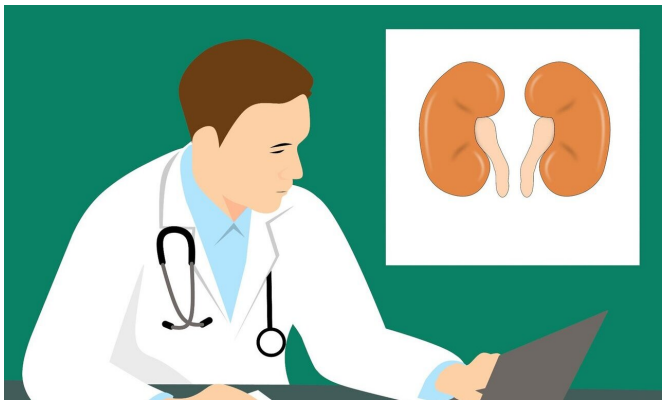
Cancer drug can rebalance kidney function in a devastating genetic disease

9 September 2020



Credit: CC0 Public Domain

Researchers at the University of Cambridge and the University of Zurich have discovered that a drug newly approved for cancer improves kidney dysfunction in a mouse model of Dent disease 2 and Lowe syndrome

The study is published today in *Kidney International* and offers hope for the first disease -modifying treatment. In addition to kidney dysfunction, characteristic of Dent disease 2, boys with Lowe syndrome also require eye cataract surgery as newborns, and suffer seizures and other disabilities. Only supportive treatments are available, such as nutrient supplements and help with learning.

These rare diseases are caused by the lack of an enzyme called OCRL that normally controls the lipid composition of cell membranes. The disruption activates a system of filaments inside the cells, called the actin cytoskeleton, in the wrong place. The actin blockage means that the cells in the kidneys that usually reabsorb filtered proteins and essential nutrients don't work properly, causing a loss of these in the urine.

Dr. Jennifer Gallop's group at the Wellcome Trust/ Cancer Research UK Gurdon Institute in Cambridge worked out how the actin system was being activated by the disruption in cell membrane lipids. "By understanding the details of what is happening in cells during Lowe syndrome and Dent disease 2," said Dr. Gallop, "we realised that alpelisib, a drug that is already approved for use in patients with cancer, could prevent the actin blockage". This is because alpelisib targets a different step in the pathway, and rebalances the lipid composition.

The Gallop group teamed up with Professor Oliver Devuyst from the Institute of Physiology, University of Zurich to test alpelisib in a humanized mouse model of Lowe syndrome and Dent disease 2. Devuyst said "amazingly, treatment with alpelisib improved the actin cytoskeleton of the kidney cells and rescued the reabsorption of the filtered proteins".

The researchers don't yet know whether the drug will work in patients and if their neurological symptoms will be helped as well. However, because alpelisib has been used before in another rare disease in children, as well as in adults, there is evidence that it is safe. These efforts of repurposing a drug could potentially lead to the cost-effective development of a treatment for these rare disorders.

Provided by Wellcome Trust