Waste products are removed from the blood by passing through filter units called glomeruli. There are approximately 1 million glomeruli in each kidney. Blood passes through glomeruli under pressure, waste products cross through the blood vessel walls and are collected in the space around the glomeruli, they then pass down the tubules to the bladder to be excreted. The first part of the tubule is called the proximal tubule.

The blood vessels in glomeruli are organised around a scaffolding of mesangial cells.

Mesangial cells are able to expand or contract and in doing so can alter the pressure under which the waste products cross the blood vessel walls.

In IgAN, IgA from blood is deposited on mesangial cells in the glomeruli. The presence of this IgA causes the mesangial cells to grow and synthesise extra proteins forming scar tissue, the presence of which damages the structure of the glomeruli, and so causes disease.

Funds from the David Mayer Research Trust supports investigations which focus on understanding a number of key areas in this process.
Do changes in the sugars of the IgA hinge increase the risk of kidney failure in IgAN?

The David Mayer Research Fund is funding Karen Molyneux, the lead scientist in the IgAN group, to study how the hinge region sugars of IgA affect the pathogenicity of the IgA molecule in IgAN.

Human IgA exists in two forms, IgA1 and IgA2. We believe changes in the structure of the IgA1 molecule are responsible for IgAN. IgA1 is unusual in that it has a number of sugar molecules attached to its hinge region. In IgAN there are subtle changes to these sugars which we can detect in the laboratory.

Karen is working with Dr Danny Gale, a nephrologist, based at UCL, London looking at the genes responsible for these changes. Karen has recently shown that IgA sugar content is genetically controlled. Karen is beginning to identify the genetic mutations that predispose individuals to produce the type of IgA we see in patients with IgAN.

Karen is now collecting samples to look at these genetic changes in more detail to see how they affect the function of the cells that produce IgA and their effect on the risk of developing kidney failure in IgAN.

Separately Karen is also looking at how IgA molecules with different patterns of sugars at the hinge region interact with different types of kidney cells. To do this Karen is working closely with Chee Kay, David and Dina who are each studying a different kidney cell type.
Understanding how IgA triggers inflammation in the kidney

The David Mayer Research Fund is funding David Wimbury, a postgraduate scientist, to study how IgA causes mesangial cells to transform into cells which form the scar tissue which leads to kidney damage.

There are approximately 1 million glomeruli in each kidney. Each glomerulus is formed of a network of small blood vessels which are organised around a scaffold called the mesangium. The mesangium comprises mesangial cells and a proteinaceous material called the mesangial matrix.

In IgAN, circulating IgA complexes are deposited in the mesangium. The presence of this IgA causes the mesangial cells to replicate and over-produce matrix proteins that ultimately lead to scarring of the glomerulus. In addition, the mesangial cells secrete chemicals that recruit inflammatory cells into the glomerulus and these further damage the glomeruli accelerating the scarring of the kidneys.

David’s work is looking at how IgA interacts with a mesangial cell IgA receptor we have recently discovered called β1,4-galactosyltransferase. David will be growing human mesangial cells in the laboratory and genetically modifying these to both enhance and reduce the activity of this receptor. He will then be able to measure the contribution of this receptor to the triggering of inflammation and scarring in IgAN.
Measuring IgA immune complex levels to predict outcome in IgAN

The David Mayer Research Fund is funding Patricia Higgins, a research technician, to study how levels of circulating IgA immune complexes might predict whether a patient with IgAN will need dialysis in the future.

Immune complexes are aggregates of antibodies and other proteins found in the blood. They can be detected in many different types of disease, not just those affecting the kidneys.

A key feature of IgAN is the formation in the circulation of large IgA-containing immune complexes which are prone to deposit in all glomeruli of both kidneys. It is believed that changes in the sugars attached to the IgA hinge region promote immune complex formation in IgAN. Currently there is no standard method to measure the level of immune complexes in IgAN. Patricia and colleagues in the laboratory are developing a way of doing this. Our initial results with this assay are very encouraging and we will hopefully be moving to validate the test in the near future.

Once the test has been validated Patricia will measure the IgA immune complex levels in the serum of 1000 patients and their relatives. These samples were collected over 10 years ago when all patients were well and had good kidney function. In the patient group we now know who has developed kidney failure and therefore we will be able to relate these historical immune complex levels to the risk of developing kidney failure.
Other research in the Leicester IgAN Group

The David Mayer Research Fund is also providing some support to a number of other IgAN projects in Leicester.

Chee Kay Cheung is a young nephrologist in the group, and he recently spent time in the laboratory of Prof. Bruce Molitoris in Indianapolis to investigate what happens to circulating IgA immune complexes in the kidney when there is ongoing glomerular damage. He found that damaged glomeruli leak IgA into the urine and that this IgA is taken up by proximal tubular cells.

Separately he has shown that when proximal tubular cells are exposed to IgA they become activated and involved in kidney scarring. Over the next few months Chee Kay will be testing whether an experimental drug can block the effect of IgA on these cells and thereby prevent kidney scarring in IgAN.

Dina Niasari is a young nephrologist who has recently joined us from Indonesia. Dina is looking at the potential usefulness of a different treatment for preventing scarring and kidney failure in IgAN. Her work has only just commenced but in the coming months she will see if this drug can block the action of IgA on mesangial cells and proximal tubule cells.

Izabella Pawluczyk is an experienced renal research scientist who is looking at the role of microRNA molecules in the kidney in IgAN. We have expanded her project to also include studying the role of microRNAs in the blood in IgAN.