Impact Objectives

- Develop a brain tissue metabolic biomarker that can be measured non-invasively at the cotside
- Identify infants immediately after birth who have suffered brain injury and improve the outcome
- Continue to develop innovative optical instruments, which can be easily integrated into the clinical environment

Improving diagnosis and prognosis in neonatal brain injury

***Dr Ilias Tachtsidis** introduces us to MetaboLight and discusses his inspiring work to engineer novel optical technologies and develop advanced computational methods to monitor the brain health of sick newborn babies*

What sparked your interest in medical physics and biomedical engineering?

I have a genuine interest in engineering, physics and medicine. From a young age I was interested in technology developments and in my teenage years I used to build audio amplifiers and radio transmitters. I was eager to do a university degree that combined engineering, physics and medicine; I wanted to learn more about these three subjects and how engineering and physics can innovate medicine.

What is the most exciting aspect of your research and what inspires you day-to-day?

The fact I can build something in the lab and then take it to the hospital to monitor aspects of the patient's health and help the medical doctors in their clinical decision-making. I am very excited when our technology, instruments and measurements are used to answer real needs in the real world, and improve patients' lives; and in this particular case, the lives of babies.

One of the most exciting aspects of my research so far was going to the Neonatal Intensive Care Unit at University College London Hospitals (UCLH), UK and seeing our instruments being used to monitor very sick newborn babies and provide much needed information regarding the health of the babies' brains. I am always inspired by the clinical team of neonatologists and nurses looking after these sick newborn babies and interacting with them gives me my everyday motivation.

Why is NIRS integral to your work?

NIRS stands for near-infrared spectroscopy, and describes an optical technique that uses near-infrared light – that is light where its wavelength is beyond the red colour and is invisible to the eye. With NIRS we can quantify the concentration of haemoglobins in the blood and monitor brain tissue oxygen levels. Besides haemoglobin there are other chromophores, and one that is of particular interest is an enzyme inside the mitochondrial, the power factory of the cell called cytochrome c-oxidase.

Do you face any particular challenges?

The major challenge I have is securing funding to drive R&D. It is important that we keep the momentum of discoveries going and to do that I need to have funding to keep the people in my team and attract other bright minds into the field. I am happy that most often the new developments and discoveries allow you to obtain and secure research funding, but that does not automatically happen, so I have to be alert and ensure these two things – discovery and funding – are in synchrony so we can achieve our major goals to improve patients care, change patients' lives and innovate clinical medicine.

Looking ahead to the next five to 10 years, what is in store for the team?

We are collecting data with our instruments within the neonatal intensive care unit at UCLH, looking at infants with hypoxic-ischaemic encephalopathy from day one to day seven of life; but we are now taking our first steps in measuring the function of these infant brains before they are discharged and following them up when they are three months, six months, one year and two years old.

Being able to stratify these infants by assessing their brain metabolic and oxygenation responses during functional stimuli and linking this to their neurodevelopment assessment is extremely important in ensuring and recognising possible treatment and physiotherapy avenues.

In terms of instrumentation development, we are about to release our new imaging system that will allow synchronous monitoring of brain tissue oxygenation and energetics at multiple locations on the infants' head. For more information see: http://metabolight.org/ and http://www.ucl.ac.uk/medphys/research/borl/mms

Neonatal innovation

*A team based at **University College London**, UK, is striving to enhance the diagnosis and management of neonatal brain injury. The researchers are aiming to achieve this by developing innovative bedside tools for monitoring neurodevelopment from day one of life*

A prolonged lack of oxygen delivery to the brain means the metabolic demand of the brain tissue is not being met, which places a patient's health in grave danger. Examples of this are in neonatal encephalopathy secondary to perinatal hypoxic-ischaemia (HI), traumatic brain injury (TBI) and stroke. Indeed, perinatal HI brain injury is an important cause of neurological disability.

