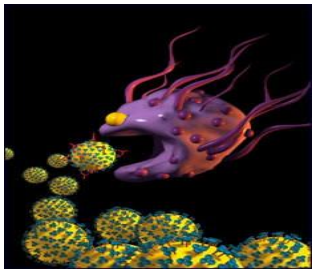
Update from Birmingham on Cutting Edge Research into Vasculitis

By Julie Williams

The term Vasculitis covers a multitude of diseases of inflammation of the blood vessels. These are sub-divided into different disorders by the size of the vessel they affect. One of the most common is that which involves the small vessels (SVV) and this is often associated with a breakdown in the immune system. It causes the body to believe that certain parts of it are alien and it attacks them. The mechanism centres around a type of white blood cell called the neutrophil. Neutrophils are cells of the immune system which are responsible for getting rid of foreign things that find their way into the body, such as bacteria. They do this by sticking to them, engulfing them and digesting them.



In order to be able to do this they have inside them a large amount of toxic chemicals.

In SVV the body produces a protein called an anti-neutrophil cytoplasm antibody, or ANCA for short, which finds the neutrophil very attractive. It sticks onto the neutrophil and this causes it to think that there are bacteria about. As it can't find any it sticks to the blood vessel wall and tries to eat that instead. This is what causes the inflammation.

At present it is still unclear what causes ANCA to form. It may be that the body sees a bug that looks a bit like a neutrophil and then gets confused between this and the neutrophil itself. Other theories are that particles of silica cause a similar effect or it could be that exposure to a particular chemical is to blame. It is most likely that no one thing is to blame and if there is an environmental factor then there are probably also a number of genetic ones that play a part too.

Over the past few years we have been investigating how the ANCA sticking to a neutrophil leads to these effects. We now know a lot about what happens inside the cell. In 2007 we showed that a particular protein in the cell was responsible for the neutrophil sticking down. Recently Neil Holden has shown that this protein is also responsible for the neutrophil attacking the blood vessel and releasing its toxic chemicals.

One of the new projects that we're working on involves the amalgamation of a number of experiments that the whole Renal Immunobiology Group in Birmingham has performed during the last couple of years. These experiments measure the strength of different neutrophil functions, such as stickiness or the ability to attack bacteria. By putting together nearly 1000 different experiments and using a range of statistical approaches we have been able to show

that there are a wide range of differences between different people's ANCA and also people's neutrophils. This may be for many reasons. ANCA come in a variety of different forms. Some of these recognise different parts of the neutrophil, some are more bendy than others and some have more sugar molecules attached to them. The differences in the neutrophils are mainly caused by the person's genes. There are at least five proteins in the neutrophil that we believe that ANCA sticks to. All of these proteins come in 2 or 3 different 'flavours'. If we multiply all of this we can see that there are hundreds of different combinations possible. We need to find out if a particular sort of ANCA mixed with a particular combination of protein on the neutrophil make someone have worse disease. At Birmingham we have the resources to be able to investigate this. From years of collecting we have amassed over one hundred different ANCA samples. In addition we have also been collecting DNA from vasculitis patients since 2001. What we are able to do is to determine what different types of ANCA are in the samples that we have. We can then look at all the DNA samples that we have and see what combinations of the five proteins that we are interested in they have. We can then look at the experiments that we have done and see which ANCA give the biggest responses and see if the patients that they came from had a particular set of proteins. By asking lots of these different questions we could try to build a formula that might predict who would get worse disease or a certain set of symptoms. We are currently applying for funding to perform this work.