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**Grant awarded £5,800 (9 months)**

***Chimeraplast-mediated gene therapy for Crohn's Disease***

Gene therapy is a promising potential treatment for disorders caused by the inheritance of an abnormal gene. Recently, for the first time a specific genetic abnormality, in the NOD2/CARD 15 gene, has been linked to risk of developing Crohn's disease (CD). Although mutations in the NOD2/CARD 15 gene account for only a small part of the risk of developing CD, and only a proportion of patients with CD inherit abnormalities in the gene, the discovery is an exciting opportunity that opens the way to developing specific gene therapy for IBD more generally. This is so for a number of reasons.

Firstly, while mutations in the NOD2/CARD15 gene account for only a proportion of patients, in some cases, particularly when the patient inherits abnormal genes from both parents, the relative risk of developing CD is extremely high. Thus, at least in this small group, targeting the abnormal gene may be beneficial or even curative.

Secondly, the abnormalities in NOD2/CARD15 that have been detected may be similar to the tip of an iceberg – there may be many other specific gene abnormalities that are associated with CD. As more genes directly linked to IBD are discovered, more targets will be revealed, and any advances we make now in targeting NOD2/CARD15 could be used over again.

Thirdly, by collaborating with Dr J wen, a Senior Lecturer in our department, we propose to use a revolutionary new technique that actually repairs the mutations in genes, rather than replacing or adding to them. This technique, called chimeraplasty, has been successfully used to repair genes causing haemophilia, heart disease and Duchenne muscular dystrophy and our collaboration would allow us to use this cutting edge technology in the intestine for the first time.

Finally, in my laboratory, we have shown that the NOD2/CARD15 gene is expressed in the affected part of the intestine in patients with CD, and not in normal intestine. Thus we could aim to correct the gene defect only in the affected intestine, which means that most of the body's genes remain unmodified. This reduces the risk of introducing new mutations and potentially causing worse side effects. In fact, just as the intestinal lining is naturally shed and renewed, the effects of gene therapy would be limited as cells in which the genes have been repaired are shed. While this means that the therapy must be repeated, it also means that side effects would be naturally limited.

Initially, as a pilot project, we propose to use chimeraplasty to repair the three common mutations in the NOD2/CARD15 gene that are associated with CD, in a cell line, *in vitro*. We have already demonstrated that this cell line expresses the NOD2/CARD15 gene, and that its expression is increased by

inflammation. The cell line at present appears to have only the normal form of thNOD2/CARD15 gene, and so we will use chimeraplasty to mutate the normal form to an abnormal form. If this is successful, it will prove that chimeraplast-mediated gene repair for the NOD2/CARD15 gene is possible in principle, as the chimeraplasty technique works equally well in both directions.

In addition to opening the way to gene therapy for patients with CD, this pilot project by itself would be extremely beneficial, in that we would generate cell lines with specific mutations in the NOD/CARD15 gene. Such cell lines would be immediately valuable to pharmaceutical companies seeking new treatments for IBD as they could be used to screen for chemical compounds that interfere with the function of abnormal forms of NOD2/CARD15. This in turn could generate new treatments for CD that would be applicable even if gene therapy itself were not feasible for the majority of patients.