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New research into nucleoside therapy aims to develop a treatment for deadly mitochondrial disease

Hundreds of types of mitochondrial disease affect up to 38 million people worldwide[1], yet there are very few effective treatments, forcing patients and doctors to rely on symptom management to battle the serious and potentially fatal genetic disorder that starves the body's cells of energy.

Now, a pioneering project jointly funded by peak patient groups in Australia and the United Kingdom aims to develop nucleoside therapy as a treatment for mitochondrial depletion syndromes, in which cells cannot extract sufficient energy from food to power vital organs.

Symptoms of mitochondrial depletion syndromes can include profound muscle weakness causing immobility and impaired breathing requiring mechanical ventilation, as well as liver failure, intractable seizures and neurodegenerative deficits. Most patients die before the age of five years.

The study, funded by the Mito Foundation (incorporated as the Australian Mitochondrial Disease Foundation) and The Lily Foundation, involves multi-disciplinary teams at mitochondrial centres attached to Newcastle University (UK), the University of Cambridge and Cardiff University.

Researchers aim to develop an effective, bioavailable form of nucleoside bypass therapy, in which modified molecular 'building blocks' are used to increase production of healthy mitochondrial DNA.

In what is hoped to be a precursor to future drug trials, the research project combines a detailed patient study with testing of treatment formulations on skin cells taken from patients with mitochondrial depletion syndrome RRM2B.

Professor Robert McFarland[2], a principal investigator from the Wellcome Centre for Mitochondrial Research at Newcastle University and a Lily Foundation Medical Board member, said he is delighted The Lily Foundation and the Mito Foundation are funding this important research project.

"We hope that by testing this treatment in cells grown in the laboratory we can optimise the type and combination of nucleosides to use in animal models, and subsequently in human trials," he said.

The announcement comes almost one year after the death of UK baby Charlie Gard, who succumbed to a form of mitochondrial depletion syndrome on 28 July 2017, just before his first birthday, following a prolonged public court battle to access experimental nucleoside therapy being developed in the US.

Approximately three Australian children are born each year with mitochondrial depletion syndrome, which occurs in at least 1 per 100,000 births, according to Professor David Thorburn, Mitochondrial Research Group Leader at Murdoch Children's Research Institute, and member of the Mito Foundation board and its Scientific and Medical Advisory Panel.

"This research project is exciting because it addresses the major issue in that we currently lack effective targeted treatments for most forms of mitochondrial disease," said Professor Thorburn, who was involved in reviewing the grant application.

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"It is absolutely critical to develop treatments that improve patient outcomes and have an evidence base to justify their use. This project seeks to do that for mitochondrial DNA depletion syndromes.

"Early-stage research from the US and elsewhere suggests nucleoside therapy may be effective in a mitochondrial DNA depletion syndrome called TK2 deficiency, which primarily affects muscles. It is not yet clear if it may work for other forms of mitochondrial DNA depletion syndrome such as RRM2B, which affects the muscles, brain and other organs."

Sean Murray, CEO of the Mito Foundation, said the organisation is committed to funding projects that will have maximum impact for the mitochondrial disease community.

"Nucleoside therapy holds real promise for a potential treatment that could improve and save lives, not just in Australia but around the world. International collaborations like ours ensure investment in high quality mitochondrial research, regardless of location, to develop treatments for this complex and devastating disease," Mr Murray said.

About nucleoside therapy

Mitochondria contain their own DNA, known as mitochondrial DNA or mtDNA, which is vital for mitochondria to generate the energy needed to power our cells. The quality and quantity of mtDNA must be maintained for the mitochondria to produce key proteins necessary for their function. Problems with mtDNA maintenance can reduce the amount and quality of mtDNA and lead to impaired energy production, which in turn can cause mitochondrial DNA depletion syndrome.

Four chemical 'building blocks' are needed to make mtDNA, collectively known as deoxynucleoside triphosphates, or dNTPs, which need to be present in a carefully balanced pool within mitochondria. If this pool is not maintained, or the relative proportions of the four different dNTPs within the pool are disrupted, then mtDNA is not made and this can result in mitochondrial DNA depletion syndrome.

Research has shown that providing deoxynucleosides (nucleosides), or similar building blocks known as deoxynucleotides (nucleotides), may correct the depletion by bypassing the block that is impairing the production of one or more dNTPs. This may restore the amount and balance of dNTPs available for making or repairing mtDNA, and lead to improvement in problems associated with the condition.

Nucleoside therapy has already been used to treat mitochondrial depletion syndrome TK2, where only two of the four nucleosides are depleted. However, extending the currently available nucleoside therapy to other depletion syndromes poses a number of challenges for scientists, including getting the nucleosides to their target in the body, and ensuring the pool of nucleosides is balanced so as not to cause further problems. As a result, no patients with depletion syndromes other than TK2 have been successfully treated with the currently available compounds to date.

This new research hopes to change this by developing modified nucleosides that are far more like a medicine than the compounds currently available, and which can be delivered to the right place in the cell and do their job effectively without any harmful side effects.

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[1] *1 in 200 people may develop a mild to moderately disabling form of mitochondrial disease during their lifetimes, while 1 in 5000 people will develop a severe or life-threatening form of mitochondrial disease, according to the Mito Foundation.*

[2] *Professor Robert McFarland will address the Mito Foundation Symposia in Sydney and Melbourne on 19+20 September during Global Mitochondrial Disease Awareness Week (16-22 September 2018).*