

## **Summary of Project**

Cystinosis is a rare disease characterised by the accumulation of the amino acid cystine in subcellular compartments known as lysosomes, in various cells and tissues of the body. This results in severe damage and even death of the cells. Clinically the first vital organ to fail is the kidney, probably due to the fact that it is responsible for transporting amino acids and sugars between the kidney tubules and the blood, so as they are not lost to the urine.

A new and emerging area of clinical biochemistry and physiology is that of the study of highly reactive molecules derived from oxygen and nitrogen. These molecules have a normal 'signaling' role in cells and between neighbouring cells but under some 'stressful' conditions (such as the presence of foreign material or excessive accumulation of amino acids such as cystine) the cell may produce too much of the highly reactive molecules thus causing severe damage and even death.

Theoretically, the sequestration of cystine in the lysosomal compartment of the cells can result in the deficit of another amino acid, cysteine, which is essential for the synthesis of glutathione (GSH), an extremely important cellular antioxidant necessary for neutralizing excess reactive oxygen species in the cells. We have now obtained evidence that in our experimental model of kidney proximal tubule cells mimicking the transporter defect in cystinosis, GSH levels are depleted which leads to excessive and unregulated generation of 'reactive oxygen and nitrogen species' and a fall in the 'energy currency' of the cell, ATP. It is this fall in ATP levels coupled with limited antioxidant capacity of the cells which precipitates physiologic cell failure. We have the evidence to believe that these biochemical alterations are likely to initiate the chain of events leading to cell injury and ultimately, to cell death which is known to occur in cystinosis.