

Repurposing of FDA approved chemical chaperones to the rescue of a mouse model of Alport syndrome
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Awarded 2017

Alport syndrome (AS) is a severe inherited glomerulopathy caused by mutations in genes encoding the α -chains of type IV collagen (COL4), the most abundant component of the glomerular basement membrane (GBM). Typically, patients present with microhematuria since childhood and over time they progress to proteinuria, renal function decline and end-stage renal disease (ESRD), usually before the 3rd decade of life.

Nearly half of mutations in AS are single aminoacid substitutions giving misfolded proteins that are secreted poorly, resulting in defective GBMs. Recent work at the Molecular Medicine Research Centre (MMRC) showed that synthesis of misfolded proteins results in activation of the Unfolded Protein Response (UPR) signaling cascade, which when prolonged leads to impaired podocyte function and/or loss (Pieri M et al, JASN 2014). The same paper included the first partial description of a homozygous knockin AS mouse model, carrying the Col4a3-p.G1332E mutation. Since then we created another AS mouse model, the Hemizygous Col4a3 Mouse carrying only one Col4a3 allele, which has the same mutation: Col4a3-G1332E (mouse model denoted as: Col4a3E/-). This mutation recapitulates the human COL4A3-p.G1334E, a founder and very common mutation amongst heterozygous Cypriot patients with thin basement membrane nephropathy (TBMN) (it is a substitution of glycine by glutamate at position 1334 of the α -chain).

CHALPORT is a pilot study, to repurpose synthetic chaperones, which proved beneficial and were approved by the USA Food & Drug Administration (FDA) for other disease indications, to test if they could guide the secretion of mutant COL4 and the formation of imperfect networks in the GBM that might be better tolerated than null or impaired secretion. We base this on the fact that positive collagen staining in patient biopsies is associated with better prognosis. "Convincing" the podocytes to secrete effectively, even partly functional collagens, will be attempted for the first time in AS, repurposing pharmacologically active chaperones, PBA & TUDCA. The proposed repurposing will be applied on hemizygous mice carrying a single mutant allele, Col4a3: Col4a3E/-.

To our knowledge this is the first time to attempt chaperone administration in AS mice, representing a paradigm of pre-clinical translational research. The results will not only shed light on the molecular mechanisms behind COL4 mutations but will also set the basis for alternative treatments.