Arizona Kitchen, del, Landhaus Scherrer, Randel, Sgroi and Tafelhaus, cooked and made donations in aid of NCL.

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NCL-ACCOUNT FOR DONATIONS

NCL-Stiftung, Account number 10 59 22 30 30
Bank Hamburger Sparkasse, Bank code 200 505 50

For all donations exceeding 200 € you will receive a receipt for tax purposes. We therefore ask you to state your name and address in the purpose field.

DONATION-SMS

Send an SMS with codeword "NCL" to 81190

For 2,99 €*, including a 2,82 € donation (*plus SMS fee)



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Special thanks also go to:

Aastra DeTeWe GmbH
A. Behrens & G. Felsch GbR
arielgrafik GmbH
Barkassen-Meyer GmbH
BILD hilft e.V. „Ein Herz für Kinder“
Budnianer Hilfe e.V.
Comedia. MDS IT GmbH
Deutsche Bahn AG
Eichhorn Bürohandel GmbH
E-Plus Service GmbH & Co. KG
E. W. Kuhlmann-Stiftung
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Scholz-Druck & Verlag GmbH & Co. KG
Springer Biobackwerk GmbH & Co. KG
Tandberg Data GmbH
WMF AG
and many other unnamed supporters
and volunteers.

The ACHSE is an association of self-help groups which campaigns for research into orphan diseases under the patronage of Eva Luise Köhler, wife of Germany's Federal President Horst Köhler. The NCL-Foundation has been an extraordinary member since 2006.



The NCL Germany Group is a self-help group which works in close cooperation with the NCL-Foundation.

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The printing and compilation of the annual report have been entirely sponsored by Max Siemen printers and graphic designer Edward Koch.
Many thanks to you!