Neonatal brain injury is a serious condition that affects millions of babies each year. Although there are a myriad of causes, the end result is often permanent neurological disorder. Prof Dr Ursula Felderhoff-Müser and her team at the Neonatal Neuroscience Laboratory, University Hospital Essen, have established rodent models for different causes of neonatal brain injury and are now using them to understand the biological basis of brain damage and to develop new regenerative therapies.
Neonatal brain injury is a serious condition that affects millions of babies each year. Although there are a myriad of causes, the end result is often permanent neurological disorder. Prof Dr Ursula Felderhoff-Müser and her team at the Neonatal Neuroscience Laboratory, University Hospital Essen, have established rodent models for different causes of neonatal brain injury and are now using them to understand the biological basis of brain damage and to develop new regenerative therapies.

How to combat brain injury in newborns – hopes and challenges for regenerative therapies

Almost half of all deaths in children under five occur in the neonatal period (the first four weeks of life). Premature birth, birth-related complications, and neonatal infections are the leading causes of death in newborns. Thanks to improvements in neonatal intensive care medicine, the number of fatalities is declining but a proportion of preterm and also term
babies suffer brain injuries leading to long-term effects, such as motor disabilities, neurosensory loss (e.g. vision and/or hearing impairment), Attention Deficit Hyperactivity Disorder (ADHD) and learning difficulties. These conditions can have major social and socioeconomic impacts.

A number of factors can cause brain damage in newborns. Oxygen deprivation occurs in four in every 1,000 term births in western societies and can cause lifelong brain damage in just a few minutes. In developing countries numbers are ten-fold higher. There are several causes by which infants may become deprived of oxygen, including constricted airways, umbilical cord problems, blood loss at birth, the placenta detaching from the uterus too early and the baby getting stuck in the birth canal during delivery.

Too much oxygen (hyperoxia) can also cause a problem. Preterm babies are exposed to much higher levels of oxygen than they would be in the womb and this has a potentially damaging effect on the brain, especially of extremely preterm infants. Inflammation caused by neonatal infections such as meningitis and encephalitis can also be injurious. Based on the multifactorial origins of brain damage in newborns, Dr Felderhoff-

EVs ameliorated inflammation-induced damage by reducing neuronal cell death, restoring white matter microstructure and reducing damage to the glial cells
Müser and colleagues Prof Dr Ivo Bendix and Dr Josephine Herz have developed experimental models of neonatal brain injury.

**EXPERIMENTAL MODELS**
The team has established protocols for inducing brain injury in infant rodents using oxygen deprivation (hypoxia), hyperoxia and inflammation. Oxygen deprivation is achieved by blocking the right common carotid artery (the vessel that supplies the head with oxygenated blood) and subjecting infant mice to 8% oxygen afterwards. Hyperoxia-induced damage is produced by exposing infant rats to 80% oxygen for 24 hours in an airtight oxygen chamber. Inflammation-induced brain injury is achieved by injecting infant rats with lipopolysaccharide (LPS) – large molecules usually found on the outside of bacteria, which illicit a strong immune response in animals. The team have used these models to investigate the biological basis of brain injury in neonates, to evaluate existing therapies and to develop novel regenerative therapies.

**THERAPEUTIC HYPOTHERMIA**
Hypothermia treatment or cooling is currently the only formally recommended treatment for neonatal brain damage in term born babies caused by oxygen deprivation (birth asphyxia). Babies are cooled to 33°C for around three days, usually by placing them on a cooling blanket. Cooling is only effective in mild to moderate cases of oxygen deprivation and 40 to 50% of cooled infants will still suffer from neurological problems later in life. By studying brain microstructure, molecular mechanisms and cognition in mice that were deprived of oxygen as infants, Dr Felderhoff-Müser showed that cooling resulted in short-term protection of brain cells, but long-term brain development was only partially saved. This work highlights the urgency to develop and assess new adjuvant therapies to use alongside cooling for neonatal brain injury.

**ERYTHROPOIETIN**
Erythropoietin (Epo) is a human protein used clinically to prevent anaemia in premature babies. Retrospective evaluation of several clinical trials suggested Epo as a potential therapeutic agent for neonatal brain injury. Epo is produced by multiple cell types in the developing brain and may have a role in protecting brain cells from damaging stimuli. Many studies have investigated the effects of Epo treatment on damage caused by oxygen deprivation but very few have addressed preterm hyperoxia. The team tested the hypothesis that a single injection of Epo in infant rats would attenuate hyperoxia-induced brain injury. They studied brain microstructure as well as cognitive, behavioural and motor function up to adulthood. They found that Epo reverted hyperoxia-induced damage to brain cells and improved neural network formation and memory function in adolescent and adult rats, highlighting Epo as an important treatment option for neonatal brain injury.

**Epo reverted hyperoxia-induced damage to brain cells and improved neural network formation and memory function**
**FINGOLIMOD**

Fingolimod is a drug used to treat multiple sclerosis – a condition where the body’s immune system attacks the myelin sheath that surrounds and protects nerves. Dr Felderhoff-Müser’s team investigated whether treatment with Fingolimod could protect neurons in neonatal hyperoxia-induced damage. A single dose of Fingolimod given at the onset of neonatal hyperoxia resulted in improved brain development persisting into adulthood. This was associated with reduced abnormalities in the white matter (part of the brain mainly made up of myelinated neurons) four months after the hyperoxic insult. Fingolimod is a promising new therapeutic option for the treatment of neonatal brain injury through protection of the myelin sheath.

