

Press Release

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Rare diseases: Publication in Cell

Sildenafil identified as a potential therapeutic approach for Leigh syndrome

A milestone in the treatment of Leigh syndrome, a rare, early-onset disease in children, has been reached: At the Hamburg site of the Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, in collaboration with Heinrich Heine University Düsseldorf (HHU) and University Hospital Düsseldorf (UKD), as well as Charité – Universitätsmedizin Berlin, a promising agent for the treatment of Leigh syndrome was identified. The researchers were able to demonstrate a positive effect of the active substance sildenafil on the disease course. The study was headed by Professor Dr Alessandro Prigione (Department of General Paediatrics, Neonatology and Paediatric Cardiology, UKD) and Professor Dr Markus Schuelke (Department of Paediatric Neurology, Charité) and is currently published in the journal Cell.

Leigh Syndrome is an inherited, progressive disease that affects the brain. It is a so-called mitochondrial disease, i.e. it affects the energy metabolism. The syndrome, which usually manifests in childhood, causes damage in the brain, which can lead to severe symptoms such as neurodevelopmental delay, epileptic seizures, muscular weakness and respiratory failure. No approved medication is currently available. The life expectancy of children with the disease is limited and most die within a few years of diagnosis.

With a case count of 1 in 36,000 live births, Leigh syndrome is classified as a "rare disease". According to the European classification, a rare disease affects less than five in 10,000 people. The low number of cases makes research more difficult, even though the need for therapy is high. There are only a few models available that can reliably represent the human disease progression. Therefore, an international research consortium from Germany, Austria, Finland, the Netherlands, Poland, Italy, Greece, and the USA has developed alternative model systems to study Leigh syndrome. To this end, researchers used skin cells from patients as a basis to develop induced pluripotent stem cells (iPSC) that have the ability to differentiate into various cell types in the lab, such as neural cells. Also, so-called brain organoids can be generated from iPSC, which can be thought of as 3D models of the brain. They served as an important foundation for the now-published research results.

So far, the largest drug screen conducted, comprising over 5,500 substances

Based on neurons derived from patient-derived stem cells, the researchers conducted an extensive drug screening of compounds, some of which are approved for other diseases and

have extensive safety and efficacy data. "With more than 5,500 compounds tested, this was the largest screening process to tackle Leigh Syndrome ever conducted. We are very proud that we have succeeded in realising this process and been able to identify a potential therapeutic agent," explains Dr Ole Pless, head of the research group at Fraunhofer ITMP Hamburg. In the cell model, the researchers were able to demonstrate that the active substance has a positive effect on metabolism and improves the function of the diseased cells. Sildenafil is currently approved for the treatment of erectile dysfunction in adults. In children, there is already an approval to treat pulmonary arterial hypertension. Therefore, sildenafil offers a good safety profile and promising results regarding efficacy in the cell model.

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In the further course of the study, sildenafil was used as an individual compassionate use (off-label) treatment for six patients. The first Leigh Syndrome patient was treated with Sildenafil at Charité. Following positive results, further patients in Düsseldorf, Munich and Bologna were also treated. Sildenafil had a positive effect on the disease course in all patients treated. The medication was well-tolerated. "Extensive safety data on the long-term use of Sildenafil in children are already available, so we can assume that this could be a safe drug candidate for Leigh Syndrome," reports Professor Alessandro Prigione, UKD. "In the patients treated to date, we were able to observe that they recovered quickly from critical medical situations, their neurological function improved and their muscular strength increased," adds Professor Markus Schuelke, Charité.

As a result of these findings, the European Medicines Agency (EMA) has granted Sildenafil an Orphan Drug Designation (ODD). The ongoing Horizon research consortium SIMPATHIC, in which Professor Prigione and Professor Schuelke are also involved, is currently planning a multinational placebo-controlled clinical trial to determine whether Sildenafil is effective and safe in this patient population, and thus whether the EMA can approve it for the treatment of Leigh Syndrome. The publication is the result of a multinational collaboration within the framework of the CureMILS consortium funded by the European Joint Programme on Rare Diseases (EJP RD) and coordinated by Professor Prigione. Dr Pless and Professor Prigione will continue their joint work on the SynLeigh project under funding from the European Rare Diseases Research Alliance (ERDERA).

Link to paper:

[https://www.cell.com/cell/fulltext/S0092-8674\(26\)00173-X](https://www.cell.com/cell/fulltext/S0092-8674(26)00173-X) doi: 10.1016/j.cell.2026.02.008

Image material

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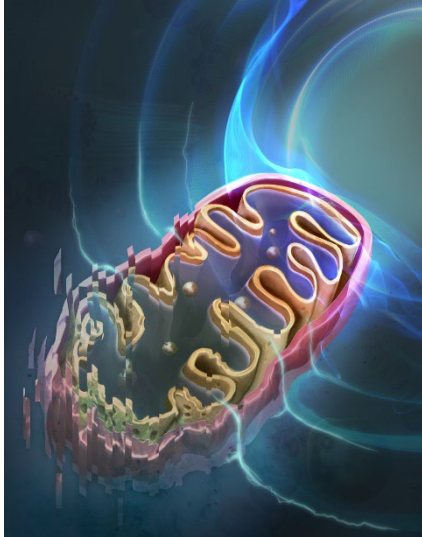


Fig. 1 This illustration depicts the recovery of mitochondrial function in Leigh syndrome as a transition from cellular instability to restored balance following sildenafil treatment. In the lower left, fragmented lines represent impaired energy production, altered calcium signaling, and cellular stress in affected neural cells. From the upper right, a blue light wave symbolizes the therapeutic intervention. As the therapy's effect progresses, it displaces the visual noise associated with mitochondrial dysfunction. The treated mitochondrion gradually shifts toward an organized and glowing structure, representing the normalization of mitochondrial activity and cellular signaling.

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