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A novel small molecule therapy rescues trafficking of misfolded podocin and corrects Nephrotic Syndrome caused by a common podocin mutation

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There are currently no targeted therapies for the ever-increasing number of podocyte diseases (podocytopathies). Currently there are over 60 different genetic disorders causing Steroid Resistant Nephrotic Syndrome - the commonest of these by far is that of mutations in the NPHS2 gene encoding podocin. Podocin is a key scaffolding protein of the slit diaphragm essential for intact glomerular filtration. The most frequent podocin mutation in European children is R138Q, causing retention of the mutant protein in the endoplasmic reticulum (ER). We provide evidence that a protein-protein interaction (PPI) of misfolded podocin R138Q (but not wild-type podocin) with the intermediate filament protein keratin 8 (K8) prevents its correct trafficking to the plasma membrane. We have also identified a small molecule that interrupts this interaction and rescues mutant protein mis-trafficking. This results in functional rescue of podocin in both human patient R138Q mutant podocyte cell lines, and in a mouse inducible knock in model of the R138Q mutation. In the mouse, complete rescue of proteinuria and histological changes are seen, when the small molecule is administered at disease induction, and also after proteinuria has commenced. Altogether, these data provided constitute the first therapeutic option for NS patients bearing the common R138Q mutation