

## Lay Summary

### Miles Parkes- NACC Grant Application: Cambridge and Eastern region IBD genetics

Of all the common diseases subjected to genetic analysis in the last 10 years studies of Crohn's disease (CD) and ulcerative colitis (UC) have arguably progressed the furthest. One gene (NOD2/CARD15) has been identified for CD, and several other genes and chromosomal regions have been implicated. Much remains to be done in clarifying the unconfirmed associations and pinpointing the remaining susceptibility genes. However there is now the realistic prospect of a major leap forward in understanding the molecular basis of CD and UC and the heterogeneity within these conditions. Over the next 10 years this should enable the more rational use of existing treatments and in the long term the development of new therapies.

This application is to support Dr Sarah Waller for 18 months to achieve 3 key aims:

1. Expanding the Cambridge / Eastern England IBD panel from 1750 to 2500 - 3000 DNAs.
2. Test the IBD panel for new mutations being detected in candidate genes by our collaborator Dr Jiahui Zhu using his novel technique of 'Genome Partitioning'
3. Contribute to data analysis for the UK-wide Crohn's disease case-control study

There is clear benefit in expanding the Cambridge / Eastern England panel over the next 18 months - both for practical and statistical / study design reasons. Up to Feb 04 we had invested 2 years of administrative effort (ethics, R&D committees, hospital visits etc) in creating a network of gastroenterologists in 15 hospitals across Eastern England. Over the past 7 months they have begun recruiting individuals with IBD to this study at a rate of 75 -100 / month, with clinical data and bloods for DNA supplied. 3 more hospitals have been initiated in the past month. This 'pipeline' of samples relies on the presence of Sarah Waller in the lab to oversee and help with extraction of the DNA and prepare it for analysis. With the supply-line being so productive of this vital genetics research resource we are keen to avoid having to shut it down.

Why the need for so many samples? There are two major benefits.

- It is clear from work already done that the genetic associations found are seen most strongly not with IBD overall or even with CD or UC alone but with sub-groups of CD or UC as defined by for example the location or pattern of intestinal inflammation. To prevent true associations being over-looked in genetic analysis there is thus a need to analyse large panels where even the disease subgroups (for example CD affecting ileum only = 30% of CD overall) are sufficiently large to be independently statistically powerful
- As the field moves towards genome-wide case-control association studies it is clear that large datasets (3000 - 6000) will be required to detect many of the genes which produce common disease and which individually may only have a modest effect. We would like to ensure that the UK IBD field is in a position to undertake such studies without the recruitment lag that will otherwise occur. Indeed as a direct result of having a large CD DNA bank available and the scientific 'visibility' this brings we have been able to successfully position ourselves at the forefront of one of the first large scale case-control genotyping efforts to be undertaken worldwide sponsored by the Wellcome Trust (WT) and due to start April 05.

Goal number 2 directly relates to the WT study. The CD panel comes from a UK collaboration (Cambridge, Oxford, London, Newcastle and Edinburgh). Sarah Waller has already benefitted from statistical training by the Clayton group in Cambridge as part of the targetted association studies that we have been undertaking. Prof David Clayton is one of the two statistical leads for the WT case-control study. Given her existing knowledge and working relationship with the Clayton group Sarah is in an excellent position to contribute to the analysis and ensure maximal statistical value is extracted from the 100 000 markers to be studied in CD, including detailed subgroup analysis. This is particularly important as statistical support is not included in the WT grant, and the study design requires prompt analysis and interpretation of large volumes of data.

The final part of this proposal is to test novel genetic variants identified by our collaborator Dr Jiahui Zhu. He has developed and patented a new technique called Genome Partitioning which has exciting potential. Originally applied in plant science it is equally applicable in all fields of genetics, and our IBD study will be its first application in humans. It produces dramatic efficiencies in identifying disease- (or other group-) specific genetic variants. Dr Zhu has run some pilot studies on 80 IBD DNAs and we already have 6 new mutations (genetic variants) that we would like to test in the full IBD panel.

The three parts of this study will each require varying levels of input over 18 months. Each is important in its own right and Dr Waller has proved over the last 18 months that she has the technical and organizational skills to undertake them in this period.