

Lay Summary- Christopher Mathew

***Genetic investigation of the role of the NF- $\kappa$ B pathway in susceptibility to inflammatory bowel disease***

The inflammatory bowel diseases (IBD) are chronic conditions that cause severe inflammation of parts of the bowel. There are two main types of IBD, Crohn's disease and ulcerative colitis. The causes of these disorders are not known, and treatment is based on anti-inflammatory drugs and surgery. These approaches treat the *symptoms* of IBD rather than the underlying cause.

Studies of the risk of developing IBD in relatives of patients as well as studies of identical and non-identical twins suggest that genetic factors contribute significantly to the development of IBD, probably in combination with environmental factors. If we can identify genes that contribute to IBD we will improve our understanding of the underlying causes of these diseases, and this should help us to design new drugs that target whatever process is blocked or deficient in the IBD patient. Several research teams around the world, including our own, showed that mutations in a gene called NOD2 (also called CARD15) increase the risk of Crohn's disease by between 3 and 30-fold, depending on whether we have one or two copies of the gene. However, since about 60% of Crohn's patients do not have these mutations, and many healthy people do have them, it is clear that other genes must be involved. The NOD2 gene appears to be involved in a cellular process that controls the activity of a key protein complex called NF- $\kappa$ B. This complex switches on a host of genes that produce molecules that cause inflammation. Also, it has been known for some time that NF- $\kappa$ B activity is increased in the cells and tissues from IBD patients.

We believe that mutations in some of the many other genes that are involved in regulating the activity of NF- $\kappa$ B may also contribute to genetic susceptibility to IBD. We therefore propose to sequence these genes in DNA that we have extracted from the cells of IBD patients (Crohn's and ulcerative colitis) and to test any changes we find to see whether they are more common in patients than in healthy controls. We have a bank of DNA from about 2000 IBD patients and sophisticated technology for DNA analysis in our laboratory, so we believe that we are in a good position to carry out this work effectively. Also, we have an interdisciplinary research team of geneticists, statisticians and gastroenterologists, who have pooled their knowledge and expertise to tackle this challenge.

We operate on the principle "know your enemy"! Each new IBD gene that is found will help us to understand IBD better and to develop new approaches to treatment.