

Tim Barrett Lay person summary

Development of a novel repurposed drug treatment for the neurodegeneration and diabetes in Wolfram syndrome.

One in 17 of the UK population suffers from a rare disease. There are over 6,000 rare diseases, many of which are life limiting, and almost all have no cure. Wolfram syndrome is a rare disease (1:700,000; about 100 people in the UK) that causes diabetes and blindness in children and young people. These children may grow up to develop other problems such as deafness, loss of bladder control, loss of balance, and sometimes depression. The disease is life limiting because of damage to brain cells and brain shrinkage. The only way to look after affected people is to treat the complications: there is no cure, and no treatment to prevent or slow down the progression of the disease. **The goal of our research team is to develop a treatment that will prevent or delay the disease getting worse.** We believe that such a treatment will offer longer, better quality of life for affected people.

Our research team at Birmingham University developed a cell model of Wolfram syndrome, and used it to screen for medicines that can treat the disease. We found one, sodium valproate, that reduces cell death in our cell model of Wolfram. Sodium valproate is a really promising candidate as it has been used for decades to treat epilepsy in children. It is licenced for use in epilepsy. We also know that it improves the diabetes in a mouse model of Wolfram syndrome. However, like all medicines, it does have side effects. It should not be used in people with liver disorders, or people with mitochondrial disorders caused by mutations in the POLG gene. It must not be used in pregnancy. It can sometimes cause mood changes, anaemia, nausea, disturbed periods, weight increase, and tremor. Therefore, we need to test its safety and effectiveness for Wolfram patients, in a clinical trial. We are only allowed to prescribe it to patients, once we have shown that it is safe; and that it works to slow down the disease process.

On 14th December, the UK Medical Research Council awarded £2million (\$2.5Million) funding to the Birmingham UK team to lead a clinical trial of sodium valproate in children and adults with Wolfram syndrome. This will be the first randomised controlled trial in Wolfram syndrome. The aim of the clinical trial is to show that sodium valproate is safe, and effective, in people with Wolfram syndrome. We will invite 70 children and adults with Wolfram syndrome to take part. These will be from people attending 5 centres: Birmingham adults (Dr Ben Wright) and children (Dr Renuka Dias); Almeria (Dr Gema Esteban Bueno); Paris (Pr Christophe Orssaud); Montpellier (Pr Christian Hamel); Lodz (Pr Wojciech Mlynarski).

The study period will run for 36 months. We will check that valproate is safe, and effective as a treatment for Wolfram. We will do this by closely monitoring for any side effects; and by careful measurements of vision, brain volume, and other features, as the trial continues. We already know how quickly the disease gets worse with no treatment. This trial will give us a clear answer as to whether sodium valproate slows down the disease process, or not.

If the trial shows us that valproate is safe in Wolfram syndrome and slows down the progress of the disease, then this will give us the evidence to prescribe valproate to Wolfram patients

in the clinic. Most importantly, we hope this trial will improve the quality and length of life in patients with Wolfram syndrome.