**MESENCHYMAL STEM CELL-DERIVED EXTRACELLULAR VESICLES**

Mesenchymal stem cell-derived extracellular vesicles have been shown to promote regeneration of brain cells and have been suggested as a potential therapy for neonatal brain injury. However, depending on the microenvironment the stem cells may not be able to exert their full potential. Extracellular vesicles (EV) derived from stem cells are packages containing anti-oxidants, growth factors and other beneficial molecules and may well be responsible for their neuroprotective effect. EVs can be produced by stromal cells in the laboratory then collected and processed for experimental use (i.e., in adult graft versus host disease conditions). The team studied the effects of direct EV treatment on brain development and function following inflammation-induced brain injury in infant rats. The study showed that two doses of EVs ameliorated inflammation-induced damage by reducing neuronal cell death, restoring white matter microstructure and reducing damage to the glial cells that surround and support neurons.

This work by Dr Felderhoff-Müser and her team at University Hospital Essen has been vital in highlighting potential and much-needed regenerative therapies for neonatal brain injury.

**Retrospective evaluation of several clinical trials suggest Epo as a potential therapeutic agent for neonatal brain injury**

Erythropoietin (Epo) is a promising new therapeutic agent for neonatal brain injury. However, depending on the degree of injury, Epo may not be able to exert its full potential. But, recent clinical trials suggest Epo as a potential agent for neonatal brain injury. For example, a single dose of Epo given at the onset of neonatal hypoxia resulted in improved brain development persisting into adulthood. This was associated with reduced abnormalities in the white matter (part of the brain mainly made up of myelinated neurons) four months after the hypoxic insult.

**How was hypothermia discovered as a treatment for neonatal brain injury and how does it work?**

It was discovered in the 1960s by Westin and colleagues (Westin et al. Acta Paediatr Suppl. 1962), who cooled newborn asphyxiated infants to 25°C(!) and found better survival. In the 1990s, rodent and piglet research started (Thoresen M. et al., Robertson N. et al.) and in the early 2000s the first clinical trials (TOBY trial by Azzopardi et al., Shankaran et al.) showed positive effects for infants. Although it was found to inhibit necrosis and programmed cell death, and is antioxidative, most effects are not yet known.

As Epo and Fingolimod are already licensed to treat other conditions, can we expect to see them used to treat neonatal brain injury relatively quickly compared to developing a new drug from scratch?

The first clinical trials for Epo have begun, which is already licensed for treatment of anaemia of prematurity, so it is feasible to be used in preterm infants and potentially also in children with stroke or birth asphyxia (in higher neuroprotective doses as for anaemia). Fingolimod still needs further experimental evaluation, especially regarding the immune system of preterm infants.

**Why did you decide to develop the experimental models of neonatal brain injury? Are there any alternative models?**

We also have cell culture models, which are used in combination with the rodents. One needs experimental research before treating patients.

**RESEARCH OBJECTIVES**

Prof Dr Ursula Felderhoff-Müser’s current research explores molecular mechanisms of insults to the developing brain occurring shortly before or after birth, e.g., perinatal asphyxia or extreme prematurity. Her major aims include the identification of biomarkers and regenerative neuroprotective therapies for brain injury in newborn infants. She is also involved in international multicentre clinical trials of intensive medicine diagnosis and treatment of severely ill children.

**FUNDING**

- Deutsche Forschungsgemeinschaft (DFG)
- European Union (EU)

**COLLABORATORS**

- Dr Bernd Giebel, Institute of Transfusion Medicine, University Hospital Essen
- Prof Stephane Szonienko, Dr Johan van der Loij Neonatal Neuroscience Lab University of Lausanne and University of Geneva, Switzerland
- Prof Dr Ralf Dechend, Institute of Molecular Medicine, Charité, University Medicine Berlin

**BIO**

Professor Dr Ursula Felderhoff-Müser obtained her medical degree from the Universities of Saarbrücken, Vienna and Heidelberg, and her Pediatric Subspecialty Training Program at University of Heidelberg and Free University and the Charité Berlin. After completing her professorship at the Charité, University Medical Center Berlin, she moved to University Hospital Essen in 2008, where she is currently Director and Chair at the Department of Pediatrics I, Neonatology, Pediatric Neurology and Pediatric Intensive Care.

**CONTACT**

Professor Dr Ursula Felderhoff-Müser
Department of Pediatrics I
University Hospital Essen
Hufelandstr. 55
45147 Essen
Germany

E: Ursula.Felderhoff@uk-essen.de
T: +49 201 7232451
W: http://zmb-net.he-hosting.de/research-community/ursula-felderhoff-mueser
Research Publishing International are not just in the business of producing cutting-edge, jargon-free scientific publications. Oh no, we specialise in a range of media services to assist scientists and research teams from all disciplines to achieve next-level communication goals.

- Sci Ani - Animating Science
- Research Features Magazine - Sending Your Research Further
- Research Features - Online portal and catalogue of content
- Social Media Management - Creating new accounts and ongoing management for research teams
- Research Project Web Design - From a single page to a complex outlet
- Research Project Posters and Displays
- Research Project Video - From 1-minute explainers to an entire movie
- Annual Reports and Research Project Brochures
- Workshop and Events - From venue hire and stand design, to event promotion and management

Partnership enquiries: simon@researchfeatures.com
Careers and guest contributions: emma@researchfeatures.com

www.researchpublishinginternational.com  www.researchfeatures.com