Introduction and Aims: Acute kidney injury (AKI) is now recognized to be an early harbinger of chronic kidney disease (CKD). There is mounting evidence to suggest that AKI triggers changes in cellular signalling that redirect cells towards a profibrotic phenotype. We have previously shown that Kirsten Ras (K-Ras) is up-regulated in the kidneys of animals with chronic fibrosis and targeting it repeatedly with Antisense Oligonucleotides (ASO) reduces both its expression and interstitial renal fibrosis. Our aim was to investigate whether targeting K-Ras during the peri-AKI period with a single dose of ASO in a novel animal model of Aristolochic Acid induced nephropathy could reduce downstream interstitial fibrosis and prevent long-term renal impairment.

Methods: CD1 mice received intra-peritoneal injections of either 3.5mg/kg Aristolochic Acid (AA) or normal saline on day 1 and on day 5. A treatment group, in addition to the injections of AA, were also given a single subcutaneous injection of 100mg/kg of K-Ras ASO 2 days prior to the first AA injection.

Renal function was assessed through a blood urea nitrogen (BUN) assay. The degree of fibrosis was ascertained through Picrosirius red (PSR) and Masson Trichrome (MT) staining to quantify collagen deposition.

Results: An acute kidney injury was observed in mice that had received AA with a 4.6 fold rise in BUN compared with normal saline controls by day 12. The BUN rise in the AA group fell by half by day 20 and returned to baseline at day 32. This was associated with a polyuric phase with urine output doubling at day 12 which then returned to baseline at day 32. Recovery from the AKI in the AA mice was followed by a gradual increase in BUN to 1.5-fold that seen in the saline control group from day 56 to day 100. There was also a 7-fold increase in collagen deposition identified at day 100 through PSR and MT staining of kidney tissue from AA mice compared to the normal saline controls, confirming the development of fibrosis and chronic kidney disease. The animals treated with K-Ras ASO showed a 66% reduction in fibrosis identified by both PSR and MT staining at day 100 compared to the untreated AA group. In addition, the ASO treatment group had BUN levels that were within the normal range at day 100.

Conclusions: A single dose of K-Ras ASO given in the peri-AKI period of a murine model of acute kidney injury can reduce downstream fibrosis and prevent the decline in renal excretory function. Our results give further confirmation that targeting K-Ras may provide a future therapeutic agent for preventing renal fibrosis and chronic kidney disease following acute kidney injury.