There are drawbacks to current monitors such as continuous EEG, which only look at the electrical activity of the brain; and MR scans that can only be done much later after treatment, requiring the infant to be moved to the scanner. There is a need for a continuous bedside biomarker of cerebral tissue function to help identify those at risk of further injury, so care can be redirected. Dr Ilias Tachtsidis, a Wellcome Trust Senior Fellow, reader in biomedical engineering and Head of the Multimodal Spectroscopy (MMS) Group at University College London, UK, provides an insight into some of these downfalls: 'MR spectroscopy can provide information of brain tissue energetics. However, the instrument is extremely large, requires dedicated staff to operate, is very expensive and involves moving a very sick infant inside the MR scanner, a procedure that carries risks,' he states. 'PET involves the use of radionuclide contrast agents and because of that can deliver high doses of radiation, which can be harmful for newborns. The fact is, there is not a monitor or instrument that can measure brain tissue energetics at the cotside. Optical techniques can fulfil that neuro-monitoring gap, and indeed my group has been developing optical methods to monitor the brain tissue redox status of cytochrome-c-oxidase, an enzyme inside the mitochondrial that produces energy for the brain tissue.'

FULFILLING A NEED

Tachtsidis' group is responding to a need for real-time non-invasive in vivo multimodal measurements of brain tissue oxygenation and biochemistry for the assessment and development of effective neuro-protection strategies; for example, hypothermia in birth asphyxiated infants. The researchers are developing and using innovative instruments and methods to non-invasively measure the metabolic status of the injured brain tissue of infants, in order to monitor problems during birth that can lead to a lack of oxygen reaching the brain and cause brain injury. Their mission is to develop a novel brain imaging and physiological monitoring modality by using optical techniques. The hope is that this will lead to the development of a bedside biomarker for neonatal brain injury, the ability to identify infants whose injury may progress and require adjunct therapies, and enable clinical care to be redirected early on, assisting with effective rehabilitation.

Tachtsidis provides an insight into how this Wellcome Trust-funded research came about and just why it is so important: 'I applied to the Wellcome Trust for funding to develop an optical instrument that will measure an optical brain tissue metabolic biomarker that will allow assessment of the brain injury in birth asphyxiated newborn babies,' he states. 'These are newborns that either in uterus or during birth, their brain became hypoxic, which means deprived of oxygen; and ischaemic which means there was a reduction in brain blood flow. These are very sick infants and some of them will grow up fine and healthy, but some will die and some will grow up with severe neurological deficits including cerebral palsy. In order to help in the clinical management of these infants and their clinical recovery, it was obvious to me that the first thing we needed were diagnostic and prognostic measurements and markers from day one of life. Having these we can then assess treatment and use preferential care to improve the babies' outcomes.'

NEAR-INFRARED SPECTROSCOPY SYSTEMS

The group has developed unique near-infrared spectroscopy (NIRS) systems that are currently used at UCL Hospitals in London, UK to monitor adult traumatic-brain-injury patients and birth asphyxiated infants. The systems are efficient as NIR light between 650-1,000 nm can penetrate through several centimetres of tissue. When it comes to the human brain, it is able to penetrate the scalp and skull to sample the brain due to lower light scatter and absorption. Further benefits include the ability to monitor at the cotside non-invasively, the safeness of the technology, that there is no need for dedicated staff and that it relatively inexpensive.

Using broadband NIRS, the team is able to monitor oxygenation, haemodynamics, oxygen delivery, oxygen saturation, metabolism, mitochondrial function and oxygen utilisation. They are able to use the system to monitor babies continuously from the day of birth and continue monitoring them during treatment, as well as being able to perform measurements inside the magnet and monitor in tandem with EGG and systemic physiology. The team has a particular interest in exploring the enzyme cytochrome-c-oxidase, as Tachtsidis highlights: 'This enzyme, this molecule exists inside the mitochondria in the cells of the tissue. The mitochondria are the power factory of the cells. They take up oxygen and fuel from glucose to produce ATP, the energy that our cells need,' he explains. 'In this process, cytochrome-c-oxidase is very important as it facilitates this turnover of glucose and oxygen to energy, and as it does that, changes colour. If there is not enough oxygen or glucose, the cytochrome-c-oxidase will not be able to facilitate normal energy turnover. This can happen during tissue injury similar to what happens in infants with hypoxic-ischaemic brain injury. Now, with our methods, we are able to monitor brain tissue oxygenation by measuring haemoglobin concentration and brain tissue energetics by measuring the cytochrome-c-oxidase concentration. To do that, we use many different light colours or light wavelengths in the near-infrared region of the spectrum.'

