

Prof. Philip Newsholme, UCD Dublin
“Why do cells die in Fanconi Syndrome”

Cystinosis is a disease characterised by the accumulation of the amino acid cystine in sub-cellular compartments known as lysosomes in various cells and tissues of the body. Amino acids are the basic ‘building blocks’ for proteins. Lysosomes function to metabolise and process various nutrients including fats and amino acids. The accumulation of the amino acid cystine results in severe damage and even death of 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 cystine) the cell may produce too much of the highly reactive molecules thus causing severe damage and even death. As a normal protective mechanism against oxidative stress, cells will activate an amino acid transporter that imports cystine (required for glutathione synthesis, which is a powerful anti-oxidant), in exchange for the amino acid glutamate. Of course, in cystinosis, this will exacerbate the problem of cystine accumulation.

The laboratory of Prof. Philip Newsholme in UCD Dublin has discovered novel roles for amino acids and energy generating metabolism in the insulin secreting pancreatic beta cell and has also been involved in identification and characterisation of a novel reactive oxygen species generating enzyme in this cell type.

Prof. Newsholme will now apply the expertise of his laboratory with respect to identifying the molecular basis for cellular dysfunction and death in cystinosis. By discovering the source of the excessive levels of reactive molecules derived from oxygen and nitrogen, Prof. Newsholme’s group may identify

novel sites for therapeutic intervention (inhibition of the generation of reactive oxygen and nitrogen molecules) which, in combination with cystine reducing therapies, may preserve the function of the kidney and other vital organs.