INTRODUCING CYRIL

Another tool the team has developed is an instrument called CYtochrome Research Instrument and application (CYRIL). 'This is a particular type of spectrometer that utilises lenses instead of mirrors, to focus the received NIR light from the baby's head to a charge-coupled device (CCD) camera that is cooled to -70 °C,' describes Tachtsidis. The group has also developed a solution that enables them to focus on CCD multiple detector fibre bundles, which provides the capacity to measure different brain locations synchronously. 'In addition, we have also been developing and customising mini-spectrometers to allow us to do our measurements with instruments that can be easily integrated within the clinical environment,' Tachtsidis adds.

> *My team and I have been actively involved in public engagement activities to communicate and disseminate our research to the public and introduce young people to the field of medical physics and biomedical engineering. Visit our public engagement portal at http://metabolight.org/ to learn more*

IN-DEPTH MULTIDISCIPLINARY KNOWLEDGE

Tachtsidis' has put together a multidisciplinary team involving engineers, physicists, computer scientists and clinicians. 'We each have our core subject area, but it is important that the engineer understands the clinical questions and the clinician understands the engineering issues,' he says. 'This in-depth multidisciplinary knowledge can only happen through interactions and contact. You need to understand the clinical need, you need to develop something that answers that need and you need to make sure that what you develop can be used, and in our specific case, by the clinical team. To achieve all the above you need a multidisciplinary team with people involved in all aspects of the research. We are very fortunate to have the support and input of our UCLH neonatologists and clinical team, who have been a vital component in our current successes.'

The team is dedicated to sharing its research as Tachtsidis reveals: 'Recently my team and I have been actively involved in public engagement activities to communicate and disseminate our research to the public, and introduce young people to the field of medical physics and biomedical engineering.' Indeed, the team has a public engagement portal, MetaboLight.org where it lists news and events.

EXCITING DEVELOPMENTS AHEAD

One important finding of the group to date is the observation of a prognostic association between the relationship of brain tissue energetics and brain tissue oxygenation as measured by their instrument with neurodevelopmental outcome. 'This discovery brought us even closer to identifying a robust cotside biomarker,' enthuses Tachtsidis.

The team is on the cusp of releasing a new imaging system that will enable synchronous monitoring of brain tissue oxygenation and energetics at multiple locations on an infant head. With exciting developments like this in the pipeline and an expert and devoted team of researchers, Tachtsidis' group is set to move from strength to strength in improving the diagnosis and prognosis of sick infants with hypoxic-ischaemic encephalopathy.

Project Insights

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PROJECT COORDINATOR BIO

Dr Tachtsidis is a Wellcome Trust Senior Fellow and Reader in Biomedical Engineering. He is a senior member of the Biomedical Optics Research Laboratory and heads the Multi-Modal Spectroscopy Group. His research is highly multidisciplinary, crossing the boundaries between engineering, physics, neuroscience and clinical medicine. The technical focus of his work is the development and use of non-invasive optical instruments and techniques for monitoring brain oxygenation, haemodynamics and metabolism. A major part of his research is to investigate the use and limitations of functional Near-Infrared Spectroscopy or fNIRS in neuroscience applications. In addition, the clinical focus of his work is the identification and use of optically measured biomarkers to assess the functional status of the brain. The principal challenge of his research is the non-invasive measurement, with NIRS, of cytochrome-c-oxidase (CCO), a mitochondrial enzyme responsible for cellular energy production.